UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and
Biocon Biologics,
Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 12, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

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Monday Morning Session,

June 12, 2023, 9:30 a.m.

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THE COURT: Thank you. Please be seated.

Madam Clerk, would you be kind enough to call our next case, please.

THE CLERK: Regeneron Pharmaceuticals, Inc., v. Mylan Pharmaceuticals, Inc., Civil Action Number 1:22-cv-161.

Will counsel please note your appearance for the record.

MR. RUBY: Good morning, Your Honor. Steve Ruby of Carey, Douglas, Kessler & Ruby for plaintiff Regeneron Pharmaceuticals, Inc. With me I have David Berl, Ellen Oberwetter, and Kathryn Kayali from Williams & Connolly in Washington, D.C. And also from Regeneron I have with me Joe LaRosa, who is executive vice president and general counsel; Larry Coury, who is vice president and associate general counsel. I'll note that Mr. Coury is a native of Mercer County.

THE COURT: Welcome home, sir.

MR. RUBY: His father is a WVU alum and his mother Marshall alum. So we're glad to have him back in West Virginia for a little while.

Also Petra Scamborova, James Evans, Andrew Deciare, and Arun Bhoumik, all from Regeneron.

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THE COURT: Good morning, everyone.

Good morning, Counsel.

MR. COPLAND: Good morning, Your Honor. This is Gordon Copland, Steptoe & Johnson, appearing on behalf of the defendants Mylan Pharmaceuticals, Inc., and Biocon Biologics, Inc. Also appearing this morning is William O'Brien of Steptoe & Johnson; William Rakoczy and Deanne Mazzochi, both with the Rakoczy Molino Mazzochi & Siwik firm.

THE COURT: Good morning, everyone.

All right. Here for day one for trial slated to start opening statements, but word was there was a request to seal the courtroom during a portion of plaintiff's opening. Is that correct?

MR. COPLAND: That's correct, Your Honor. The motion's not opposed by the plaintiff. We did prepare a brief just in case, which I'll hand up if I may, Your Honor.

THE COURT: Sure. Which slides are we talking about?

MR. COPLAND: It's 14 through, I believe, 45, but may I double-check that, Your Honor, when I get back to my seat? And there are about 142 slides, maybe a little more. So only the portion between the first slide, which is 14, and the last one that has an issue, 41, would we request sealing. And, of course, that would not apply to anyone already under the protective order, only to third parties present in the courtroom.

We do have an agreement that certain counsel for Regeneron may attend even though outside-counsel-eyes-only material will be some of the material, and we just ask that their counsel confirm that they're agreed to be under the protective order pursuant to the parties' prior agreement.

THE COURT: Understood.

Counsel?

MR. RUBY: We agree to that, Your Honor, yes.

THE COURT: Understood. And note that we have a spectator or two today. I'll leave it to counsel to police who is permitted to attend -- remain in the courtroom under the Court's protective order and who is not.

MR. COPLAND: If Mr. Berl will just give us notice before he hits Slide 14, and we can pause.

THE COURT: Understood.

A couple housekeeping matters for everyone. There are additional restrooms. Since we've got a bigger crowd than we had for naturalization on Friday, the line will back up quickly here. There are additional restrooms up on the third floor and either the elevator or stairs at the end of the hall will get you there.

As folks may have noticed, in addition to our looming asbestos abatement project, some preliminary work is ongoing on the roof of the building. So please continue to refrain from trying to park immediately adjacent to the courthouse, those

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spots abutting the building. One, it'll save your cars or rental cars some damage -- potential damage, I should say -- and we need whatever slots they randomly let us have on any given day for the court personnel.

With that, Mr. Berl, sir, the floor is yours.

MR. BERL: Good morning, Your Honor. David Berl for Regeneron. This case is about Eylea, a product that made Regeneron what it is today. More specifically, this case is about the discoveries that made Eylea what it is.

Before the discoveries at issue in this trial, Regeneron was a small fledgling company with virtually no products or revenues. The discoveries of the patents-in-suit led to Eylea's groundbreaking treatments for diseases that are the leading causes of blindness.

Eylea is responsible for a majority of Regeneron's revenues. It funds Regeneron's research and development into the hardest diseases to treat, from cancer to Alzheimer's. Regeneron had and has a culture of innovation.

To take just one example, when COVID struck and most of the world shut down, its scientists, led by George Yancopoulos, its cofounder, sprung into action immediately and quickly developed a treatment that saved many lives, including possibly the then-president of the United States.

That's who the plaintiff is.

The defendants in this case are Mylan and Biocon.

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Mylan filed an abbreviated biologic application to FDA to sell a biosimilar version of Eylea. Mylan then transferred that application to its successor in interest, Biocon, in Bangalore, India. Biocon will be selling this product if the defendants succeed in this case.

In order to understand the issues a little better, some background on the anatomy of the eye will be helpful. This is a diagram of a healthy eye. It's not drawn to scale. It's intended to show in two dimensions what's obviously three dimensions in real life.

The important components here are the retina, shown in pale yellow, which is supplied by blood vessels, that are shown in red; and the vitreous, which is a gelatinous area of the area that abuts the retina. In between the vitreous and the retina is a barrier called the ILM, the inner or internal limiting membrane.

There's also a protein in the retina, shown in green here in the little dots, called VEGF. And when VEGF is present in the right amounts, it supplies the healthy blood vessels of the retina and everything is fine.

But when there's too much VEGF in the eye, things go wrong. The blood vessels increase, and the blood vessels get too thick, and blood and fluid starts to leak. That creates significant problems and diseases, including macular edema, shown here, and other diseases that cause blindness.

Regeneron developed Eylea to try to solve that problem. The active ingredient in Eylea, aflibercept, shown in purple here, blocks VEGF -- two hands on the football -- and thereby inactivates it.

Now, Eylea is administered into the eye through a needle, so-called intravitreal injection. When it's administered into the vitreous, however, it must get into the retina to do its job. It must pass through that barrier, get into the retina, and inactivate the VEGF there, where there's a disease state. And when it does that and inactivates much of the VEGF in the retina, the VEGF essentially goes away and the disease recedes. You can see the blood vessels come back to their healthy state and vision is restored.

Now, Eylea has a VEGF inhibitor called aflibercept, but there were lots of VEGF inhibitors out there, not just one, for many different companies. This is the story of why a product with one of those inhibitors, from a sea of potential inhibitors, won out. This is the story of the two inventions that made that happen.

There are two inventions here. One on the left is directed to the product that is administered. Because of witness schedules, we'll start with that one this week. And it came first in time. The second invention is treating using aflibercept, the VEGF inhibitors in a particular way that has been proven to be very successful.

Now, starting with the product patent, the '865 patent, you will hear from two of the inventors of the product patent, Dr. Furfine and Graham, about their invention and the research that led to it.

The products they invented, one example of which was Eylea, were transformative. They bucked the conventional wisdom to invent a stable formulation with a high concentration of aflibercept, 40 milligrams per milliliter, required by all the asserted claims through incorporation of the independent claims. And that high dose and formulation of Eylea facilitated the product's eventual success.

Now, in order to market a biosimilar version of Eylea that copies from the patent the 40 milligrams per milliliter of aflibercept as well as the organic cosolvent it uses of polysorbate, Mylan and Biocon advanced various defenses of noninfringement and invalidity. I don't think you'll hear in detail about many of these defenses given how many there are, but Mylan has not narrowed what it proposes to present at trial; so I'll try to cover them all this morning.

The first dispute is whether Mylan infringes the organic cosolvent limitations of the claims. And they do.

And this is the point where I'm going to hit material that I think they want the courtroom sealed for.

THE COURT: Understood.

The Court would then seal our proceedings. Those not

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specifically permitted to be here in the Court's protective order, if I could ask you to depart, please.

(The following proceedings (10/3 to 20/7) were sealed and are filed under separate cover.)

THE COURT: Thank you.

If I could ask court security to unseal our courtroom and extend an invitation to those out there to rejoin us if they'd like. Thank you.

Welcome back, everyone.

Mr. Berl, go right ahead, sir.

MR. BERL: Next are Mylan's invalidity defenses, and we'll start with anticipation.

The patents at issue in this case were issued after substantial examination by the US Patent and Trademark Office, and they were duly issued and entitled to the presumption of validity.

Mylan bears a heavy burden -- clear and convincing evidence -- to prove the facts necessary to show invalidity. It can't do so. Anticipation requires that a single record, just one, disclose each and every limitation of the claims expressly or inherently arranged as in the claim.

The first of Mylan's two anticipation references called Fraser doesn't even come close to meeting that

requirement. It's mincing lots of limitations from the claim. This argument of theirs reminds me of the old Coffee Talk Joan Rivers skit on Saturday Night Live. The Holy Roman Empire is neither Holy nor Roman nor an empire. You may remember that. That's what this is.

Fraser discloses neither an ophthalmic formulation nor intravitreal administration nor glycosylated nor aflibercept nor 98 percent native conformation nor 40 milligrams per milliliter. It's got none of it. And it has to have everything.

Mylan tries to plug at least some of the holes in the dam by suggesting that anything written in an article that Fraser cites or, in fact, anything written in an article cited by an article that Fraser cites somehow magically becomes part of Fraser because anticipation, they have to have only one reference.

First of all, that's implausible; but second, it's contrary to consistent federal circuit precedent, that the host document -- here Fraser -- must identify with detailed particularity what specific material it incorporates. Simply adding the footnote and citing a reference isn't close to enough. You've gone from Joan Rivers to Six Degrees of Kevin Bacon in one article.

Now, the second anticipation argument that they advance is this, and the assertion of Dix requires the Court to

address a subsidiary question, which is whether Regeneron is entitled to a priority date of March 21, 2006, or earlier because that's before the time that Dix was filed.

Now, the answer to that question is yes. In fact, the invention here was made far earlier in the fall of 2005, but for present purposes, because Mylan has only asserted Dix, we only need to show priority back to March 21, 2006, or earlier.

If Regeneron is entitled to that date -- and we think it's clear that it is -- then Dix simply is not prior art. Everything you hear about Dix the next two weeks -- and I suspect you'll hear quite a bit -- is totally and blessedly irrelevant to this case because it's not prior art.

But even if Dix were prior art, then it would still not anticipate the claims because it too, like Fraser, is missing at least one limitation, in fact, several, including intravitreal administration and an ophthalmic formulation. It has none of that.

Now, for the 40 milligrams per milliliter formulation, which is a very important limitation in the claim, what they rely on is a disclosure of 10 to 50 milligrams per milliliter in Dix.

First of all, that disclosure is not about aflibercept in particular; so it's not arranged as in the claim. But more importantly, the federal circuit repeatedly

has been clear, including earlier this year, that the disclosure of a range, like 10 to 50, is not a disclosure of discrete points within that range like 50, like 40. 10 to 50 does not anticipate 40. It can't do that under controlling law.

Now, with that, I'll move to obviousness, which is their backup prior art argument. And the first problem with Mylan's obviousness argument is their selection of references. They pluck out of prior art various references, most of which have nothing whatsoever to do with the issue here, which is intravitreal injection that can treat diseases in the retina. But that's not allowed under the law.

The question is not whether the so-called person of ordinary skill, or the POSA, with the two prior art references in front of him could combine them and arrive at the patent-in-suit, which, by the way, it couldn't even if they had them in front of them.

Mylan and Biocon don't even get to that question because the question, as the federal circuit said in the WBIP case, is whether the skilled artisan would have plucked one or more of those references out of the sea of prior art in the first place. And Mylan's experts skip over that analysis and choose their references without any contemporaneous justification or basis.

There were many VEGF inhibitors in the prior art. It

was a sea of VEGF inhibitors. And Mylan just assumes without basis that the POSA would have chosen one of them, aflibercept. Not so.

As I mentioned earlier, there's a barrier between the vitreous, where the drug is injected, and the retina and other associated tissues where it needs to go. And whether the molecule would get from the vitreous to the retina was understood to depend on its size. And aflibercept at the time was considered too big.

Now, the prior art taught -- and this is the Gaudreault reference from Genentech in 2005. And we'll hear a lot about this reference. It taught that penetration of ranibizumab -- that was Genentech's product at the time. They were developing a different product called ranibizumab that later became Lucentis, which is a product on the market. They were ahead of Regeneron; so they were publishing already.

And what they said was penetration of their molecule, ranibizumab, into the retina is critical for its credible use. You've got to get to the retina. Or as people in the field often say, the tissue is the issue. So you've got to get to the right tissue. And why do they say their product gets to the retina? Because of its small molecule size, 48 kilodaltons. Kilodaltons is just a measure of weight like pounds or kilograms.

And they contrasted it with what they called a

full-length antibody, something that was 148 kilodaltons that they said was not able to penetrate the retinal layers of the monkeys. So 148 was too big; 48 was good enough. And what the art said -- not just Genentech but others -- is that things that are over about 70 kilodaltons or about 76 kilodaltons were too big.

Now, we all know that aflibercept, in fact, did end up penetrating the eye into the retina. If it didn't, none of us would be here today. Okay? We'd all be somewhere else. But that's not what matters for obviousness. What matters is what everyone thought and knew at the time of the invention about 16, 17 years ago. And at that time aflibercept was simply considered too big.

This is ranibizumab, what we just saw, 48 kilodaltons. Aflibercept was 115. And it actually behaved like it's even bigger because of its unusual size. The idea of using aflibercept via intravitreal injection straight into the eye was actually tried in mice in the prior art, and it didn't work very well.

The figure on the left is subcutaneous injection. That's systemic injection that Your Honor is used to, less scary than intravitreal injection. And what you want to look for here is does the problem go down. You want the numbers to go down. This is golf, not bowling.

And when you did this systemic administration, what

we see is the bar goes way down. That works well. But when you do intravitreal administration straight into the eye, the bar doesn't go down very much. And what people at the time said -- and not just people. This on the right is an article by Genentech and in particular someone called Napoleone Ferrara. He's the godfather of VEGF. He actually discovered VEGF. And he, while at Genentech, developed the first two anti-VEGF therapies: Avastin and then Lucentis. And what he said is he looked at these data and he said there's limited efficacy, despite the high binding of the molecule. And it may be due at least in part to the existence of a barrier to penetration of large molecules such as the VEGF Trap.

That's what people were thinking and saying at the time. It's too big. And without showing that you want to do intravitreal administration of aflibercept, that claim can't be obvious because all of the claims require it.

But the claims actually require more. Mylan has to show much more than that. They have to show that the person of skill would have wanted to use 40 milligrams per milliliter of aflibercept, this high concentration of aflibercept. They have to show that by clear and convincing evidence.

And the presentation from them that you'll see in a moment has all sorts of prior art showing all sorts of buffers and organic cosolvents and stabilizing agents, almost nothing about 40 milligrams per milliliter. That was never done in the

prior art for aflibercept. And they can't meet that burden, including because people thought that increasing concentration increases aggregation. That's the problem I discussed earlier.

In fact, Genentech in this same Gaudreault article tried 40 milligrams per milliliter, and it went poorly. What happened when they did 40 milligrams per milliliter was that they got ocular inflammation that was moderate to severe. Bad news. You don't want inflammation. It resolved after eight days, but keep in mind this is a product that's administered every month. No one wants their eye to be inflamed for one week out of every month, let alone inflamed potentially with particles that can hurt your vision and cause real problems.

So Genentech, the leader in the field, ditched the 40 milligrams per milliliter idea and instead pursued lower doses, 6 milligrams per milliliter or 10 milligrams per milliliter, which is what they ultimately used in Lucentis.

The argument based on Fraser of obviousness fails for this reason alone. Not only does it fail to disclose aflibercept or intravitreal injection, it has only 24.3 milligrams per milliliter, and the claim requires 40. The skilled artisan would have used less than 24, not more, and certainly wouldn't have gone all the way up to 40 when Genentech, the prior art, was teaching away from it.

Now, the second prior art reference for obviousness

that Mylan advances is Dix. And the assertion of Dix would require the Court to answer a second question in the event that the Court does not believe that Regeneron is entitled to an earlier priority date.

If we are entitled to an earlier priority date, as I said, Dix goes out the window completely. But if you answer that question no, Your Honor, then you have to answer a second question. Is Dix subject to the safe harbor of 103(c) in the statute so that it cannot be used for obviousness?

And the answer to that question is that Dix is subject to the safe harbor. The statute is very clear. You can't use as an obviousness reference a reference owned by the same person as the patent or subject to an assignment of -- to an obligation of assignment to the same person. Your own prior art can't be used against you for obviousness under 103(c).

There is no question but that Dix shown here on the right and other such references and the product patent at issue were owned by the same person, Regeneron Pharmaceuticals. And all of the scientists working at Regeneron at the time, of course, had an obligation to assign their inventions. That's how pharmaceutical companies work. If you work for them and use their labs, you don't get to keep your invention. It belongs to the company, of course.

Now, even if Dix could be used for obviousness, it doesn't really help Mylan and Biocon. It does not disclose

40 milligrams per milliliter. And based on the prior art that we've seen, the skilled artisan never would have used that high a concentration. It would have used a much lower concentration for the intravitreal injection, just as the prior art repeatedly taught.

In any event, even if Mylan could show motivation to make the claimed invention, it cannot show expectation of success, an independent requirement of the obviousness inquiry. And moreover, the objective indicia of nonobviousness, including commercial success, demonstrate clearly that the invention was not obvious, as you'll hear from Dr. Richard Manning, our expert economist.

Now, Regeneron did not succeed because it had a molecule that inhibited VEGF. Lots of companies had that. But consider what happened with Genentech. They were the big 800-pound gorilla in the field, the leaders in the field of biotechnology in general and VEGF in particular. They had a big first mover advantage with their product, ranibizumab.

And there were lots of companies out there trying to compete with Genentech, who had the leader in the field, Dr. Ferrara, leading their program. None of the other competitors succeeded, none of them. Only Regeneron succeeded. And Regeneron succeeded wildly with a product Eylea that ended up being the market leader and, in fact, overtaking Genentech's ranibizumab.

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Now, because the prior art does not invalidate the patent, Mylan next turns to Section 112 defenses. Now, these defenses, as I pointed out at the pretrial conference, are so blatantly inconsistent with their prior art references that Mylan actually has to bring two separate experts in order to advance these arguments -- prior art on the one hand and Section 112 on the other -- because one person couldn't possibly keep them straight, let alone testify lucidly as to both.

They start with enablement, but their theory on enablement suffers from a repeated fatal flaw. Mylan runs enablement in the alternative in saying if the patent is not obvious, then it must not be enabling because it's either hard to do, in which case it's not enabled, or it's easy to do because it's obvious.

The problem with that argument, as the federal circuit repeatedly recognized, including in the Allergan case, is that enablement and obviousness are different because, for obviousness, you don't have a patent. You don't have the benefit of what the inventors did and taught the world. For enablement, you do. And the question is, whether reading the specification, then you can practice the invention without undue experimentation.

The Supreme Court addressed enablement last month in the Amgen v. Sanofi case. And what they said, among many other

things, is that enablement is a problem where you have to do as much work without the patent as you do with the patent, where the patent doesn't really help you in any way. That manifestly is not the case here.

The claims here require 40 milligrams per milliliter of aflibercept, not taught for intravitreal injection in the prior art. Taught in the patents. They require organic cosolvents disclosed in the patent. They require stabilizing agents disclosed in the patent. The patent tells you what pH to use so that you can choose an appropriate buffer.

The notion that the skilled artisan is in the same position with or without the patent, respectfully, is not plausible. And the prior art does not disclose all of this, including and especially 40 milligrams per milliliter of aflibercept. But the patent does.

Mylan's argument is premised on the very notions that the Amgen supreme court decision rejects, that it's about the cumulative time and effort it takes to make all the embodiments or that enablement is about exhausting the genus, making every single embodiment in the claim. That's not what we have here.

In the cases where nonenablement is found, each and every embodiment of the claim must be made and tested. So you've got a big research project of making absolutely everything. But in this case, as their own Section 112 expert explained repeatedly, the skilled artisan wouldn't need to make

every formulation in order to practice this claim. You'd be able to eliminate a lot of candidates and narrow yourself down to acceptable candidates and then do some experimentation. So the premise of cases like Idenix and others from the federal circuit -- you have to make each and every one; therefore, it's not enabled -- is simply not present here.

Now, Dr. MacMichael says for enablement that it would be really hard to make these formulations of the claim. He's wrong. The POSA could have made the formulations with the patent in hand quite easily. But you don't have to take it from me. You can take it from Mylan's other expert, Dr. Rabinow.

When we asked him, in your view, the POSA could have made and used the formulations within the claims even without the specification with one hand tied behind his back. And he answered quite simply yes. It is impossible on this record to find that the claims are somehow not enabled when their own expert agrees you can make the formulations even without the help of the specification.

Now, finally, Amgen is a mismatch for this case. Justice Gorsuch said the problem is where a patentee seeks sovereignty over an entire kingdom. You claim everything that works, which is what they did in Amgen, without limitation as to what particular structures should be used to practice the claim.

Our claim, unlike Amgen's and all the others that go down, is full of structural limitation. It has to have aflibercept. That's a structure. Organic cosolvent. Buffer. Stabilizing agent. Those are all structures that limit what formulations are in the claim. If you don't have an organic cosolvent or a buffer, you're out of our claim. Whether it works or not, it's structurally limited. And, therefore, enablement cannot -- nonenablement cannot be found.

Mylan's written description argument is advanced on the same basis as its enablement argument, and it's wrong for similar reasons. The federal circuit in Alcon made clear that all that matters for written description is whether the skilled artisan can recognize what was claimed. It's not about whether the patentee has proven that it will work.

So Dr. MacMichael's enablement -- the written description argument that there aren't enough examples, you haven't proven enough, simply isn't required. He's looking for something that the law does not require.

And written description is present where claims are limited to known sets of structures. And he admitted over and over in his deposition, and will admit it again at trial, that the claims are limited to particular structures that were known. Nonwritten description is present where a skilled artisan doesn't know what structures to use and so can't visualize what was claimed. When it's clear what structures

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can be used, the written description requirement is met.

The last invalidity argument on the treatment patent is indefiniteness. And Mylan asserts that the terms "suitable for intravitreal administration" and "measured by SEC" are somehow indefinite. They appear now only to be running one of those arguments, but both of them are wrong. And they're wrong including because their own experts were able to understand and use that term repeatedly.

And so if their experts understand what it means and skilled artisans understand what it means, then the claims simply are not indefinite, as the federal circuit has held.

And, with that, I'll move to the treatment patents.

You'll hear momentarily from Dr. Yancopoulos, the sole inventor of the treatment patents. There are two sets of claims at issue in the treatment patents. The first is Claim 6 of the '572 patent. It claims treating an angiogenic eye disorder with an extended eight-week dosing regimen, that you dose every eight weeks, with an isotonic solution of aflibercept. And isotonic refers to the amount of substance dissolved in the formulation.

The other claims at issue relate to treatment of specific diseases: diabetic macular edema, DME, and diabetic retinopathy, DR, using a specific dosing regimen that requires five monthly loading doses. In the claims called an initial loading dose and then four secondary doses, one plus four being

five. That five loading dose regimen was never disclosed, never suggested in the prior art.

These claims do not involve any of the terms that the Court construed in its claim construction order, and none of them were asserted or admitted to be invalid by stipulation, as Mylan misleadingly asserts in its slides.

Now, a little background about how this works. The claim in the patent discusses initial doses and secondary doses. And those together are called loading doses. Loading doses is loading the patient up with initial doses to try to get the disease under control. And then the patent talks about maintenance doses, which are also called tertiary doses. And what we see here is an every-eight-week dosing regimen. Every eight weeks, a dose is administered. An extended dosing regimen of eight weeks rather than four weeks, which was typically used in fixed-dosing regimens of the prior art.

Now, the number of loading doses in the patent can change. It can move back and forth. And, in fact, in the DME and DR claims, as I just mentioned, five loading doses are required. The claimed dosing regimens were nothing short of transformative. Everyone agreed that you wanted fewer injections. Obviously, everyone wants injections into the eye less often.

But Regeneron was the only one who figured out how to made that happen. And they did so with a particular

fixed-dosing regimen that was disclosed in claims in this patent and that are at issue in this case. They did that by going against the conventional wisdom which taught going in a different direction, and they did something different.

Now, Mylan has again a host of defenses, throws up everything against the wall, but none of the defenses are meritorious. Somehow, Mylan and Biocon still continue to assert noninfringement. But the expert testimony as to the two inquiries that underlie the infringement analysis will be uncontested.

That is because, even though Mylan insisted that its noninfringement expert, Dr. Russell, would testify when it submitted the pretrial order on May 18, it reversed course a week later and agreed that no expert would testify about noninfringement. Dr. Russell vanished.

Our expert, by contrast, Dr. Karl Csaky, a renowned retinal specialist who practices in Dallas, Texas, will address both validity and infringement. And as to infringement, it's no mistake that Dr. Russell capitulated. Mylan and Biocon do not seriously dispute that their label teaches each and every limitation of the claimed dosage regimens. And as a result, under the federal circuit's law, that is dispositive of the induced infringement inquiry.

Now, they then move to invalidity, to excuses for why they should be able to sell their product anyway, starting for

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anticipation, which again requires a single prior art reference to each and every limitation in the claim. And the problem with their anticipation theory here, based on the prior art Dixon reference, is that it never discloses the isotonic solution required by Claim 6 of the '572 patent.

Instead, it discloses something different, the suitable -- suitable for the comfortable, nonirritating direct injection into the eye. That doesn't say isotonic, and Mylan knows it. So what Mylan does instead is rely on the doctrine of inherency to prove anticipation, but inherency is a tall standard. That's a tall hurdle to meet. It requires that the missing material -- here, isotonic solution -- is necessarily present in the prior art, necessarily present in Dixon, not there by probabilities or possibilities.

In his report, Mylan and Biocon's expert said that it is inherent because you have Dixon, and comfortable, nonirritating injection into the eye must be something that is not -- must be something that is isotonic. But that flimsy opinion did not survive even moderate cross-examination.

We asked him quite clearly, "Do you think that even a hypertonic solution, one that's not isotonic, nonetheless could be comfortable and nonirritating to the patient?" It could still be within Dixon so that Dixon could include isotonic and nonisotonic.

And he said, "I don't know. I'm not sure." Anything

but clear and convincing evidence that the isotonic solution necessarily and always must be present in Dixon.

He further testified, not shown here, that the skilled artisan would want to administer intravitreally nonisotonic solutions in the prior art. Now, remarkably, based on the deck we got yesterday, Mylan and Biocon intend to resuscitate this argument at trial. But they cannot succeed in doing so given the testimony.

So Mylan and Biocon shifted to a different anticipation theory in summary judgment argument. And it is equally wrong. Their new theory is that Dixon, which discusses a clinical trial, is somehow to be conflated or combined with the clinical trial itself shown here on the right where people actually were injected.

But these are two different references. Dixon is just a publication. It's a piece of paper. It's not actual injections that happened. Mylan could have relied on the actual clinical trial saying that those uses of aflibercept somehow anticipated the claim, but it can't really do that because the clinical trial itself was confidential and not prior art.

So what they've done is suggest that, because the clinical trial, unbeknownst to anyone in the field at the time, used an isotonic formulation, that must have been present somehow in Dixon. But that's not so because that isotonic

formulation and the trial itself is not part of Dixon. It's part of something else.

And the issue of inherent anticipation for Dixon is whether someone practicing Dixon necessarily and always -- always -- would practice the claim. It's not enough that they could practice the claim, as in the federal circuit's Glaxo v. Novopharm case; they have to do it every time. And Dr. Rabinow agreed that you could practice with isotonic; you could practice with something that's not isotonic.

Now, on obviousness, they've also made a fundamental legal error. The Court's Markman decision held that various language here in the claims is not limiting. However, the Court did not rule that the longstanding principles of obviousness jurisprudence somehow magically do not apply to this case. They do. And Mylan asks the Court to cast them aside improperly.

First, it is black letter law that obviousness must consider the claim as a whole. It's right in the statute. And it's improper to disaggregate the claim piece by piece -- A plus B plus C, as the federal circuit says -- and say, well, this was here and this was nonlimiting and this was here, and so, therefore, because I can find something everywhere or it's not limiting, the claim is obviousness.

That's not how obviousness works. You have to look at the claim as a whole and assess whether it's obvious. And

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their approach, crossing certain things out because they're not limiting and finding isotonic formulations somewhere else, is wrong.

Now, second, let me be clear about the effect of the Court's claim construction. We understand that the Court held those limitations about certain eye improvements to be nonlimiting. And so they don't need to show those limitations in the prior art. They don't need to be shown.

But that does not mean that the inquiries about motivation to practice the invention and expectation of success get thrown out the window. The skilled artisan is not somehow lobotomized and all the sudden doesn't care about treating patients and improving their vision just because language is not in the claim.

The federal circuit has been clear that whether those goals of the POSA are in the claim or out of the claim or, in this case, in the claim and not limiting under Your Honor's construction. It doesn't matter. There's still relevant motivation and expectation of success.

They have to show someone would have been motivated and expected to succeed in practicing the claim, and they can't do it because the prior art simply did not disclose that this every-eight-week regimen would be successful. What they do instead is rely on disclosures of people trying -- of Regeneron trying this eight-week regimen, which, of course, we were. We

were doing clinical studies with it. But not that it would succeed. In fact, people thought it was a bad idea in the prior art, which forecloses a finding of obviousness.

The prior art shown here was moving in an entirely different direction, towards so-called pro re nata, or prn, dosing, which is evaluate a patient and then dose if you think he needs it rather than a fixed dosage regimen where there's a prescribed amount of time between each dose.

Mylan's own expert agrees that individualized assessments, this so-called prn dosing, is what most people were doing at the time. And those who tried extended fixed dosing, including Genentech, failed spectacularly, including in the important peer trial in the prior art, where patients lost a whole lot of vision with extended fixed dosing.

The prior art was clear here. Extended fixed dosing was a bad idea. It provides less benefit to patients. And, in fact, Genentech tried and failed with every-eight-week dosing as well.

Regeneron at first tried prn dosing too. That's the way the wind was blowing. I want to explain the nomenclature for just a moment. You'll see often a number followed by a Q followed by another number in connection with these documents. The first number is the dose. That's how much of the drug people are getting.

THE COURT: The solution itself? That's not

reflecting how much aflibercept is in the solution?

MR. BERL: That's how much aflibercept is in the solution, not the solution itself. So the solution itself has other things, and they usually get up to 50 microliters into the eye. And so that 50 microliters can either have a lot if it's really concentrated, or it can have a little if it's less concentrated.

THE COURT: So the first number is actually the active ingredient?

MR. BERL: That's the amount of the active ingredient. Exactly right.

THE COURT: Thank you.

MR. BERL: .502. And the -- after the Q is how often it's given, every 4 weeks, every 12 weeks, every 8 weeks, et cetera. And in this trial, which is in the prior art, the CLEAR-IT 2 trial, they did every four weeks, for example, with .5. And in all of these cases followed by prn dosing. They were doing this pro re nata dosing too, just like everyone does.

But then Dr. Yancopoulos shifted course contrary to the conventional wisdom and chose to pursue a fixed-dosing regimen at every eight weeks rather than prn as in the prior art View 1 and View 2 trial.

The difference between what Regeneron did and what the prior art previously did before the invention is stark and

important.

The prior art trial did not disclose every week -- every eight-week dosing, did not use three loading doses before that, did not compare aflibercept to ranibizumab -- Genentech's leading product -- in order to see whether it would work as well, and switched to prn rather than having extending fixed-dosing.

Now, quite surprisingly, Dr. Yancopoulos's invention worked, and he showed that dosing aflibercept and Eylea every two months, extended fixed-dosing will work as well as the ranibizumab, Genentech Lucentis, treatment every four weeks.

As you'll hear, this was enormously consequential for patients and caregivers alike, and it helped drive the success of Eylea.

Claim 6 reflected in this invention here is not obvious as a whole. But even if obviousness inquiry were limited improperly, as Biocon and Mylan urged, to the isotonic aflibercept limitation added by Claim 6, they still would fail. Their clinical expert, Dr. Albini, has no opinions about formulation. He defers to their formulation expert, Dr. Rabinow, on this.

For his part, Dr. Rabinow in his report relied on the Hecht prior art reference for a motivation to use an isotonic formulation. But then at deposition he agreed in no uncertain terms repeatedly -- and this is his word, not mine -- that

Hecht is inadequate -- it's inadequate -- to motivate the POSA to use an isotonic solution for intravitreal administration. It's not good enough. It's not even close. And Mylan should not be able to advance a new theory of obviousness here now that its experts crumbled under oath as to the theory they actually advanced.

Now let me turn to the DME or DR dosing, which require five monthly loading doses. An initial dose and four secondary doses make five.

No prior art disclosed that regimen. Zero. It's a big goose egg.

The published dosage regimen for the Phase II trials shown here had a lot of different regimens but never, never five loading doses followed by every eight weeks.

Now, Mylan's anticipation theory is actually based on the prn arm of this published trial, of this published regimen. What they say is that with prn dosing, it's possible somehow that someone could have gotten a fourth and fifth dose at weeks 12 and 16 and then possibly, magically, could then have gotten doses every eight weeks pursuant to his pro re nata treatment appropriate after UR-inspected regimen.

But that potential treatment by happenstance is exactly what inherent anticipation is not. The furthest their expert would go is that this prior regimen could easily result in the claimed regimen. But of course "could easily result"

isn't good enough. That is probabilities or possibilities. The law requires that it necessarily must result, and not even their expert thinks that.

So their main argument here is obviousness. And the argument that they propose is contrary to what the inventor actually did.

Dr. Yancopoulos chose a different regimen, never disclosed in the prior art, and he used it in the ensuing trials, called VIVID and VISTA. Mylan must prove that it was obviousness to do this, with an expectation of success. And it can't.

But, briefly, in order to evaluate what's prior art and what's not, Your Honor will have to decide what the priority date is for this invention, whether it's 2011, based on Regeneron's claim to its initial application filed with the patent office, or only 2013, if the initial application does not support the claims.

Mylan and Biocon disputed this issue, unlike in the product patent where they agree that the 2006 application supports the provisional application and never fought it and asserted the 2006 date in its expert reports.

But the 2011 application here supports the claim. It discloses the exact treatments that are in the claim, the diseases of diabetic retinopathy and DME, the initial dose, and four loaded doses. That's five loading doses and then every

eight weeks.

Mylan's argument, essentially, is that Regeneron disclosed too much in the 2011 application, that along with five loading doses, it also disclosed three or four or six or seven or eight.

But that doesn't work under the law. If you disclose the invention and more, you still describe the invention and you get priority, as the federal circuit explained in the Streck case where the disclosed priority application disclosed the particular molecule and a bunch more. That's good enough. You don't have to disclose only your invention; you just have to disclose your invention.

Now, on obviousness with the 2011 date, Mylan pretends that it's really easy to go from three loading doses to five. They say you just add a box here and you add one treatment. But while it might look like that on a piece of paper that you do that, that's not actually the intellectual exercise one must go through in order to get the five loading doses. Rather, if one starts at three -- and let me be clear.

There's nothing in the prior art showing a problem with three. No one ever would have said they used three in the prior art; that's a problem; I want to change that. No reason to do it. And if you're going to do it, you actually want to use fewer not more injections.

But even assuming that one considered it, it's not

just adding one treatment. If you add one loading dose, there you are, there is treatment at Week 12, and then you've got to push out the ensuing every eight-week doses because, if you keep that dose where it was before, at the 16-week point, you're not doing every four weeks any longer -- every eight weeks any longer after the four loading doses; so you push it out.

And then the skilled artisan would have said four isn't good enough -- even the prior art doesn't say go to four -- I'm going to double down for some reason -- who knows why? -- and go to five. And then people dose at five, again push out the ensuing treatments off the board, and change the regimen entirely.

Mylan pretends here, and in its presentation today, that whether you treat at these time intervals of 12 weeks, 16 weeks, or 20 weeks, it's just a simple coin flip exercise -- yes; no. Do I do it? Do I not? That's not what's going on here.

These are physicians and scientists actually trying to make a decision about a dosing regimen. They're not doing it by law. They're doing it based on analysis, based on the prior art. And the prior art told over and over fewer doses, not more, relieve patient discomfort. Don't make it worse, especially for DME, where you don't need to use as many loading doses, the prior art taught.

Indeed, Dr. Albini, their sole expert on this point, agrees that there was a move toward reducing the number of injections, not increasing them, flatly contrary to the theory that Mylan must prove in order to go from three loading doses to five.

In fact, the prior art itself, which is what matters rather than coin flips that Mylan is conjuring in its demonstratives, talked clearly -- and this the Lalwani article, PTX 703 -- that treatment of DME will be more of an art form with the tailoring of individual treatments for individual patients, prn, treat each patient individually, not a fixed extended dosage regimen like is claimed in our trial.

Now, with a 2013 priority date, there's one additional piece of prior art that Mylan asserts, which is the Do 2012 reference, which shows the initial data from the three loading dose trial, and the every-eight-week regimen with three loading doses is shown here in pink.

And what Mylan says, with classic impermissible hindsight, is that these data somehow would have motivated the skilled artisan, of all things, to add two loading doses.

That's not true. The contemporaneous evidence will show otherwise, including the fact that Regeneron, with all of the assembled experts together staring at the data, never thought that these published data tell you to use five loading doses rather than three. No one said it at the time, only

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someone who comes in 12 years later and says it would have been obvious.

The objective indicia of nonobviousness, including commercial success, further confirm nonobviousness. No one would have wanted to use this regimen. No one would have wanted to do it or expected that it would work.

Finally, we get to Mylan's dog's breakfast of different 112 defenses that it asserts. There are, like, eight of them. It's not clear what they're actually running, but I'll address a few that they actually mentioned in their pretrial briefing.

The first is that somehow the patent doesn't disclose treatment of angiogenic eye disorders in general.

Now, again, these arguments are so contradictory, they have to bring two different experts in to advance them, which they'll do again, because they're saying you wouldn't have any idea, even with the specification, how to disclose, how to treat these diseases. But the specification tells you how. It tells you very clearly which diseases to treat, and it tells you how to treat them, the extended eight-week dosing regimen with different numbers of loading doses.

Now, this is sufficient as a matter of law. Mylan's complaint is that we didn't treat enough diseases in the specification using actual clinical data that we said what we should treat, but we had to prove somehow with clinical trials

that each disease would work, that more diseases would work.

But there is no requirement in the law of written description that the disclosure contain either examples or an actual reduction to practice. On the contrary, Alcon v. Barr again, the patent need not guarantee that the invention works and efficacy data -- exactly what Mylan asserts is missing here -- are generally not required -- not required -- in a patent application. And we do have clinical data in our specification. We meet this requirement easily.

Finally, Mylan and Biocon assert that the term "approximately," which appears in the claim, somehow is indefinite.

Now, first of all, that's wrong because their experts know exactly what it means. So it has to be reasonably certain for people because it's used frequently in the art. But more importantly what we see on the right is the proposed label that Mylan and Biocon would send if their product gets approved to doctors. This is what they're telling doctors to do with their product. And they use the word "approximately" in their instructions to doctors.

Mylan and Biocon surely aren't trying to confuse doctors by using a word that doctors have no idea what it means so they'll have no idea how to use Mylan and Biocon's treatment. The real Occam's razor answer here is that everyone knows in the field what "approximately" means and would have no

difficulty implementing this patent claim. In fact, the federal circuit, time after time, has clarified that words of approximation -- "about," "substantially," and what we have here, "approximately" -- are perfectly fine in patents in order to provide some breadth to the claim rather than numerical specificity. And they are not here, and they never have been indefinite.

With that, I thank Your Honor for patience. We look forward to presenting the case to Your Honor, and at the end we'll ask for a judgment that the patents-in-suit are both valid and infringed. Thank you very much.

THE COURT: Understood. Thank you, Counsel.

As a housekeeping question, how long do you anticipate opening statement to take?

MR. RAKOCZY: Probably an hour, Your Honor. Do you want to take a quick break?

THE COURT: Yes, let's take a quick break. That will give you all a chance to set up, and then we'll roll from there. We do have -- as I promised, we do have a proceeding that's set for noon. We can -- they can wait a few minutes, but I'll give everybody a heads-up at noon we do have a criminal hearing that we had to tend to. So I'll ask everybody to, as best you can, move some stuff back a row. That shouldn't take all that long, but this will all flow nicely. If we can do that, we'll take a lunch break at that point.

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So 15 minutes enough for you guys to switch?

Let's take 15; then we'll resume with defendants' opening statement.

(A recess was taken from 10:45 a.m. to 11:01 a.m.)

THE COURT: Counsel, are you ready to proceed?

MR. RAKOCZY: I am, Your Honor.

THE COURT: The floor is yours, then.

MR. RAKOCZY: William Rakoczy on behalf of Mylan and Biocon. I will briefly address the '865 formulation patent, after which I'll turn it over to my colleague Ms. Mazzochi to address the dosing patent.

I'd like to start by hitting the reset button, Your Honor. Suffice it to say you're going to hear quite a different perspective from me than what you just heard. In short, the evidence will show that the asserted claims of the '865 patent are not infringed and they are invalid. Before I preview that evidence, three quick introductory points.

Number one, in simplest form, the case on the '865 patent breaks down like this. The Court finds that the polysorbate 20 in the Yesafili accused formulation is not an organic cosolvent as construed by the Court and as we believe the evidence will show. There could be no infringement, and judgment should be entered for the defendants. But if that polysorbate 20 is, in fact, a cosolvent, despite what we

believe the evidence will show, then if it is, the claims are anticipated and obvious.

Beyond that, the Court will hear additional evidence demonstrating that the claims of the patent are invalid under another section of the patent statute, Section 112, including lack of enablement, written description, and indefiniteness.

Point two, I think we can step back and talk about what the '865 patent is not about. It is not about a groundbreaking new drug or use. Aflibercept and its use have been in the art for years. Aflibercept is the subject of a different patent not at this current trial, a patent that's about to expire. They've enjoyed their over 20-year monopoly on that aflibercept patent.

The '865 patent is not about that. It's about taking the old drug and putting it into an old prior art formulation. Tried and true blueprint using excipients known in the art, which I'll get to more in a moment.

Point three, I think we heard more accusations of copying, that somehow Yesafili is a copy of the '865 patent, or Eylea, in a word, nonsense. Regeneron's the me-too that copied the prior art blueprint for a stable protein formulation in the '865 patent. Yesafili practices that prior art blueprint as well. It's not a copy of Eylea or the '865 patent.

So let's start with the art of protein formulation to provide some context.

As Your Honor can see here on DDX 1, Slide 4, protein formulations go back many decades, to the late 1990s at least. And in this area, Genentech was the trail blazer. They had formulated a number of stable protein formulations, starting with Herceptin in 1998, up to the VEGF antagonist formulations, some of which you heard about -- Avastin in 2004, Lucentis in 2006.

And these all had one thing in common. They had used the blueprint -- a buffer, a surfactant, and a stabilizer that you can see here on Slide 4 highlighted in blue, yellow, and purple. Those were the tried-and-true known excipients in the art for making a stable protein formulation.

And one ingredient you're going to hear a whole lot more about is the surfactant polysorbate 20.

Here on Slide 5 I have a snapshot from the literature. This is the Randolph and Jones reference. This is one that Regeneron and its expert relies on. And as you can see, the Randolph reference teaches that surfactants are used as, quote, stabilizing agents, end quote, in protein formulations.

I'm going to pause and emphasize that terminology. Stabilizing agents. Not cosolvents, not solvents, not some other agent used to dissolve the drug, but stabilizing agents.

Randolph goes on to teach that Tween 20, which is another name for polysorbate 20, is often added to formulations

due to its ability to protect proteins from the surface-induced denaturation. That's the exact use of surfactant in these protein formulations, and it had been used for decades to do that as a stabilizing agent.

So let's talk about a couple of those prior art VEGF antagonist formulations. We can start with Genentech Avastin here on Slide 6. This is the VEGF antagonist bevacizumab, a powerful VEGF antagonist, just like the drug at issue here, and I might say an even larger molecule than aflibercept.

You heard some argument that somehow no one thought aflibercept would work because it was too big. This molecule is even bigger, and it worked. And the skilled person would know from this drug that if you used the blueprint from the art -- a buffer, a surfactant, and a stabilizer -- you would get a stable protein composition that could be used for intravitreal administration. Avastin, case in point, models approved for treating cancer in 2004; by 2006 this had been used in the eye by intravitreal administration.

The art didn't stop there, nor did Genentech. Here on Slide 7, you have Lucentis, another VEGF antagonist called ranibizumab. Your Honor will note the common blueprint from the art -- using a buffer, a surfactant, and a stabilizer to get a stable protein formulation for intravitreal administration.

So the art had evolved considerably before the '865

patent, and the blueprint was known and was simple. Use these tried-and-true components -- the buffer, a surfactant like polysorbate 20, and a stabilizer -- and the skilled person knew they could get a stable composition for intravitreal administration, just like the '865 patent purports to claim.

So knowing that, knowing that, Your Honor, what did Regeneron do when it formulated Eylea, the alleged commercial embodiment of the '865 patent? No surprise, they followed the prior art blueprint. Why wouldn't they? Why reinvent the wheel?

Here on Slide 9 we have a snapshot from the Eylea BLA. That's the biologic license application submitted to the FDA. The BLA is when you seek approval for the stated effective use of a drug in humans. BLAs are supposed to be truthful and accurate. They are checked over by many folks, and they are representations to the FDA to get approval. You have to tell them what the drug is, what the ingredients are, and what their functions are.

So two take-aways from the Eylea BLA, you see here on Slide 9. Number one, Eylea uses that same prior art blueprint -- the buffer; surfactant, polysorbate 20; and a stabilizer. No question about it, following that prior art blueprint from Genentech and others.

Point two, I want to pause and focus, what did Regeneron tell the FDA regarding the function or the role of

polysorbate 20 in the formulation? They said, quote, stabilizing agent, end quote. Say it again, stabilizing agent. They didn't say cosolvent. They didn't say solvent. They didn't say an agent used to dissolve the drug. Why? Because you don't need something else to dissolve the drug.

The solvent, as you can see, Your Honor, is water. Aflibercept is fully soluble in water. It doesn't need anything else to help dissolve it or increase its solubility. That's why Regeneron told the FDA polysorbate is a stabilizing agent, not a cosolvent.

That's perfectly consistent with the art and the literature, but it's a far cry from their litigation-inspired theory they're running with here where they want to rewrite not only history but the science and somehow call polysorbate 20 in a protein formulation a cosolvent. It's not, as the evidence will show.

So what did Mylan do when formulating the Yesafili, the accused formulation or product here? No surprises. Mylan is also practicing that prior art, that blueprint -- the buffer, the surfactant, and the stabilizer.

And here on Slide 11 we have a snapshot from the Mylan BLA. And again, you see the buffer; the surfactant, polysorbate 20; and the stabilizer. And what did Mylan represent to the FDA regarding the function and role of polysorbate 20?

We can see it right here in yellow in the red box. Just as Regeneron represented to the FDA, Mylan represented polysorbate 20 functions as a stabilizing agent. Again, stabilizing agent. Not a cosolvent. Not a solvent. And, again, it's not used to dissolve the drug or increase its solubility.

That's what the water is for. Water is the solvent. Aflibercept is fully soluble in water alone. Doesn't need anything else. Doesn't need a cosolvent. Polysorbate 20 is a stabilizing agent, just as the art identifies, just as the literature says, just as Regeneron represented to the FDA.

Nor did Mylan or Yesafili copy Eylea or the '865 patent. This is a very quick comparison table of the prior art VEGF antagonist, Avastin and Lucentis versus Yesafili and Eylea. Your Honor can see Yesafili follows the prior art blueprint, but it doesn't use the phosphate, the sucrose, or the sodium chloride from Eylea.

Yesafili practices the Lucentis prior art. We can see it right here, uses the same histidine buffer, the same polysorbate 20 surfactant, the same trehalose stabilizer. That's classic practicing the prior art.

If the '865 patent somehow covers Yesafili, then it also covers that prior art. It would be invalid.

That illustrates what's going on here. Regeneron followed that prior art blueprint from Genentech and others,

then went out and filed their own patent on it, and they now want to prevent others from using those tried-and-true known excipients.

So let's get to the infringement position. Before we do, I think we need to recap the claim construction and the Markman again.

I want to repeat the construction, Your Honor. "'Organic cosolvent' means 'an organic substance added to the primary solvent to increase the solubility of the solute, here a VEGF antagonist.'"

Now, Regeneron paid lip service to that construction, but they left out some of the underlying rationales and context for it from the Court's opinion.

Simply put, quote, cosolvents are used to dissolve another substance, end quote. It's that simple. As the Court also observed, cosolvents work in conjunction with a primary solvent, quote, to better dissolve the drug substance, end quote.

The Court also noted that polysorbate's role is as a surfactant, which is not interchangeable with cosolvent.

So what does it mean to be a cosolvent to increase solubility? It's simple. It's something you're using to help dissolve the active ingredient or the drug substance.

Now, why are we here on these particular claims, then? Why these claims? Why not others? What is this patent

about and not about?

And the Court provided some context for that in its opinion as well, as we see here on Slide 16. This patent does have claims or embodiments to the so-called polysorbate embodiments. To those formulations, like Eylea, it used polysorbate 20 as a stabilizing agent. That would be unasserted Claim 51 and its dependents. As the Court noted, Claim 51 corresponds to embodiments like Example 3, which is the Eylea fingerprint.

But that's not -- that is not the claims asserted here. Regeneron instead, they can't use these because Yesafili doesn't use all the components here, doesn't use the phosphate buffer or the sucrose stabilizer. So they're trying to stretch other claims that were never designed to cover a polysorbate embodiment like that. They're using all the claims that depend on Claim 1, which require the organic cosolvent.

And as the Court noted in its opinion, Example 2 is an embodiment of Claim 1. That's a formulation using a cosolvent like polyethylene glycol or PEG. That's a far different animal than the polysorbate embodiment like Eylea or even Yesafili that uses polysorbate 20 as a surfactant and stabilizing agent.

So let's get to it, then. What is the noninfringement case? Just to recap, the asserted claims are 4, 7, 9, 11, and 14 to 17. They all depend in one fashion or

another on Claim 1. They all require an organic cosolvent.

We see here on DDX 1, Slide 20, our noninfringement case is simple and straightforward. Evidence will show that there's no organic cosolvent in Yesafili. None. The only solvent we can see in this formulation is water. And there's no dispute that aflibercept is fully soluble in water. It doesn't need anything to help dissolve it.

The evidence will show polysorbate 20 is not a cosolvent. It doesn't increase the solubility of the active ingredient, doesn't work in conjunction with water or anything else to dissolve the active ingredient. Not at all. And the arguments you just heard from Regeneron are unfounded.

You heard Regeneron talk about -- I have it right here on Slide 32 -- somehow the most important document in the case, some data they cite from the Mylan BLA, some so-called DLS testing. What they didn't mention, Your Honor, is that testing was not on the Yesafili formulation. They rely on testing on a formulation that is not Yesafili.

They also left out that other data in the BLA shows and undermines their aggregation theory, that the Yesafili formulation, even without polysorbate 20, isn't subject to aggregation.

So when the evidence is in, Your Honor, it will show that their arguments are unfounded and they make no sense. They're premised on this circular idea somehow that

polysorbate 20 is increasing the solubility of something that is already in solution and soluble in water. They will not be able to carry their burden of proving that there is an organic cosolvent in Yesafili.

Now, this issue, the Court will hear from our expert, Dr. Gregory MacMichael. He's an expert in biopharmaceutical formulation and development, over 38 years of experience. Your Honor may recall Dr. MacMichael from the claim construction proceedings. His declaration evidence was unrebutted. He will testify consistent with those opinions and explain why polysorbate 20 is a non -- is a surfactant stabilizing agent, not a cosolvent.

So as I began, Your Honor, when the evidence is in, the Court should find Yesafili does not contain an organic cosolvent and, therefore, Yesafili cannot and does not infringe.

Now, as I began, if polysorbate 20 is a cosolvent, the evidence will show the claims are invalid as anticipated and obvious.

On anticipation, one quick note. It doesn't matter the prior art expressly discloses every element verbatim of the claims. That's not what anticipation is about. If the prior art discloses the elements expressly or inherently, as understood by a skilled artisan, not by laypersons or lawyers, as understood by the skilled person, then the claims are

anticipated, and that's what the evidence will show here.

The evidence will also show, if not anticipated, the claims are obvious. And I won't belabor this point, Your Honor. I'm not going to go through every single reference, every piece of art disclosing the supposed claimed embodiments or formulations, but I've got a timeline here, DDX 1, Slide 25. And it looks very busy and for good reason, because the art was very crowded. It was chock-full of stable protein formulations, starting with VEGF antagonists like Avastin and Lucentis that we see here and the Gaudreault, the Avery, and the Shams references.

And beyond that, there were actual references, like Fraser in Dix '226 that actually disclosed aflibercept, the molecule in question here, in a formulation using that prior art blueprint, the buffer, the surfactant, and stabilizer. The bottom line, as our expert Dr. Rabinow will explain, the skilled artisan knew from all this art exactly how to achieve a stable composition suitable for intravitreal administration, and that was using that buffer, surfactant, and stabilizer.

The evidence will show that the claims are anticipated by the Fraser or the Dix reference. And, again, these references disclose, expressly or inherently, all of the composition and the functional stability elements of the claims. But even if not anticipated, the evidence will show that the claims are obvious over Fraser or Dix, over other

references.

But let's not forget Lucentis. Lucentis kind of got short shrift in Regeneron's opening. This is the VEGF antagonist that Yesafili practices, a drug just like the one here, a formulation with all the elements of the claims -- the buffer, the surfactant, and stabilizer -- that the skilled artisan knew was stable, the skilled artisan knew could be used for intravitreal administration.

It's an understatement to say the skilled artisan would have been highly motivated to use aflibercept, with references like Fraser and others, in the Lucentis formulation. That's exactly what Yesafili and Mylan did practicing that prior art. That claims would also be obvious over the Lucentis art in combination with other references.

On these issues the Court will hear from our expert Dr. Barrett Rabinow. He's an expert in pharmaceutical formulation and development with over 25 years of experience. And, again, he will explain much better than I can how all of this art and more renders these claims anticipated and obvious.

Now, I also mentioned the other evidence will demonstrate the claims are invalid under Section 112, including for lack of enablement. I want to start there with nonenablement and focus on Slide 29 because recently the Supreme Court in the Amgen decision made absolutely clear if a patent claims an entire class of compositions, just like the

patent here, the specification has to enable the skilled person to make and use that entire class, all of the compositions, without exception. In other words, the specification must enable the full scope of the claims.

I'm not even sure I heard the word "full scope" from Regeneron's opening. That's the requirement. And the Court made clear that the more a party claims, the broader the monopoly it demands, the more it must enable.

The problem for Regeneron here is it claimed very broadly; it disclosed very, very narrowly. Now, this issue our expert Dr. MacMichael will testify these claims cover countless -- millions of formulations, but the specification provides very little guidance, very few working examples beyond a few.

He will testify this specification can't possibly enable the skilled person to practice countless numbers of formulations, millions of formulations, without undue experimentation. And this is a classic nonenablement case. As a matter of fact, in one of the last cases tried in this court before Judge Keeley, the AstraZeneca v. Mylan case, Judge Keeley found very similar claims invalid for lack of enablement precisely because the specification was far too thin to enable the skilled person to make all of the claimed compositions.

Now, that decision was vacated pursuant to a

settlement of all things --

THE COURT: I may have heard about that.

MR. RAKOCZY: But it's quite a decision. And it illustrates exactly how the Amgen decision and enablement works when you try to claim the world, when you try to claim all of the compositions, countless numbers, but your specification can't carry the water necessary to enable the full scope. And there is nothing inconsistent or contradictory about our obviousness and our nonenablement theories, nothing.

In a case like this, the specification discloses no more than the art, and, in fact, even less. The claims can't be both nonobviousness and enabled. If that art doesn't render the claims obvious and if the specification has no more than the art, then the specification can't possibly enable millions of other compositions. It's just not possible.

Another way to look at it is like this: To prove obviousness, we don't need to show that a single formulation in the prior art falls within the scope of the extraordinarily broad claims here covering countless formulations. That would render the claims obvious.

But those same claims would be equally invalid for lack of enablement precisely because of their extraordinary breadth because they claim countless formulations. So there's nothing inconsistent about these theories. The only inconsistency may come from Regeneron and its expert.

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On the one hand on obviousness, they may say there would be no reasonable expectation of success in achieving the claimed formulations based on the teachings of Shams. That's the Lucentis article that you saw he was practicing. Yet in the same breath on enablement, they may say that a skilled person could have used that exact same art to make a formulation with the histidine buffer which is not even mentioned in the patent. That makes no sense.

If Lucentis art can't render the claims obvious, then it certainly can't enable. And I apologize. My cocounsel here said I may have misspoken. What I meant to say -- if I didn't say it, Your Honor, I want to make it clear.

To prove obviousness, we only need to show a single formulation in the art is obvious and falls within the scope of the broad claims. But that broad claim, because of its breadth, would also be invalid for lack of enablement. So nothing inconsistent about our positions here.

The evidence will also show that the asserted claims lack written description. Written description is just like it sounds. The written description or the specification itself, the four corners of the patent, have to show that the inventors actually possessed and invented the full scope of all of the formulations claimed.

As Dr. MacMichael will testify here again, these claims are directed to a broad genus of formulations, countless

numbers. But the specification shows possession of only several very narrow formulations, a phosphate buffer and a sucrose stabilizer, if that. That is inadequate written description.

And on written description, Regeneron can't point to the art and try and fill in the holes in its specification using the prior art. It is based on the written description itself. And here it is very thin.

Lastly, on 112, Your Honor, the evidence will show that the asserted claims are indefinite precisely because of the use of purely subjective language like "suitable for intravitreal administration."

The federal circuit has cautioned on using subjective language like that. And as Dr. MacMichael will explain, the guidance here -- the specification here provides very little guidance on what components would and would not be suitable for intravitreal administration. And, again, I expect Regeneron to come and point to the prior art and say, well, the prior art teaches you all kinds of things about what's suitable and not suitable.

Again, they don't get to fill in the gaps in their specification with the prior art. And here the zone of uncertainty based on this specification renders these claims fatally indefinite.

Finally, Your Honor, I wasn't sure if I had to

mention this or not, but we heard more complaints and attempts by Regeneron to somehow disqualify the Dix art as prior art. It sounded a lot like rearguing the summary judgment motion that was denied. And we think that is better argued in posttrial briefing. So I'll be very brief; two quick points.

Number one, on this so-called 103(c) safe harbor theory, Regeneron continues to ignore the fact the entire theory is based on them being able to claim priority all the way back to this June 16th, 2006, application. There were ten intervening applications between that provisional and the issued '865 patent.

Regeneron is supposed to come forward with evidence showing written description with support in every single prior application all the way back to the provisional for every single limitation in its asserted claims in the '865 patent. They have not done that, and they cannot do that.

A simple comparison of the issued patent and the provisional shows that they added all kinds of new matter to the '865 patent, likely to try and provide that written description support which is missing from the prior applications. So they won't be able to carry their burden of production. They won't be able to show they're entitled to that June 2006 priority date.

Lastly, Your Honor, apparently they're not content with this argument, this 103(c) argument; so now they're also

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saying, well, forget about the June 2006 date. We actually invented this well prior to that. We submit they won't be able to show that either. They won't have the evidence to show that they invented anything covered by the claimed patent.

So, with that, Your Honor, I will end as I began. When the evidence is in, the Court should enter judgment of noninfringement and invalidity for the defendants on the '865 patent. And, with that, with Your Honor's permission, I'll turn it over to my colleague Ms. Mazzochi to address the dosing patents.

THE COURT: Understood. Thank you, Counsel.

MS. MAZZOCHI: Thank you very much.

Good morning, Your Honor. Pleasure to see you again. Deanne Mazzochi for Mylan and Biocon to discuss the '601 and '572 dosing patents.

Now, with Regeneron, the invalidity concessions -- and they were concessions -- we're down to four claims. For the '601 patent, Claims 11 and 19, which are boxed here in red. But because we are going to be looking at the claims as a whole, we also have the underlying independent claims, Claims 10 and 18, respectively, that are incorporated into Claims 11 and 19.

Now, before we go on, you heard Mr. Berl talking about the extended fixed dose and how this was a big part of the invention. Let's be clear about what these claims are

actually requiring on their face. 2 milligrams approximately every four weeks for the first five injections followed by, in Claim 18, 2 milligrams approximately once every eight weeks or two months. Ask them, as they try to start pushing this new theory on some type of super extended eight-week dosing regimen, where that actually appears in their claims.

Now, when we get to the '572 patent, you're also going to hear about two claims boxed in red, Numbers 6 and 25. Here again, some of the invalidity defenses are tied to the underlying independent claim and some of them are actually within the asserted claim.

So for Claim 6, isotonic solution, for -- dependent Claim 25, four secondary doses, has to tie back to the single initial dose that's part of Claim 15 so that we get the five loading doses all together.

So with that framing the claims, let's now go first with what the evidence will show when it comes to anticipation and obviousness.

Our expert Dr. Thomas Albini is going to put a lot of this science together for you. He is an expert from the renowned Bascom Palmer Eye Institute with the University of Miami which is rated the best in the nation for ophthalmology. He has incredible experience in the design and use of dosing regimens, how to treat patients, how clinical trials work, and what those of ordinary skill in the art knew and understood,

particularly in the relevant time periods here.

Now, if we start with the '572 patent, again, Regeneron has accepted summary judgment of invalidity of a bunch of claims. That's because what these claims discovered undisputedly is not new. A method of treating an angiogenic eye disorder in a patient is not new. The drug aflibercept is not new. Administering by intravitreal injection was not new. A 2-milligram dose was not new. A dosing regimen with three loading doses followed by eight-week dose intervals, also not new. And then the last part of the claim is not going to confer patentability under the Court's claim construction.

So after we've looked at the drug, the dose, and the schedule, what actually becomes left in Claim 6? Just this, the aflibercept formulated as an isotonic solution. That's all that Regeneron has pointed to.

Now, when it comes to Claim 25 of the '572 patent, Regeneron points to the method of using this single initial dose followed by secondary doses, which Claim 25 specifies it for, for a total of five doses before starting eight-week dosing. And that's the identical issue that we see for the '601 patent, Claim 11, and then for another disease state called diabetic retinopathy that we see in Claim 19. Again, all they're focusing on is the existence of five loading doses in the regimen.

So as we go forward, let's talk first about Claim 6,

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the doses formulated as an isotonic solution. Then we'll talk about the loading doses. You'll hear from Dr. Albini as well as our formulation expert Dr. Rabinow to explain how and why the prior art taught that an isotonic solution was not new and also obvious. And they are going to defend that position in testimony, notwithstanding Regeneron's doing what it's done a lot through this case in trying to cherry-pick some things and give incomplete quotes to try to say they said something that they didn't.

When we get to invalidity, you're also going to hear that one of our main prior art references continues to be the Dixon publication. Now, Regeneron is taking the position in this case that Dixon does not, quote/unquote, disclose any isotonic solutions, usually because it doesn't use the word "isotonic" itself.

Of course, the evidence will show that they will never find the word "isotonic" itself appearing in the Yesafili labeling that they say infringes. So as we go through trial, we want to be clear -- and I think the Court will make sure Regeneron is clear -- that when they and its experts are talking about the term "disclose," are they using it to mean is a particular word actually written there verbatim or are they looking at disclosure in terms of what a person of ordinary skill in the art would understand?

Because what the federal circuit has stated is that,

when it comes to what's actually in the reference, it's not just what is expressly said; it's also what is inherent within the reference.

Inherency means that we're going to look at how things can be known or understood from the perspective of that person of ordinary skill in the art. And the way in which I would like to think about it, Your Honor, is like this.

Let's say I were to write home today and say I used the elevator to get to Judge Kleeh's courtroom today. Now, Regeneron would say I only disclosed in that letter there's an elevator in the courthouse. In reality, from the perspective of someone like you, who is certainly the person of skill when it comes to this courthouse, you are going to know that there are features and properties and behavior that's inherently a part of this existing elevator. You know that it has buttons to three floors, it has a motor, cables, hopefully a maintenance schedule, a door that automatically opens, and that it travels to all three floors.

THE COURT: There are a lot of assumptions about our elevator in that statement, Counsel, but go right ahead.

MS. MAZZOCHI: But the person of ordinary skill in the art, Your Honor, knows that's what's going to be part of a working elevator in this courtroom.

THE COURT: "Working" being the operative term.

MS. MAZZOCHI: I am not relying on that for

inherency.

Now, when the prior art does, however, reference a real thing that exists, that person of ordinary skill in the art can use their knowledge and their skill sets to figure these inherent properties out. And that's really all that Dr. Albini and Dr. Rabinow have done here.

They've looked at how a person of ordinary skill in the art would see Dixon. They applied the skill and knowledge from their respective fields. And they can assess things like what's in the composition, what's in the dose, and then follow -- also follow what are some of the steps involved in the dosing regimen and how these Phase III clinical trials even work before the FDA. So with that framing, with that background, let's now apply it to the Dixon reference.

The evidence will show here that Dixon did describe an isotonic solution inherently, as required by the '572 patent's Claim 6, and has happened through two independent and, yes, inherent disclosures. Now, here's the first one.

The description in Dixon of the VIEW 1 clinical trials. Now, we agree that it expressly describes that there's a VIEW 1 Phase III clinical trial going on. A 2-milligram dose was being given to patients for three monthly dosing intervals then followed by an eight-week dosing interval after that. What does a person of ordinary skill in the art know is happening, just like we know there's buttons in the elevator,

they know that there's a dose there that actually exists and which is being given to patients while the trial is underway.

So we just need to look up what were the inherent properties of that 2-milligram formulation dose that actually existed and was actually used in the VIEW 1 clinical trials.

The evidence will show that it was the Eylea formulation. So all of the features and properties of Eylea that were inherent in the Eylea formulation is also inherent in this disclosure of the prior one VIEW 1 uses of the 2-milligram dose in the existing regimen.

And since Regeneron does not dispute that Eylea was isotonic, that's why we will meet our burden on inherent anticipation.

But that is not the only description of aflibercept doses in Dixon. Dixon tells us another thing, which is our second inherent disclosure. Dixon expressly taught that VEGF Trap-Eye, aflibercept, was formulated with buffers to be suitable for the comfortable, nonirritating direct injection into the eye.

The evidence will show that a person of ordinary skill in the art understands that this description is using signal words like "buffered to be comfortable" and "nonirritating," which is part of the whole goal of an isotonic formulation.

Now, Mr. Berl accused Dr. Rabinow of abandoning his

positions. He didn't. And, again, the context of the deposition will make that clear. But let's also make clear that Regeneron's own experts for anticipation purposes never disputed that this aspect of the inherent disclosure in Dixon was actually going to be inherent disclosure of isotonicity. So that's why, when it comes to the isotonic formulation that we see in Claim 6, it's inherently anticipated and not new.

However, Your Honor, let's assume in Regeneron's favor that the person of ordinary skill in the art does want to know more about these buffered ophthalmic formulations that are suitable for the comfortable, nonirritating direct injection into the eye. What are they going to want to make?

The evidence will show -- and this is the thing that formulators like Dr. Rabinow knows -- that it would have been obvious for the person of ordinary skill in the art to prepare an isotonic formulation. And how do we know that? Because it's basically textbook, Your Honor.

Remington Science and the Practice of Pharmacy is the go-to resource when it comes to drug formulations. The evidence will show that Remington's has been described as the formulary which is known to all pharmaceutical chemists. Dr. Rabinow will explain that the Remington's textbook does have a whole chapter authored by Gerald Hecht, PhD, senior director of pharmaceutical sciences, who explains the fundamental basis of what is in these ophthalmic formulations.

And, again, Mr. Berl citing deposition testimony asking Dr. Rabinow about a formulation for the cornea in the context of irrigation of surgical wounds is not going to somehow change the fact of what a person of ordinary skill in the art would learn from the context of Dixon or also learn from Hecht.

Dr. Rabinow is going to also explain that the term "isotonic" is right there in the Hecht chapter when talking about Remington's. He says that there are things --

You can go to the next slide.

-- that things -- formulators are required to consider, and one of them is tonicity. When you look at the buffer system, that also must be considered with tonicity and comfort in mind. And Hecht didn't just say this as a casual mention. And when it came time to pick what type of tonicity he wanted to talk about, he said ophthalmic solutions are formulated to be sterile, isotonic -- not hypertonic, not hypotonic -- and buffered for stability and comfort.

Again, that's exactly how Dixon described their aflibercept formulation. Buffers. It was going to comfortable and nonirritating to the eye. So an isotonic formulation would be the conventional and known thing to do. And it also wasn't just a known choice. The evidence will clearly and convincingly show that, given a choice, isotonicity is always desirable in the context of injections like this. And it thus

would be reasonable to use, make, and expect success as a consequence.

Thus, the evidence will show that, not only were isotonic formulations of aflibercept not new, they were also obvious, including for use in the claimed dosing regimens.

So with that, Your Honor, let's now turn to this issue of the five loading doses. And I'll put up Claim 11 here as one of our illustrative claims which again depends on Claim 10.

So when it comes to what the evidence is going to show here, Your Honor, the aspect of the claimed method, what Regeneron calls five loading doses, not three, for DME, that also was not new and also obvious. And Regeneron has been emphasizing these five loading doses in the DME regimen and that you see the number 3 and you don't see the number 5.

But, first, I think we should take a look at what it actually means in practice in the context of these types of dosing regimens when you're going to actually go from three loading doses based four weeks apart to five loading doses spaced four weeks apart.

It means -- and you can see this in the bottom regimen here with the red arrow. It means that there's one extra dose in there. You don't have to shift everything else down; you've still got an eight-week schedule at every single point from 16 weeks forward on this chart. You just have to

keep putting in one extra dose at the four-week mark.

So was this really anticipated? Was it obvious? The answer to that question, the evidence will show, is yes. And, for example, to illustrate this, we're going to take a look at a reference that the evidence will show specifically talks about diabetic macular edema, DME, which is one of the specific disease states called out in several of the claims.

This is a press release from Regeneron. And they specifically confirm that VEGF Trap-Eye, aflibercept, was being used in Phase II DME clinical trials. So here again, we have the use of the drug aflibercept; we have the specific indication, DME. So those two things, not new.

How about the dose and the schedule? Dr. Albini will explain that in this September 14th, 2009, press release we've also got the dose. And we actually have several schedules. So, again, dose is not new. And now let's talk about the schedule.

Now, here again, Regeneron says that only says three. We agree that there's a minimum of three loading doses that are required for the every-eight-week dosing regimen and for what's described as the 2 milligrams on an as-needed regimen. But this again is why you have to read these references, not just superficially, but as a person of ordinary skill in the art understands how they are applied in practice. And Dr. Albini is going to walk you through these schedules.

So on Slide Number 60 here's an illustration of what these dosing regimens look like. Now, in the yellow box, in the first one, the 2 milligrams, so 2q4, 2 milligrams being dosed every four weeks, that's effectively the monthly schedule.

The next one in the box, 2q8, has the specified three loading doses denoted by the black boxes. Then they skip a week -- I'm sorry. Then they skip a box, which is another four weeks later. And then they dose again at week 16. Then they skip another one at week 20. Then they go again at week 24. So black box, white box, black box, white box, that's how you're getting the eight-week dosing interval.

Now, what about the prn dosing schedule? So a person of ordinary skill in the art, again, is going to read what -- the dosing regimen that Regeneron was talking about in the press release. They're going to see that there were required three black boxes at the start. So 4 weeks, 12 weeks, et cetera -- I'm sorry -- baseline zero, then 4 weeks, then 8 weeks.

But when it comes to the gray boxes, again, the context of this press release, having a primary end point at the 24-week mark, the person of ordinary skill in the art knows they've got very limited options. They've got a limited number of dosing and a limited number of options in terms of how to fill the box. Now, those boxes are put there in gray because,

in a prn dosing regimen, the doctor does have some discretion to decide are you going to make it black? Are you going to make it white?

But that doctor is still going to necessarily know and envision that you've only got one of two options there. So, you know, if we look, for example, at the treatment needed, if we're looking at weeks 12, 16, and 20, it's going to be yes/no week 12, yes/no week 16, yes/no week 20.

So then when we actually apply -- once the doctor is then thinking what are these dosing regimens going to look like for my patient, well, for those gray boxes in the prn dosing they're going to know that if their patient needs dosing at weeks 12, 16, and 20, all the boxes are going to be filled in black. That's going to be effectively just like what you're seeing with the monthly dosing.

If the treatment is not needed at Week 12 but their patient does need it at Week 16, their patient doesn't need it at Week 20, does need it at Week 24, that's actually the same thing as what Regeneron has described as three loading doses plus eight weeks.

If the treatment is needed at Week 12, not at Week 16, then your patient slips so you need it again at Week 20, that is going to give you four loading doses plus an eight-week interval.

That leaves us with the next set of yes-or-no options

that a doctor is going to envision for their patients when it comes to Weeks 12, 16, and 20. And guess what it is. Week 12, yes; Week 16, yes; then your patient is good enough that you can skip a dose at Week 20; and then you go back to a dose at Week 24. That is going to be the five loading dose option. I've circled the five loading doses in red on Slide 63.

And then when you skip a dose because your patient actually got them to where you needed them to be, then you dose them again at Week 24; that's your eight-week dosing regimen.

So this is also, by the way, why we will fit the cases relating to disclosure of -- in the prior art of either a genus or a range, is that this is a very limited number of things to envision. The person of ordinary skill in the art understands how these dosing regimens work. They understand what the treatment choices are going to be at each of these approximately monthly intervals with regard to whether it's Week 12 or Week 16. And they're going to be able to carry out the dosing. And when they do, this is absolutely 100 percent going to be a dosing regimen, they will understand, is on the list in the context of this prn dosing for DME.

So that's why we say these two other dosing regimens, the one, for example, with four loading doses or this one with five, they may not be expressly disclosed, but the person of ordinary skill in the art understands that they are necessarily a type of regimen that can be envisioned because those are two

options for the gray box -- yes or no, black or white. And Dr. Albini will explain why this is readily easy for a person like him of ordinary skill in the art to envision. So the regimen, again, is not new.

But, again, let's talk about obviousness, and let's assume that Regeneron maybe is right, the person of ordinary skill in the art somehow just can't envision how to pick something in the range of three to six doses, they can't understand if those boxes should be black or white when they're outlining their treatment regimen.

The federal circuit has said the choice is still obvious. In Galderma v. Tolmar, 737 F.3d 731 at 738, Federal Circuit, 2013, the federal circuit explained that, if a range is disclosed and a claim falls within the range, then the patentee has the burden to produce evidence that there was teaching away, unexpected results, or some other kind of secondary consideration tied to this deviation or this particular species within the range.

This Galderma case is why you're going to hear from Regeneron their theory that somehow a person of ordinary skill in the art would be terrified to have five loading doses and instead would only want to limit themselves to three.

Frankly, Your Honor, we don't even think that that evidence is credible, especially, you know, their concerns that it's going to be dangerous to have more than three maybe having

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four or five. It's not credible when their own press release specifically said they were also running a monthly dosing regimen. A monthly dosing regimen for a -- for six months is going to give you six doses, which is greater than five.

So if there was really something that was going to actually inhibit someone of ordinary skill in the art from using five, the press release and the fact that this trial was actually running with six monthly doses would certainly put that to rest.

And, furthermore, as for the question of whether there is a trend towards fewer injections overall, what the evidence is going to show that doctors do want to treat their patients to get their retinas dried out. They try to actually get their patients' retinas dried out, get rid of the fluid on the eye, bring down that inflammation, then they'll move to the extended dosing period.

So when Mr. Berl was quoting Dr. Albini saying, hey, is there a trend to reduce the number of doses? Of course it is. But as a general rule, the way in which doctors like to think, particularly today, is they want to get the macula dry, they want to get the retina dried out, and then they're going to move to their extended dosing regimens.

So there was nothing new about this. This was a theory that was already known in the prior art about how to get the patient's macula dry. So to suggest that somehow there's

anything new or novel or nonobvious about what's being done here as opposed to just optimizing a treatment regimen for patients, the evidence is going to show that this was not new and it was also obvious.

Now, also, for secondary considerations, Dr. Albini is going to explain why there's no teaching away, why there were no unexpected results, why there's not other secondary considerations that show nonobviousness.

Much of Regeneron's secondary considerations evidence, for the reasons we stated in our motions in limine, is utterly irrelevant. A lot of the things that they've identified, well, somebody else didn't extend the regimen for Macugen or Lucentis, but number one, it's not actually accurate, but even so, the fact that there was already data and information about the VIEW 1-VIEW 2 clinical trials going on already indicated that dosing regimens that could be extended were underway.

Furthermore, it also doesn't matter to claims like Claim 10, Claim 11, Claim 19, Claim 25 because those are involving a different disease state than AMD.

The praise for the VIEW 1-VIEW 2 wet AMD clinical trials likewise has nothing to do with their claims that are limited to DME and diabetic retinopathy. Their claim that it was unexpected that a fixed extended dosing regimen worked is not supported by the evidence.

And they've also got a really interesting commercial success position here. Now, Mr. Berl, I believe, indicated that there were only two inventions that were driving success. I would argue that that concession is actually fatal because what he's basically saying is that there's two completely distinct and different patent families that he's trying to tie to the commercial success.

Well, the federal circuit has said you have to have a nexus that is actually tying what is in the claims to what you're claiming is the source of your success.

So the sheer fact that they're trying to split it amongst two families actually undermines the whole premise that they've demonstrated a nexus between the alleged success and the claims.

And the other big thing that they have forgotten about in our economics expert, Mr. Ivan Hofmann, who is a CPA and certified licensing professional who has looked at the family of patents that Regeneron has, he's also going to point out, by the way, you also have this patent to a little molecule called aflibercept, which has also kept all kinds of competition out of the market. So, yes, you've managed to get some success, but you've been able to do it because you're a monopoly with no competition.

When that aflibercept molecule patent is protecting their entire franchise, on the verge of expiring, which is one

of the reasons why we're here, that is also a problem for them in terms of establishing nexus because what they haven't been able to show is that what doctors really like about their product isn't the property's intrinsic to the molecule as opposed to something about the dosing regimen itself.

If I can, Your Honor, let me switch gears to another part of the patent statute, 35 U.S.C. Section 112. Now, you heard Mr. Berl earlier. I think he said that nonenablement depends on whether you're better off with or without the patent.

The evidence here is going to show that every single thing they complain about with the prior art -- too many options, no clear teaching in this direction versus that direction -- their own specification doesn't resolve most of those problems.

Now, Dr. Jay Stewart has looked at a lot of these issues. Dr. Stewart is the head of ophthalmology and a full professor at the University of California San Francisco Medical Center. He has gone through this specification in depth, and he's going to be able to explain to Your Honor, particularly from the perspective of the dosing and disease treatment issues, why the claims do not comply with Section 112.

In addition, we're going to have Dr. Rabinow talk about some of the formulation-related issues for Claim 6, isotonic.

Now, when it comes to the claims here, a claim like Claim 6 which claims a lot but enables very little, is exactly the type of claim where the inventor claims a lot, enables a little, and the public does not receive the benefit of the bargain.

But here's another part of Section 112 that the federal circuit has discussed. And the federal circuit has also discussed this question of written description. The federal circuit have also said, if you have a disclosure in your specification that's very broad with lots of choices, then you try to get claims that are very, very narrow. You can't say "Here's the forest, and now I claim the tree. Here's the haystack, and now I want to claim the needle." You've got to give blaze marks that are going to direct a person of ordinary skill in the art towards that particular tree, and it's got to be in your originally filed disclosure.

So here's how this is going to play out for Claim 6. Dr. Stewart will discuss the dosing issues, and Dr. MacMichael will discuss the formulation -- I'm sorry; this is Dr. Rabinow. Dr. MacMichael will be discussing the formulation issues.

So what does the specification do when it came to some of the -- what I'm calling -- broad terms, like angiogenic eye disorder and secondary doses?

Well, first of all, I think Mr. Berl brought up the sovereignty of the kingdom. Well, look at that first line

there when it comes to angiogenic eye disorder. They said can be used to treat any angiogenic eye disorder. That is trying to cover the kingdom, any angiogenic eye disorder.

But even for this list that they then follow, which I think has, like, over 18 different indications, even today doctors don't use aflibercept to treat those indications. They don't even use VEGF inhibitors to treat those indications because the drug class just doesn't work for those indications. So they claim broadly, but they cover things that don't work. That's classic nonenablement.

Similarly, while they like to put the little circle around the number four when it comes to the number of doses you're going to use in these regimens, look at what they actually said. When it comes to the number of doses at any particular phase of these regimens, two or more, e.g., two, three, four, five, six, seven, eight, or more. That's not a narrow disclosure. That's an incredibly broad disclosure. That's something too that they have not enabled.

And even with all of their patent examples, it doesn't provide the requisite support that would be needed so that the person of ordinary skill in the art can read the specification and be confident that it's actually going to work.

And, ultimately, Your Honor, what we see here in the specification, we are not seeing blaze marks towards four or

five loading doses. What we are seeing is a CYA memo, where they're trying to cover the universe until their hindsight data allow them to pick something later on.

Now, when if comes to the term "isotonic," there is nothing in this specification saying this was a key part of invention, that this was something that Dr. Yancopoulos invented, and then that's one of the things that Dr. MacMichael is going to be talking about as well.

Now, when it comes to the loading dose claims, here we're in the situation where they're trying to claim something very narrowly, but here again, as we saw, they disclose the forest. So Mr. Copland was very insistent that I pronounce the forest name. The Monogahela forest.

THE COURT: Close enough, Counsel. Close enough.

MS. MAZZOCHI: He told me if I got it wrong, you would catch it and I would be humiliated forever. But that being said --

THE COURT: It's a little harsh, but probably closer to accurate than inaccurate.

MS. MAZZOCHI: I'll make sure he schools me during the break.

But that being said, you know, they basically disclosed in their patent specification we want the entire forest; but then when it comes to those claims, they're saying, Well, what we really want is the ten-foot holly tree with a lot

of berries that's at the end of the trail that's over by the waterfall.

If you want to do that, you have to actually have some guidance in your patent specification that's going to help the person of ordinary skill in the art follow that path. And so if we take a look at the next slide, what we see is what the federal circuit wants to see is some clear blaze marks down the middle, but what we actually have are a bunch of twisted paths going in all sorts of different directions. That's why these claims fail under the written description requirement.

Dr. Stewart will also be explaining why the term "approximately" is indefinite. And this is not a question of Regeneron being able to find some context where somebody actually knows how to use the term "approximately" to mean some type of variability.

Part of the problem is is that Regeneron isn't even using the term "approximately" consistently within its own claims. So that's part of what leads to the difficulty here when it comes to indefiniteness, is that their inconsistent internal use within their own claims is what's not apprising the public as to what's available to them.

Likewise, to the extent there's going to be a priority fight on this, Your Honor, I want to be clear and give you a heads-up. We are going to be challenging whether Regeneron has actually done the work that they needed to do

during fact discovery to actually put us on notice of what their claims and theory was going to be, let alone whether they actually have the evidence to back it up.

So when we're done, though, reviewing claims as a whole, the evidence is going to show these claims are not valid and they are, for a whole host of reasons, anticipation, Section 103 obviousness, as well as Section 112.

Now, let's finish up on explaining why Regeneron will not be able to meet its burden of proof on infringement. Mr. Copland told me I got two minutes left; so let me roll into it.

THE COURT: I don't know why Mr. Copland became in charge in this courtroom.

MS. MAZZOCHI: I think he's trying to make sure you are served and your interests are served, and that is what local counsel is supposed to do.

THE COURT: Understood, Counsel.

MS. MAZZOCHI: So Mylan concedes that Regeneron and Biocon do not directly infringe. They're say it's the doctors who infringe. But the problem is they're not going be able to meet their burden of proof to even show that they've got a requisite direct infringers here.

Now, Your Honor, they gave you the label, and that label has a very rigid schedule. But after five years of this rigid label being on the market, their so-called wanted

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extended fixed-dose regimen doesn't even make the list of what ophthalmologists who are surveyed say this is how they actually treat their patients when it comes to this drug class.

So we're not disputing that doctors really like Eylea. The problem is they're not actually using it the way in which the label instructs. And when we know that doctors aren't using it the way that the label instructs -- and Mr. Berl seems to actually admit that Dr. Albini thinks that we should be custom-tailoring these treatment regimens to the patients -- they're not going to be able to meet their burden of proof, they're not going to be able to prove that you should infer an intent that we want doctors to use the rigid schedule as opposed to what's actually happening in practice, and with that, Your Honor, they're not going to ultimately be able to meet our burden of proof of infringement.

And in terms of why we don't need to bring our expert, when that particular fact does not appear to be in dispute, I don't need an expert to tell you something duplicative about a fact that's not in dispute.

With that, Your Honor, that's why the evidence is going to show that Regeneron cannot meet their burden of proof, Mylan and Biocon will meet their burdens of proof. And we do very much thank the Court and your staff for your time and attention. We look forward to working together with you over the course of the next two weeks as the evidence comes in. And

we respectfully submit that, once the evidence is in, the Court can and will enter judgment for Mylan and Biocon on all claims and defense.

Thank you, Your Honor.

THE COURT: Thank you, Counsel.

All right. We'll take -- from your-all's perspective we'll take an hour for lunch. If I could ask trial counsel, we do have to take up one hearing here in a few moments. It won't take all that long. If you wouldn't mind, as best you can, sort of moving your stuff back a row for us, that would be tremendously helpful. Then we'll resume with the first witness at 1:05 or so.

We'll take a break. We'll see you all at 1:05 or so. Like I said, our 12:05 shouldn't take all that long; so we should be ready for you then. Thank you.

(A recess was taken from 12:05 p.m. to 1:14 p.m.)

THE COURT: At least a few moments behind schedule. With that, plaintiff may call their first witness.

MR. COPLAND: Your Honor, one housekeeping matter. The Court usually wanted demonstratives filed with the Court. If that is the operative rule, then Mylan and Biocon request that the public filing of demonstratives be redacted so they can file a full under seal and redacted in public.

THE COURT: Any objection to that, Counsel?

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MS. OBERWETTER: No, Your Honor.

THE COURT: Thank you, everyone. Without objection, so ordered.

Also, any objection to the Court ordering filed the bench memo on sealing that portion of opening statements?

MR. COPLAND: They've already been filed, Your Honor, by Mr. O'Brien.

THE COURT: I withdraw my question, then.

MS. OBERWETTER: Your Honor, the parties have had discussion about moving into evidence as a whole exhibits used during the course of direct. If that meets with your approval --

THE COURT: It does, absolutely.

MS. OBERWETTER: Thank you, Your Honor.

In that case, Regeneron calls its first witness, Dr. George Yancopoulos.

GEORGE YANCOPOULOS, PLAINTIFF'S WITNESS, SWORN

THE COURT: If I could trouble you to adjust that mic so everyone can hear you clear. Don't worry; you can't break it.

Counsel.

MS. OBERWETTER: Thank you, Your Honor. We're just making sure the witness has a binder. Thank you.

DIRECT EXAMINATION

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BY MS. OBERWETTER:

Q. Good afternoon, Dr. Yancopoulos.

A. Good afternoon.

Q. As you know, my name is Ellen Oberwetter. I'm here on behalf of Regeneron.

Could you please introduce yourself to the Court.

A. My name is George Yancopoulos. I'm cofounder, cochairman, president, and I guess most relevant and important, chief scientist at Regeneron.

Q. And in your role as chief scientist at Regeneron, what have been your general responsibilities in that role?

A. To oversee all aspects of research and development at Regeneron.

Q. Okay. And can you describe briefly what kind of company is Regeneron.

A. Yeah. We like to think that we're a very different kind of company. I know everybody says it, but we do have a lot of things that I think can objectively attest to that.

We're the only major biotech/biopharmaceutical company that was started and still run by physician scientists. We think that keeps our focus uniquely on the science, and that is our goal, to use science to change the practice of medicine. As you know, most companies are headed by commercial or business people.

We had started over the years with this focus on

science, and for many years we were viewed as a failure. My partner, Leonard Schleifer, likes to say we became a success after 20 years of failure, an overnight success after 20 years of failure. What we were actually doing during those 20 or 25 years was really building the technologies, the break-through technologies that allowed us to then become very successful as a company.

So in the first 20 to 25 years we were not profitable. It's amazing that we actually survived, but we used those technologies eventually to start developing and creating and inventing new medicines. And over the last ten years or so, many have recognized us as one of the most successful biotech or biopharmaceutical companies in the world.

We've invented out of our own laboratories ten important new medicines, and it is worth putting that into perspective. You may or may not know there's over 5,000 biotech and biopharmaceutical companies in America alone, and there's only 20 to 40 new drugs approved every year, and most of those are actually me-toos. They're not really new, innovative medicines.

So as you might think, 5,000 companies, 24 years -- it's rare that one company even invents one new medicine, but over the last ten years or so, we've invented ten new medicines and most of them really break-through new medicines.

And so that makes us a real outlier in the industry.

Even the biggest companies, what they do is they -- they don't generally invent their own medicines; they license them from one of these rare companies that has come up with something. So that puts us in a really unique position, and we've been recognized for that.

So, for example, many times over the last ten years we've been on Forbes list of the 10 most innovative companies in the world, often the only biotech or biopharmaceutical company on the list.

So we like to think we're a very special kind of company, one of the most innovative biotechnology companies on the planet. And we have our focus on R&D, as reflected by the fact that over the last ten years, we've had one of the highest percentage of our revenue spent in research and development trying to come up with new medicines. So in addition to the ten FDA-approved or -authorized medicines, we have over 60 medicines that are in the clinical stage of testing right now.

Q. Thank you. And we'll, obviously, talk more about one of those in particular today as we go through this.

First, just briefly, where is Regeneron based?

A. Regeneron is located in Tarrytown, about a half hour north of New York City.

Q. And how many U.S. employees does Regeneron have?

A. We now have about 10,000.

Q. And how many did it have when you started the

company?

A. There was just a couple of us when we started, and we built up slowly. And as I said, for the first 10 and 20 years, we were struggling. And we slowly built up. It's only been in the last five to ten years that we've really ramped up to the levels that we're at now.

Q. And, Dr. Yancopoulos, are you the named inventor on any patents?

A. Yes, I am.

Q. Approximately how many U.S. patents are you the named inventor on?

A. Over 150.

Q. Okay. And you understand that this trial includes two of your patents; is that right?

A. Yes, I do.

Q. I'm going to hand you a copy of two documents --

MS. OBERWETTER: If I may approach the witness, Your Honor.

THE COURT: You may.

BY MS. OBERWETTER:

Q. -- which we've marked as demonstratives PDX 1-1 and PDX 1-2.

A. Do I take them out of these folders?

Q. Yes, if you would, please, sir.

And you can just take those one at a time, but what

do you recognize --

A. This chair is --

THE COURT: We've already talked about our elevator, Doctor. Add the chair to the list.

Go right ahead.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, can you identify those two documents that I just put in front of you, please.

A. Yeah. These are two patents about the use of a VEGF antagonist to treat angiogenic eye disorders.

Q. And do you see that one of those is the '601 patent and one of those is the '572 patent?

A. Yes, I do.

Q. Okay. And you should have a binder in front of you, sir, with the direct examination exhibits. If you take a look at PTX 0001 and PTX 0003, and if you could let us know if those are copies of those same two patents that you just looked at in official form.

A. PTX 001 and PTX 003.

Q. That's correct.

A. Yeah.

Q. Okay. Thank you. You can put those aside, and we'll come back to the patents.

I'd like to talk briefly about your work and your background. First of all, if you could describe briefly for

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us, what are some of the scientific awards and recognitions that you have received for your work at Regeneron?

A. Well, I've been recognized as one of the top scientists in the world based on what they call citation index, how often other scientists refer to your work. I was among the top ten in the world at various points.

In large part based on that, I was elected to the National Academy of Sciences, which is an organization that has the top scientists in the country and in the world.

I was elected to the Biotech Hall of Fame. I was selected by Ernst & Young as entrepreneur of the year. And --

Q. Did you receive any recognition for your work in connection with the pandemic?

A. Yeah. I was recognized by Forbes magazine as one of the heroes of the pandemic.

Q. And we'll touch on that, but if you could also tell us, approximately how many publications are you an author on?

A. Over 500 or about 10 a year over my long career in science.

Q. And if you could just tell us briefly how you first got interested in science.

A. Yeah. Well, I was born into an immigrant family. My parents were refugees from northern Greece, which had suffered through both World War II but then subsequently a war against the Russian-supported communists.

So my parents never got -- never finished their education. But they had the -- I don't know how they did it, but they had the courage to just come on a ship to America. And they believed very much in America, and they believed that education was the route to success in this country. So they pushed their kids into education and education.

And what they wanted, like many immigrant families, they wanted me to become either what they called a real doctor or a lawyer. Since English was not my first language, and I'm still struggle a little bit -- you guys might be able to tell -- I was not going to become a lawyer, but I was always very good at math, and I was always one of those kids who was playing with gadgets, making electric motors, ham radios, and so forth when I was a kid. So I was always interested in the sciences.

And when I was in -- I was going to the New York City public school system. When I was in what they call junior high school, 7th and 8th grade, the teachers there -- I remember Mr. Shackle and Mr. Michaels said, "Hey, you know, in New York City, there's a public high school for science called the Bronx High School of Science," and that "You should consider taking the test and seeing if you can get in."

So I did that, and I got into the Bronx High School of Science. It literally changed my life because I met a whole bunch of other science nerds and geeks just like myself, and it

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really sort of opened my eyes into what could be done. But the other really special thing about the school was that the heroes -- or the students who were really looked up to in the school were the kids who won what they called the Science Talent Search.

It was sponsored by a company called Westinghouse at the time. And it was like the American Idol for science geeks. And as I said, the school would have, occasionally, winners in this competition. They would encourage everybody to enter. And the winners were looked at as stars and heroes. So that became a goal of mine. And I had to come up with a science project to work on so that I could eventually enter into the Westinghouse Science Talent Search.

And, tragically, at around that time my grandmother -- in immigrant families, you're often raised largely by your grandmother -- she had early onset Alzheimer's and was dying, clearly. And so I decided I was going to -- for my high school science project I was going to cure Alzheimer's disease. And I worked on a project initially called regenerating neurons to try to help her.

And though I did not save my grandmother, my project -- I ended up being a winner of the Westinghouse Science Talent Search. Getting that recognition and that award just made me believe that I could become a scientist. And that was really the start of my commitment and devotion to try and

become a scientist.

Q. Okay. And after your experience at Bronx School of Science, where did you go next for your education?

A. I went to Columbia College in New York City, because, these immigrant families, we want to stay close. Never really left that area because all of my family is in that area.

Q. And what was your experience at Columbia?

A. It was a great experience. I continued to try to work on becoming a scientist.

Q. Did you graduate with any honors?

A. Yes, I did. I graduated as valedictorian of Columbia College. I was also a two-sport athlete, and I was selected as the top student athlete at Columbia for two years in a row.

Q. What did you do next after Columbia College for education?

A. Then, once again, stayed close to home. I went to Columbia for my MD and my PhD degrees.

Q. And why did you end up getting both an MD and a PhD?

A. Well, because, as I mentioned, my parents -- my father particularly wanted me to become a real doctor -- sorry -- I think of my dad; it gets me -- wanted me to become a real doctor. And so it was sort of a compromise or a negotiation that I could pursue my interest in science in getting a PhD, but I would get the MD so I could become a real doctor.

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Q. And when you worked on your PhD at Columbia, what was your area of study? And let me know if you need a break.

A. Yeah.

It was in the early days of cloning genes. I became an expert at cloning genes. I worked for one of the world leaders in that field at the time. And particularly we were using cloning genes to understand how the immune system worked and how genes came together to form the immune system.

Q. Okay. And did you end up with a lab at Columbia?

A. Yes, I did. I was given a faculty position.

Q. What ultimately caused you to leave Columbia?

A. Well, when I got my faculty position, I applied for grants. And I received a very large grant at the time. This was in, like, 1987 and -- or so. And it was for $2.5 million, which was a lot of money back then. It still is. And I thought I could finally make my father proud of me.

So I went up to Queens where they lived to share the news. And instead of being super proud of me, my dad was a little disappointed. And though he had no education, he was a pretty smart guy. And he was challenging me about why this was so great. And I said, well, I really think that I have the ability to make -- understand how a disease works. And I might be able to actually someday cure some disease, maybe even Alzheimer's. And he said, well -- he was a very big believer in America. I'm sorry. This whole thing is unusual and

emotional for me.

But he said in this greatest country in the world, if you really believe what you just said, that you can understand and cure a disease, you can get a lot more resources to do that instead of -- he considered getting -- you know, no matter how poor we were, he never took money from the government. So he said you don't have to be a beggar from the government getting grants. You can go to the private sector. You can raise a lot more money, get a lot more resources, and really live your dream.

Q. What happened after that conversation?

A. So remarkably, within a couple weeks of that conversation, I got a call from the man who is now my long-time partner at Regeneron, Len Schleifer. And he was trying to start a company. And it turns out that he had a son who was born with severe growth disorder in his brain. And his dream was actually to regrow his son's brain, but he didn't have the skills. And he thought that somebody like me bringing my skills from what I was doing in gene cloning, since I was one of the world's first gene cloners to clone genes for the brain, we could together regenerate neurons.

And we were both interested in regenerating neurons, me from my first science project, him now with his problems with his son. And our company was called Regeneron, which actually stands for regenerating neurons.

Q. And when did you form Regeneron with Dr. Schleifer?

A. In the late '80s.

Q. Dr. Yancopoulos, do you want to take a second?

A. No. That's okay.

Sorry. This is ridiculous.

Q. All right. Families are emotional.

Dr. Yancopoulos, what was Regeneron's focus in the early days?

A. Our focus was on regenerating neurons. We actually did clone some of the world's first nerve growth factors with the goal of using nerve growth factors to grow neurons in the brain. We were young and inexperienced and didn't know a lot about how things like clinical trials worked and so forth.

And I guess this is a rule in the industry, this is why there's 5,000 companies and less than 20 to 40 approvals every year. Most things fail. The estimates vary between 95 to 99 percent of things that enter clinical trials. And that was the case for our whole first series of work and clinical trials that were all in the neurodegenerative field. We were working on Lou Gehrig's disease and Parkinson's and Alzheimer's disease. And all of our trials over our first 10 to 15 years failed.

Q. Okay. Are some of those diseases you just listed things that Regeneron is still working on?

A. Yeah. They are some of the things that we are still

most intensively working on. My dream is, you know, before I'm done, to make a difference for Alzheimer's disease still. And so we're still working incredibly hard on these neurodegenerative diseases.

Q. And a couple of other questions. Can you describe, at Regeneron today, what are some of the drug development projects that Regeneron has underway?

A. Well, as I said, we spend a lot, from the outside world's perspective without that much to show for it, in neurodegenerative diseases, including Alzheimer's, Lou Gehrig's disease, Parkinson's, and Huntington's, though I hope, just like we came out of nowhere in other settings, we'll do so here as well. But we also have major efforts and approved drugs for various forms of cancer, lymphoma, myeloma. We have efforts in asthmatic disease, emphysema, allergic diseases, and also in infectious diseases.

Q. We touched briefly on the heroes of the pandemic award. What was Regeneron's contribution during the pandemic?

A. Well, as I said, we had spent our first 20 years without outward success in terms of getting drugs approved and so forth. But we invented some of the world's leading technologies for developing drugs known as biologicals, which is what we're experts in. And we realized -- well, actually, we realized it first during the Ebola breakout in the Congo a few years earlier, that we could apply our technologies. And

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we came up with the world's first treatment for Ebola.

And then when the COVID pandemic broke out, we realized we could take advantage of these same breakthrough technologies. And we came up with the first monoclonal antibody cocktail treatment for COVID. We supplied millions of doses to the U.S. government. And it saved many, many lives, including one of the first people who was actually treated was the president at the time. In fact, the effort was done under the auspices of Operation Warp Speed, which had been supported by that prior administration.

Q. As you know, Dr. Yancopoulos, the drug at issue in this case today is Eylea. So we're going to turn to talking about that part of Regeneron's history in particular.

What is the name of the active molecule in Eylea?

A. Well, the scientific name is VEGF Trap. And then when you work with the FDA, they assign a technical name or a generic name, which is aflibercept. And then the brand name is Eylea. So there's three names -- I know it's complicated -- VEGF Trap-Eye, aflibercept, or Eylea.

Q. And if we use aflibercept mostly for today's purposes, that will work fine for you?

A. Sure.

Q. How would you describe what aflibercept is?

A. Well, the way the cells inside your body communicate is they literally throw signals to each other. And then one

cell throws it; the other cell catches it using what is known as a receptor or a -- it could be viewed -- it sort of looks schematically like an antenna. It receives the signal that's thrown by the other cell.

And VEGF is a signal that's thrown by one kind of cell to act on what are known as -- VEGF stands for vascular growth factor blood vessels. So it's received by blood vessels, receptors on blood vessels, the antenna on blood vessels. And the cells respond by growing. And in certain environments like the back of the eye and so forth, the last thing you want is to start growing new blood vessels. All hell breaks loose. And the retina is supposed to be this totally pristine -- like a photographic film, you don't want blood vessels growing and leaking and bleeding all over that. Otherwise, you can lose vision.

So I had the idea to essentially make a new kind of blocker. We cut off these receptors that are normally found only on the blood vessel cells. And we made a form that literally floats around. And so the VEGF signal, before it can actually find the receptor on the blood vessel cells, there's these -- called soluble decoy receptors floating around.

They can literally intercept the VEGF before it hits the cell. And that's how it blocks the signal. So basically it's a soluble decoy version of the normal receptor found on the cell surface. We give it so that it floats around, and it

intercepts the VEGF before it gets to the blood vessel cell.

Q. Okay. And at this point let's actually take a look at a document to talk about some of this.

If we can please pull up PTX 3333.

And you should have a copy of that there in your binder in front of you as well.

So we've put this PowerPoint up on the screen, Dr. Yancopoulos. Can you please describe what this document is that we're looking at.

A. Yeah. This is a PowerPoint presentation that I personally prepared back on February 16th, 2007. We had invented Eylea under two prior partnerships, one in the mid-1990s with Procter & Gamble. They lost faith in the molecule, and they actually did a commercial assessment. And they said that it would never be an important drug, that the total worldwide sales for it would be less than $100 million a year. So they gave it back to us. We were a small company. We couldn't afford to develop it on our own.

We developed a second partnership with a company that was known then as Aventis. It's now Sanofi. They came to the same conclusion. They also gave it back to us. This is why we think it's important to put physician scientists in charge of companies instead of these people making commercial and business-type decisions because we believed in the science here.

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So finally we found a third company Bayer. So BSP stands for Bayer Schering Pharmaceuticals, now known as Bayer. And they had agreed to become our third partner for the VEGF Trap. And they would help us fund the clinical trials because we were a small company at the time and we needed help funding these things.

And when we finally got together this -- we were going to have a kickoff meeting where I was going to describe to my new Bayer collaborators and colleagues the basic science behind the VEGF Trap, or aflibercept, and how I thought that there might be some ways to turn it into an important drug. And by this time -- by this time Lucentis had just been approved. And so there were concerns about that.

We had gone from being on our own to now being behind here and -- but in the presentation I talked about how there was still room to maybe come up with a way to show that maybe we could even be better than Lucentis, which was truly a miracle drug.

Q. And we will come to that, Dr. Yancopoulos.

I'd like to look first if we could look at page 16 of PTX 3333. There is a slide here that's got a title at the top "Regeneron's Traps." And then there's a diagram on the left-hand side of the page.

Can you please explain the diagram and what that's -- that was meant to illustrate.

A. So this thing on the left is a schematic diagram of the so-called VEGF Trap. Okay? And what you can see here in red, that oblong thing, that is VEGF. It's sort of pictured sort of like a football. Okay?

The green and the purple here are one side of what you can think of as a VEGF receptor. And the green and the purple on the other side are another VEGF receptor.

And so the magic of what we came up with was a way to essentially hold onto the football on both sides. I used to use the analogy of holding onto the football with two hands. You know, every coach tells you, when you start playing football, not to run around holding to the football with just one hand but hold it with two.

Well, that's what the VEGF Trap does. And this is why it's such a potent blocker. It binds so tightly that the argument could be made that we had invented the most powerful potent blocker of VEGF ever described.

Q. Okay. And once you arrived at the VEGF Trap or aflibercept molecule, how did you realize that aflibercept might have some promise?

A. So when we first started testing it in what we call in vitro, in a dish or in a test tube, it was, as described on the slide here, hundred- to a thousandfold more potent than anything else that had ever been described that could bind and block VEGF.

Q. Once you had a molecule that you thought had some promise, what else did you have to do to try to get it to market eventually for an ophthalmology indication?

A. Right. So as I said, this is a business of failure. Most things fail because there's so many steps involved and you need to get almost every one of them right in order to ultimately succeed.

And so, of course, you would have to start with the world's greatest blocker. But that's not enough. You have to be able to just manufacture it. That's a major process. Manufacturing can make enough for all the patients.

There's millions of patients that are being treated now with this drug. But you not only have to manufacture it, you have to purify it to a degree because any -- particularly if you're going to inject it in the eye, it has to be incredibly pure. And many drugs in this space have failed because they've caused what's called inflammation or other side effects leading to actual blindness. So the cure can be worse than the disease if you inject something that can almost immediately cause blindness. So you have to purify it.

And you can only put tiny amounts in the eye without disrupting the eye. So you have to concentrate it into a very, very small volume. As we all know, it's very hard sometimes to concentrate things. Like, if you put in, like, sugar in your coffee, you can only put so much before it starts falling out.

It's the same thing with proteins. If you put a lot of it into small amounts, it can clump and fall out, and that would cause bad reactions in the eye.

So it's called concentrating and formulation, coming up with a formulation that is suitable and allows for high enough concentration in the eye. That is a major challenge.

And then, of course, you have to come up with the right clinical trials, which is a whole art and science form. How you do inclusion, exclusion criteria, how you design the regimen and the dosing schedule and so forth that you're going to use.

So there's a myriad of steps, and history shows us by just looking at the failure rates in the industry, it's very, very hard to get it all right, starting from a great molecule, finishing with a great clinical trial that actually shows what you want to show.

In this case, it's even harder because there was already a competitor that was now ahead of us that was really good. So in order for it to really make a change in the practice of medicine, we had to actually show something not only that it worked but that it actually worked in some way better than what was already out there.

MS. MAZZOCHI: Your Honor, if I may, I understand that Dr. Yancopoulos has a very significant role at Regeneron and he has a quite intricate -- storied background. However,

Regeneron did not present Dr. Yancopoulos under Rule 26(2)(C) as someone who would be offering expert testimony in this case. And it seems like a lot of these answers are starting to get into more what I would consider to be the realm of expert testimony as opposed to what he did and who he talked to.

So I just want to be careful that we're actually focusing on the relevant facts here to the patents at issue as opposed to veering off into expert testimony because Dr. Yancopoulos is just here as a fact witness.

THE COURT: Understood. Overruled at this point.

Counsel.

MS. MAZZOCHI: Thank you.

MS. OBERWETTER: Thank you, Your Honor.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, how did you get to the decision that aflibercept would be administered through an intravitreal injection into the eye?

A. Well, it's much harder to consider treating directly into the eye. In fact, I was the first person to consider treating into the eye with growth factors back in the early 1990s. Those efforts actually failed, like all of our efforts did in the 1990s.

And so, in fact, people told us that people would never accept direct injections into the eye. So our first approach, probably five or ten years before I made this

particular slide, is we started by trying to inject the VEGF Trap or aflibercept under the skin -- it's called subcutaneously -- and hoped that it would float around and get to the eye and do its business.

In some ways you didn't need as important a focus. You still needed it but not as important a focus on the whole formulation and all of those aspects that are so special for the eye. It was a lot easier. And so our first formulation was more easy to get into the body subcutaneously.

In very early studies, the studies suggest that it worked that way. On the other hand, since it blocked VEGF, it also caused constriction of blood vessels through the whole body, which is not something that you want. Constricting blood vessels causes increase in blood pressure, or hypertension. And many of these people suffering from these diseases are older people that you wouldn't want to cause high blood pressure to and increase their risks of disease of strokes and heart attacks and so forth.

So then it took us a couple of years to pivot from our first studies that were subcutaneous administration to developing the formulation and moving on to eye administration.

Q. Okay. And I want to touch on the concept you mentioned earlier about developing a usable formulation of aflibercept. If we can take a look at page 36 of the same PowerPoint that we've been looking at.

There's a slide now up on the screen with a title that says in part "VEGF Mini-Trap." Can you please describe what was the Mini-Trap idea?

A. So schematize on the left is the original VEGF Trap. But then for a couple of reasons we thought about making a smaller version of it. So what you can see here is the part that I described, this is -- the colors are different; it's a little different. The left side is one receptor; the other side is the other receptors; and the middle is the VEGF, here shown as a double football. Okay?

This is the business end of the molecule. This is the part that is not really the business end of the molecule. It's required for sort of putting it together and manufacturing.

So we thought that we could maybe cut the molecule in half, literally, get rid of the nonbusiness end of the molecule and now have something that was about half the size that was just the business end of the molecule.

Why would we want to do it? The first, the parental VEGF Trap was bigger, and there were some theories and some signs, though we had evidence, actually even in this presentation that I put together, that suggested we didn't have a problem getting into the back of the eye, penetrating into the back of the eye; but there was a lot of people and there was a lot of signs and there were concerns.

And so this was a backup. In case this did make it to the back of the eye, we would make this as a backup that had a better chance of penetrating in back of the eye.

The other thing is, as I said, one challenge is getting enough protein into a tiny small volume that you could inject into the eyeball. The theory was, if you cut it in half, you could get twice as much of the business end in there into the same volume.

So we started working on this shortly after we invented the VEGF Trap. We're actually, unbelievably, still working on this. We have not yet gotten a successful formulation of it that has the advantages that I wanted but luckily -- shows how hard this business is -- but luckily, as we all know now it turned out, there was no problem with this penetrating and, due to our formulations efforts, we were able to concentrate this sufficiently.

So the parental molecule ended up penetrating, and it ended up getting formulated to a high enough concentration that it would work. So we spent a lot of time, and we're still working on this, but we haven't gotten a satisfactory formulation yet.

Q. If we look just very briefly at the next book, page 37 of this document, there's a box of text up at the top. And what does that refer to?

A. These are the two problems that I talked about. At

the top is there was concerns that the full length, the original VEGF Trap, couldn't penetrate deep enough into the retina to do its business and that a smaller molecule would penetrate deeper. And that was one of the two reasons that we developed the Mini-Trap or tried to develop the Mini-Trap.

Q. Thank you.

And we can take that slide down.

Approximately when did aflibercept enter into preclinical development?

A. Well, I don't know the year exactly, but it would have been under the Procter & Gamble collaboration in the mid-1990s.

Q. And after coming up with the aflibercept molecule itself, what was your role going forward in the development of Eylea?

A. Well, I continued to lead all of the science and clinical development efforts for the molecule.

Q. Did you have a role in the clinical development program?

A. Yes. So I headed both the research, the science, and the clinical development.

Q. And over the course of your work, did you educate yourself on angiogenic eye disorders while working on Eylea's development?

A. I certainly did. I immersed myself in the field. As

I said, I'd already been interested in the eye and was involved in clinical development of other programs that didn't work in the early '90s, and I continued to further immerse myself in the field during this whole experience.

Q. Okay. During the early clinical development of aflibercept, were there other anti-VEGF agents that were under development?

A. Yes. I'd already mentioned Lucentis, but the first one that was approved was Macugen. It was quite a game changer when it came out, but it was a rather poor VEGF blocker. So when, a few years later, Lucentis came along, it completely displaced Macugen, and Macugen sort of disappeared because the Lucentis was better. And then we were hoping to do to Lucentis what Lucentis did to Macugen.

Q. During the time period of the development program, was Regeneron paying attention to what was going on with those other drugs?

A. Yes. Certainly, we were constantly looking at everything that was coming out and was known about those programs.

Q. Okay. If we could, I want to go back to the PTX 3333 PowerPoint slides that we were looking at, and in particular if we pull up page 42.

There's a section of the PowerPoint that says "VEGF Trap-Eye in the clinic," and it has a reference there to

"Lucentis sets a high bar," and you should feel free to refer to this page and the following two pages.

But what was the purpose of referring to Lucentis here?

A. Yeah. So this was in my presentation to Bayer, and as I said, we acknowledged that Lucentis was a real game changer, really provided a lot more benefit to patients in terms of gaining and maintaining vision in these otherwise blinding eye diseases, but we thought, just like Lucentis was an improvement over Macugen, that there was reasons why maybe with a better molecule, with a better program, and so forth that perhaps we could even improve on the Lucentis.

Q. And if we pull up pages 43 and 44 of the PowerPoint deck, what were these two pages signifying?

A. Right. There was two ways to improve on Lucentis that I acknowledged in this presentation more than 15 years ago now. One was maybe we could be better than Lucentis in terms of, when you give Lucentis, you gain vision and then you maintain it. But in order to do that, you need to give Lucentis on a monthly level. We thought that maybe because our molecule was better, at least in the test tube, you might actually gain more vision -- so that is beating it on its visual acuity efficacy -- that it would be better.

The other way we could beat Lucentis, even though it was a, really, miracle drug that now, for people who would

otherwise go blind, it actually restored vision and maintained it, the problem was was all sorts of studies, that are referred to in the text below, show that once you deviated from the monthly interval -- you had to give Lucentis every month; otherwise the gains that you initially got would disappear.

And so since we thought we might have a better molecule that we formulated to a higher concentration and so forth, that we could design a clinical program that might be able to show that the treatment burden, getting monthly injections --

You have to understand these are all drugs for generally elderly patients. My own mother had macular degeneration. I would take her to the doctor all the time. This is a big burden on patients and their caregivers. You essentially have to take a whole day to bring them in, and this is a whole procedure and so forth.

So we thought that, if we could reduce the very significant onerous treatment burden of monthly treatments, that could provide a very, very important benefit to patients as well.

So we thought that Lucentis set a high bar, but the opportunities were we could either restore more vision or we could do exactly the same as Lucentis but perhaps, as it turns out, cut the number of treatments by half, which would really be game-changing for these patients and their caregivers and

the doctors and so forth.

Q. And we'll talk more about that in a moment.

On the left-hand page there's a couple bullets I want to touch on briefly. The first, if you could go down to the fourth bullet on that page, that bullet refers to "Genentech was limited to max dose of .5 milligrams because of inflammation arising from unoptimized early formulation."

Do you see that bullet?

A. Yes.

Q. What were you referring to there?

A. This is exactly what I was talking about before. It's very hard to cram in a lot of protein into a very small volume so it can safely be injected into the eye. And with Genentech, they couldn't come up with a formulation beyond this ability to put in .5 milligrams into a single suitable injection of the eye without causing damage and inflammation into the eye. And we thought -- well, we did have an incredible formulations group that was able to much more highly concentrate our drug. So in addition to the fact that we had a better drug, we could actually deliver more because we could more highly concentrate it in a form that we thought was safe.

Q. And if we just look briefly at the last bullet on that page, what is that last bullet, "We can deliver 4 milligrams," in reference to?

A. Already by that time we had done early studies to

show that we could highly concentrate it into a purity that, in early small studies, we could deliver up to 4 milligrams or eightfold more than Genentech was actually delivering.

We have to say, though, that when you're dealing with these things, we were a little nervous that in large studies, even though in very small studies it appeared safe, we were very worried about the formula gram dose that maybe it was too much; it might cause locally problems by trying to put in too much or, because some of it would leak out and could work on the rest of the body, it might show side effects in the rest of the body as well.

So even though we were able, and in early studies, to deliver 4 milligrams, we actually backed off at a certain point and only in the major studies delivered 2 milligrams because of this concern that maybe too much of a good thing might cause problems.

Q. Okay. And we can take that slide down.

What was the first eye disease for which Eylea was eventually approved?

A. What is known as the wet form -- because that's the form that's due to excess blood vessel growth and leak -- the wet form of age-related macular degeneration, or AMD, wet AMD.

Q. And very briefly, what are the -- what are some of the symptoms or consequences of wet AMD?

A. As I said before, blood vessels start growing and

leaking --

MS. MAZZOCHI: I'm sorry, Your Honor. Again, I'd like to object to some of this, and here's the reason why. I realize that this is the first day of trial, Your Honor, but we have the benefit of their expert reports and knowing some of the issues that they're trying to do. And I'd just like to reiterate again to the extent he's talking about his own personal knowledge or experience, but a lot of the questions and the answers that are being given are being framed very broadly on this is what other people know, this is what -- trying -- either counsel needs to represent that she's not going to try to argue this is reflective of the state of the art, persons of ordinary skill in the art, then go to town. Otherwise, I think it's really not appropriate because this is, again, bringing in new expert testimony that we had no notice of in through a back door.

THE COURT: Understood. The witness is not called as an expert. His testimony won't be treated or received by this Court as such, regardless of the witness' credentials or the rest.

So let's stay on target, Counsel.

MS. OBERWETTER: Yes, Your Honor.

THE COURT: To that extent, sustained, but also understanding a lot of this is background and context.

MS. OBERWETTER: Yes. Thank you, Your Honor.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, we were just talking about what are some of the consequences of wet AMD.

If you could please go ahead and finish your answer.

A. So when you disrupt the normal pristine anatomy of the back of the eye, it swells, it gets distorted by the blood vessels, and vision gets fuzzy, and in fact, you can go legally blind.

Q. Okay. And when it came to clinical development of Eylea, did you have goals for Eylea vis-a-vis Lucentis?

A. Yeah. As I said, that was on my presentation from 15 years ago. We wanted to try to do better than Lucentis. Lucentis was a real advance, a real miracle drug. We wanted to either get even better vision or we wanted to get to the same point and maintain it but with a less onerous treatment burden.

Q. I'd like to turn briefly to some of the approaches that you were familiar with in the 2006 to 2007 time period that other people were using.

If we can go back to your PowerPoint PTX 3333 and go back to page 42. And then if we can scroll forward a couple of pages to page 45.

There's a slide up on the screen that says "Lucentis Phase III MARINA and ANCHOR."

What were you conveying with this slide, Dr. Yancopoulos?

A. May we just blow up on this one because it's hard to see. Perfect.

So what this just shows is the results in a clinical trial with Lucentis. And on the vertical axis is number of letters gained or lost from the beginning of the trial. So the beginning, everybody at their baseline is at zero. And you see the horrific consequences of this disease. Basically, patients, over the course of months -- this is 12 months -- they're losing vision. They lose about 12 letters in 12 months, a letter a month. That's two to three lines on an eye chart. This is why many patients go legally blind just in one year.

The miracle of Lucentis was you give it and immediately you see a gain in vision. The patients are gaining, as you can see here, significant amount of vision, and then it's actually maintained.

But this is done using a monthly regimen.

Q. Okay. Let's advance to the next slide, page 46 of PTX 3333, and there's a reference at the top of this page to the PIER study.

Can you describe what you were trying to convey here?

A. Right. Well, this was the beginning. I believe that I was the first person to try to come up with understanding what is the interval at which Lucentis fails? That's what I want to know, because if we knew when Lucentis failed, we knew

what we had to beat with our VEGF Trap or with aflibercept.

And what I indicated here, I actually just took this figure from the label, but then I mocked it up and I put this box to make my point on the right side.

So what you can see in the red arrows that I added to the figure is every time you give an injection of Lucentis, you gain vision; but then in this so-called PIER study, because of the treatment burden, they switched to every-three-month injections instead of every-month injections. And what you can actually see very clearly on the figure is with monthly injections, they're gaining vision, and then they maintain it for a bit; but then as soon as they go to every-three-month injections, they start losing vision almost at the same rate as the untreated people.

What this clearly showed was that Lucentis fails as an every-three-month drug. It just can't sustain the initial vision gains you get with monthly treatment.

This was approved and made in the label that proved how important the treatment burden was, that the FDA would actually approve such a suboptimal treatment where patients gain but then lost their gains. But it's showed to me what the room for improvement was, that, for sure, they couldn't work every three months. In my mind, though this made it into the label, this was really a failed study.

Q. And let's go on to the next slide of this slide deck,

and this one says at the top -- this is page 47 of PTX 3333 -- on the top says "Lucentis DME Study."

What were you trying to convey here?

A. Once again I don't know if you would cut out just the bottom one here. But it's the same point. But now I had narrowed the point to where Lucentis failed at two months. I mean, it's very clear on this figure. And once again, I used these brackets of where I say 1M for one month, 1M for one month and two months and two months. And the red arrows that I drew in here show when you're giving the actual Lucentis injections. And when you give them once a month, the month after the first injection, you gain vision. You gain vision. But then as soon as you go to two months after that injection -- you see that first asterisk at two months? -- you actually go up, and then you lose vision. So it's not even -- and then you do it again. You give one injection, gain vision, and then you lose vision. You do it a third time, you gain vision, you lose vision.

So Lucentis couldn't even last two months. So I had found -- so I was convinced, in my own mind, that I had found the weakness. Lucentis was a great drug, but you had to give it every month. If you didn't give it every month, you were going to lose the gains that you were making.

And that, to me, identified where we could do better, and that's what set me on this path of devising a clinical

strategy that was built on giving our drug every two months. And if our drug could magically work every two months, it would halve the treatment burden and it would provide a major advance. Instead of decreasing this onerous treatment burden, it could cut it by half.

Q. And if we take this slide down, another question about this general time period, were people at this time also using an approach called pro re nata, or prn?

A. Yeah. I believe it's a Latin term that means "as needed."

Because of the treatment burden and bringing in patients every month was so onerous, what doctors were doing is they were literally waiting for patients to fail before they treated them. And at the time this was -- the so-called other experts in the field were all moving towards this. They thought this would be the way to get patients treated and decrease the treatment burden, by waiting for them to fail.

I thought -- I'm sorry. I thought it was just the dumbest thing that you could be doing. It would be like saying you got an infection, and you know what we're going to do? We're going to treat it with an antibiotic, and then you're going to get better. And then when you start getting worse again, then we're going to give you more antibiotic. And then you're going to get better -- and it was just a regimen that just seemed so clear to me that it would be destined to fail.

So I was a speaker at major ophthalmology meetings and so forth where I was considered an expert, where I was railing against this, where I thought that prn was just a way to cause systematic loss of vision across the entire nation. Millions of people were being subjected to this. And, subsequently, I was validated by later studies that came out, like CATT and HARBOR, that showed that indeed this was a formula for losing the benefits of Lucentis by deviating from the monthly regimen.

Q. Ultimately, were you able to achieve for Eylea a fixed extended dosing interval in wet AMD?

A. Yes. This was ultimately proven in the two large VIEW trials, Phase III trials.

Q. And you're referring to trials called VIEW 1 and VIEW 2?

A. Yes.

Q. And what was the regimen that you arrived at?

A. So we had this notion of doing intense dosing for a short while, and then could we maintain it with a less intense dosing regimen? And that's what we designed. And, you know, you had to -- in this world of clinical trials where so many things fail, you had to just get everything right. And what we settled on was three monthly doses, then followed by a switch to every-other-month dosing. That was one of the three arms in the trial.

We had three arms in the trial because -- in both trials because, of course, this was sort of a bet. It was based on my best guesses and thinking. And I was hoping it would work, but as I said, most of things that you do in clinical trials failed.

So we had two other arms where we were sticking to the monthly paradigm because, as a small company, just getting a me-too. So most drugs that people invent are me-toos. They don't really have big advantages. So just getting a me-too as a small drug -- as a small company at the time would have been a big advance. But we had this third arm which was a bit of a reach where, if it really worked -- and there was reason to think it would work but, obviously, no guarantees -- if it would work, it could really change the practice of medicine.

Q. And we have prepared a demonstrative to help walk through the arms of the VIEW trials.

If we could pull up PDX 3.001.

And, Dr. Yancopoulos, have you had an opportunity to review this in advance of today's testimony?

A. Yes, I have.

Q. And can you just put briefly in context with reference to this demonstrative exhibit what the arms of the VIEW trials were.

A. Right. So on the bottom is ranibizumab, which is the generic or technical name for Lucentis. And here, this arm,

it's given at its every monthly regimen, which was the gold standard at the time that had been shown in the ANCHOR and MARINA studies that you already showed which were the ones that showed the best way to get the best visual outcomes in patients and what was in the FDA label. So this is Lucentis monthly with a .5 milligram dose.

We used three doses. We wanted to try our high dose. But once again, we didn't do the 4 milligram because we were too worried that there might be some toxicity that we hadn't seen in early trials. Once you go into large trials, you see things that you don't see in smaller trials. So we stuck with two milligrams as the high dose, but we also kept a .5 milligram arm because we worried that these two might have some sort of toxicity that we hadn't been able to see in the small trials. So this arm was pretty much a me-too, just showing that it was just like Lucentis.

This was an arm where we used our higher dose monthly. So this the same dose as Lucentis monthly, a higher dose like Lucentis monthly. This one we hoped maybe would see better vision gains, but this was really the reach and the one that could really change everything, which it ultimately did, which is 2 milligrams. After three monthly loads, you then switch to every-eight-month dosing after that.

And if you could really do with this what Lucentis does with monthly dosing -- as I showed you already in the

earlier slides, Lucentis fails as soon as you go from monthly. If this could work, it could literally half the onerous treatment burden on patients.

Q. Okay.

THE COURT: Counsel, I don't mean to interrupt.

But I think you said, Doctor, every eight months. I think you meant every eight weeks.

THE WITNESS: Eight weeks. I'm sorry.

THE COURT: No, it's fine. I just wanted to make sure our record is clear.

THE WITNESS: So I should say it's either every two months or -- I asked you guys to put "every two months or every eight weeks" on there because I do get confused. But it's every eight weeks or every two months, yes.

THE COURT: Sorry, Counsel.

MS. OBERWETTER: Thanks very much, Your Honor.

THE COURT: Hey, you're welcome.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, I think we have the terminology from the left-hand down, but can you explain what the -- can you remind us what the q is for on the left-hand side?

A. Yeah. Once again, you know, Latin. I don't really know what it means but q means every. 0.5 refers to the dose; q means every four or first week. So 0.5 q4 means 0.5-milligram dose, q means every, four means four weeks, and

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then 2 milligrams every four weeks, 2 milligrams every eight weeks.

Q. Dr. Yancopoulos, who came up with the three loading dose every-eight-week regimen?

A. So I was the initiator and the driver of this strategy.

Q. And how did you arrive at the concept of doing a three loading dose eight-week fixed-dosing interval regimen?

A. It was based on what I showed you before, and it was exactly the rationale that I had developed over the preceding years, which I showed to Bayer at this kickoff meeting. I had come to the realization that Lucentis could not work every two months, which meant that if we could work every two months, it would change everything.

But I also knew and saw that I didn't want to endanger those early gains, and the early gains seemed to sort of maximize it around after the third monthly injection.

So I said let's give them these three injections. Let's get to the maximum point. And then if we could just maintain it with this regimen, we would really be changing the practice of medicine.

Q. Okay. Prior to the VIEW trials, had Regeneron ever tested the three loading dose 2q8 regimen?

A. No.

Q. Did Regeneron's inclusion of the 2q8 regimen in the

VIEW trials mean that you expected that it would work?

A. Well, we certainly hoped and dreamed that it would work, but the whole --

MS. MAZZOCHI: Sorry. Your Honor, here again, you know --

THE COURT: State the objection.

MS. MAZZOCHI: Yes. My objection is that, again, he's starting to get into this area -- the issue of expected results and unexpected results, which, again, he was not designated as an expert to talk about.

THE COURT: He is the inventor. It's his experience and belief. Overruled.

Repeat your question, please, Counsel.

MS. OBERWETTER: Yes, Your Honor.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, did Regeneron's inclusion of the 2q8 regimen in this trial mean that you expected it would work?

A. The reason we designed this trial exactly as is -- or I designed the trial exactly as is because I was afraid that it wouldn't work and I wanted to have these backups as I just explained.

So at worst, we were a small company. As I said, we had been losing money every year. We would have been -- at a minimum, we needed to have at least a me-too that could be like Lucentis. Okay? That was our minimal -- if we had gotten

that, we would have been happy with that.

But these were reaches over here. And the reason we have three arms is we didn't know, frankly, if any of them would work. The one that had the highest chance of working was the top one, and the bottom ones were real reaches.

Q. Okay. We can take that slide down.

I want to talk briefly about another aspect of the Phase III trials, which was the formulation that was used.

If we can pull up briefly PTX 0003 and take a look at Claim 6.

Dr. Yancopoulos, do you recognize this as Claim 6 from the '572 patent?

A. Yes.

Q. Okay. And if you look at the language in Claim 6 referring to formulated as an isotonic solution, why did your method of treatment include an isotonic formulation of aflibercept?

A. Well, so as I said, there's a million decisions that have to go into how you design your experiment. And as I said, unfortunately in this world of clinical trials, most experiments fail. So you have to try to get everything. You think of everything, and you hope and you try to get everything right. And you don't have all perfect data at that time.

But we had a formulations group. I was not an expert myself, and I was not the one who was doing the formulations.

But our formulations group said that they had developed this very concentrated but pure form of what is known as an isotonic solution.

Isotonic means it has the same tonicity, the same concentration of molecules, as the normal fluid in the eye. You want to have something as natural as possible because what we're deathly afraid of and what has killed many drugs in this field is a reaction because what you're injecting is not natural.

So isotonic, in our minds, was something that was giving us a formulation that might be as natural as possible, has the decreased risk of seeing adverse events, even in a small percentage of patients.

Remember, what you're looking for, if you have side effects in just a few percent of the people, which you will only see in large Phase III trials. So we want to increase our chances that we were going to get something without even relatively rare side effects that could kill the drug. So that's why we chose the isotonic solution for our regimen.

MS. MAZZOCHI: Your Honor, I'd like to make an objection for the record. We had asked Regeneron, both during discovery as well as in interrogatory responses, to identify any conception of the invention story that they were going to present at trial.

This is nowhere in those discovery responses. So if

I may, what I'd like to do is have an objection to this line of questioning. We'll brief it for you, and then you can decide whether you're going to strike it from the record or not.

THE COURT: Understood.

MS. MAZZOCHI: Thank you, Your Honor.

MS. OBERWETTER: For the record, Your Honor, obviously we disagree that our disclosures were inadequate, and we will brief it accordingly.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, were there other formulations of aflibercept available to you?

A. Yeah. The formulations group came up with dozens, if not hundreds, of distinct formulations.

Q. And who chose to use the isotonic solution of aflibercept in Regeneron's Phase III trial?

A. Well, like I said, it was in consultation with my team of experts. They're the ones who came up with it. But based on their recommendations, I was the one who made the decision.

Q. I'd like to talk a little bit more about Regeneron's earlier Phase II trial in wet AMD. We talked about the VIEW 1 and the VIEW 2 trials.

If we can pull up PDX-3.002.

Dr. Yancopoulos, have you had a chance to review this demonstrative in advance of today's testimony?

A. Yes, I have.

Q. And does this slide summarize aspects of the Phase II study that Regeneron conducted in wet AMD?

A. Yes, it does.

Q. That was also called the CLEAR-IT 2 trial?

A. Yes.

Q. Can you just briefly describe the arms of this trial from the earlier Phase II trial.

A. This goes from the lowest dose, 0.5 milligrams, the same dose as Lucentis, to this eight times more concentrated dose, the 4 milligrams. And then we tested it in a variety of ways. We gave it every month to see how it would do when given every month, and we also gave it just once and then repeated the dose again at Week 12. But we were mostly interested in what the results would be at this point. So monthly dosing versus a single dose.

Q. Did this trial have any arms that used three loading doses of aflibercept?

A. No.

Q. And did it have any arms that used fixed extended-interval dosing?

A. No. Obviously, you couldn't test that in the short early trial; so no.

Q. And what was the strategy instead tested here after 12 weeks?

A. Well, at the time, as I said, most of the experts in the field believed in this prn dosing. And in order to engage all the sites and all the investigators that we needed, we agreed that after they did this dosing, it would be followed by this so-called prn dosing, which I personally felt was going to be proven to be suboptimal.

Q. Did the Phase II data that came out of the CLEAR-IT 2 trial tell you what visual acuity gains you would then get from a Phase III trial?

A. No. The Phase II trials are early preliminary data that you try to use to design your definitive Phase III. It's preliminary data. It's data that you hope points you in the right direction, but you can't really count on those numbers and the information that you get there.

Q. Okay. We can take that slide down.

I'd like to take a look at a different document.

If we could please pull up DTX 212.

And if you need it, you probably have it either on your screen or in your binders, Dr. Yancopoulos. If you take a look at DTX 212, can you please describe what this email is that we're looking at.

A. It's an email from Neil Stahl to myself and others.

Q. Okay. And what is the date of this document?

A. It's January 2006.

Q. Who is Neil Stahl?

A. He is my long-time colleague for over 30 years and, really, my right-hand person for a lot of the work involving the VEGF Trap.

Q. The subject line of the email is "AMD expert meeting."

Do you see that?

A. Yes, I do.

Q. And what was that a reference to?

A. Well, as we already talked about, when you're involved in clinical programs, you try to engage and get the perspectives and opinions of key opinion leaders. So we were having a meeting coming up with the AMD outside experts.

Q. Dr. Stahl starts his email with a sentence that says, "These are some more explicit questions that I would like to understand better." And then if you go down a number of lines, one of them says, "They're thoughts on our Phase II trial and end point. Do they concur with our perspective that it is impossible to get meaningful VA data without doing a Phase III study?"

Do you see that?

A. Yes.

Q. What is the VA data there?

A. The visual acuity data.

Q. What is this sentence a reference to?

A. Well, it refers to the fact that, despite whatever

you do in these small Phase II studies, you really are not going to get your real answers until you do a Phase III. And we just wanted to make sure that our experts agree and were on board on that.

Of course, the most important experts that count on this issue is the FDA. And the FDA, of course, doesn't consider anything in terms of your end points and efficacy that you see in Phase II. That's why they demand not only one large Phase III but two large Phase III trials to make sure that you see it in very large numbers of patients and you repeat it and confirm it.

Q. And Dr. Stahl refers there to "our perspective."

Was that a perspective that you shared?

A. Yeah. Neil and I were sort of joined at the hip at the time.

Q. You referred to a need to have two Phase III trials sometimes by the FDA.

Why did you have two VIEW trials when you got to the Phase III program?

A. Right. Because that's what the FDA demands. They don't only need one large trial to get at what you think your effect is, but many times even one large trial could be misleading and so forth. So they require you to do two large Phase III trials to confirm what you think you're seeing.

Q. Okay. We can take that document down.

I'd like to look briefly at another document that's been marked as PTX 491, if we could pull that one up. And if we could zoom in at the top.

Dr. Yancopoulos, can you tell us what this document is?

A. This is a press release about -- from Regeneron and Bayer announcing "Encouraging 32-week follow-up results from the Phase II study of VEGF Trap-Eye in age-related macular degeneration."

Q. And there's -- the date on this is April of 2008, correct?

A. Yes.

Q. If we take a look at the second page of this document, there are some portions near the top of the second page I'd like to direct your attention to.

Do you see the line that says about that Phase III program in wet AMD?

A. Yes, I do.

Q. Okay. And in this press release did you make any predictions about what would happen in Regeneron's Phase III VIEW trials?

A. No. We're very careful about what we say in press releases. And as my quote actually says, it says these results, in this press release, resulted -- or further increase our confidence in the design of our Phase III clinical program.

So I wasn't speaking about the results that we would get, but I was confident that we had designed a very good Phase III study that would get at the truth, which is what we wanted to get at. We had designed the study that I thought could give us more information, tell us whether our drug worked, how well it worked, and whether it would work with the extended every-eight-week interval.

Q. Okay. If we take that document down, there's another document I'd like to look at briefly that we've marked -- has been marked as DTX 228. If we could pull that one up.

We touched earlier on some of the decision-making around the Phase III trials, but can you first identify for us what this email and attachment are.

A. This is an email from me to the leader of the clinical development program on VEGF Trap-Eye at Bayer, Darlene Jody.

Q. What is the date of this document?

A. April 4th, 2007.

Q. There's a line a couple down from where it says Darlene Jody called April 4th, 2007, that starts "Here at Regeneron we like a top-down approach."

Do you see that line?

A. Yes, I do.

Q. Could you please explain what you were conveying to Ms. Jody in that line.

A. Well, in the next line it talks about the fact that there was a lot of discord at the team level. So, basically, we had been arguing for weeks, if not months up to that point, about the design of the Phase III.

I knew in my mind what I wanted our Phase III design to be, and I had gotten consensus with the most important people, from my perspective, which were people like Neil Stahl, for example. And I found that this -- the way Bayer was working things, they were trying to get the teams to decide and come to some sort of unanimity at the lower levels and then sell it to senior management.

That's not how we do things at Regeneron. I was frustrated how long it was taking to get at what I thought was the clinical trial design that we thought was the right design. So I was just trying to stop the bickering and the arguing and the discord and just get down to it and get on to the study that I thought was the right study to do.

Q. Okay. There's a reference down at the bottom of this excerpt that says "VT 2.0 q8 week."

Do you see that?

A. Yes, I do.

Q. And what were you describing in that section of this document?

A. Well, it was one of the four arms. All three arms were the arms that we actually used in the two Phase III

trials, but that's the particular arm that ended up working and changing everything which was the 2q8, 2-milligram dose given eight weeks after the three initial loading doses.

Q. If we go up just to that middle sentence that's highlighted that "in this regard, after carefully reviewing the P2 data as well as all prior P1 data, which is also quite relevant," do you see that line?

A. Yes.

Q. What are those references to the P2 data and P1 data about?

A. The Phase II data, the Phase I data, but also the fact many other pieces of data, Bayer kept wanting to get what's that one piece of data that will justify exactly this design? And what I was trying to convey to them and communicate to them, that it's a gestalt. You have a million pieces of data that you try to put together, and the people who are successful in this business manage the design trials that work.

My first ten years, I didn't learn how to do that and I failed every time. But at a certain point I learned how to look at all of the data and put it together. And sometimes it's very hard to explain to other people what's that one piece of data. And I was trying to convey I looked at everything, and this, this is the design that all the data suggests that we could come up with, even though there's not one piece of data

that says we should do this.

Q. Okay. We can take this document down.

I'd like to touch briefly on the results of the VIEW 1 and VIEW 2 trials, if we could take a look at PTX 311. Just blow up the title and the authors.

Dr. Yancopoulos, what is this document that we're looking at?

A. This is a published manuscript that described the data from the two Phase III studies, VIEW 1 and VIEW 2, with VEGF Trap-Eye in wet age-related macular degeneration.

Q. Okay. And you were one of the authors on this publication?

A. Yes, I was.

Q. And who is Dr. Heier who is the first person who is listed there?

A. He's one of the principal investigators who was running our clinical trial.

Q. Did you participate in drafting this paper?

A. Yeah. I played a major role in designing the experiments and working with everybody else to carry them out and analyze the data and put together the manuscript.

Q. If we advance forward through this manuscript a little bit and go to page 8, there is a Figure 3. And then if we can look at -- we have a demonstrative that is the Exhibit B version of this page where we have added some color to make it

a little bit easier to read.

Dr. Yancopoulos, can you describe what the data shows here in this Heier paper.

A. Right. These show the results of the VIEW 1 and the VIEW 2 studies as well as what they call the integrated data. What you can see is, even in these large Phase III studies, there is noise. That's why you can't tell anything from Phase I or Phase II. Even Phase III studies are very large. I point at the data here to see the noise.

Here the yellow line is above; the green line is the worst one. In this one the green line is the top; the yellow line is the worst. But when you just average these two studies together, they're all right on top of each other, which leads -- and, honestly, the journal and everybody else agreed to the correct conclusion that all these arms are essentially on top of each other. As you can see in integrated analysis, they're indistinguishable so that basically, what had we had shown? That all three of our experimental arms, including this dream arm of 2q8, actually worked as well as Lucentis given every month.

And this is why it was a huge advance, because whenever you deviated from the monthly regimen for Lucentis, you didn't achieve Lucentis monthly-like data. And we had now done it with the every-other-month-arm regimen.

Q. Okay. And just for the sake of clarity in the

record, can you explain with reference to those dots down at the bottom of the screen what these arms are again.

A. Right. So, basically, it's the forearms that were described in the previous study. The blue line is Lucentis monthly; the yellow line is 2 milligrams of aflibercept every four weeks or every month; the green line is the 0.5 milligram dose every month; and then the red line, this last line, is the 2-milligram arm after three loads given every eight weeks or every two months. So that red one is the key arm, which you can see is right on top of all the other lines.

Q. And we can take that document down.

Dr. Yancopoulos, what was the reaction within Regeneron when the VIEW results became available internally?

A. I guess you could describe it as elation.

Q. And why is that?

A. Well, we had not been viewed as a very successful company up until that point because we had had only one small drug approved for a very rare disease. We would probably never ever make our money back from the investment we had made in that small drug. We were losing money every year. And now we had something that looked like it had an advantage over one of the most important medicines in the world. And we thought that the data suggested that this is something that a lot of doctors might consider having advantages for their patients.

So we -- our goal was to change the practice of

medicine. We had done that for an orphan disease, but now we thought that maybe we had changed the practice of medicine for a major disease.

Q. Is the VIEW 2q8 trial regimen the one that eventually was approved by the FDA?

A. Yes. It's the one that was approved, and I think this is why we're in the courtroom today, because the world adopted it as the new gold standard of care.

MS. OBERWETTER: Okay. I'm going to turn to talking about diabetic macular edema and diabetic retinopathy, and I can -- I have a bit more, just for the Court's awareness.

THE COURT: Go right ahead.

BY MS. OBERWETTER:

Q. So changing topics a little bit, Dr. Yancopoulos, let's talk now about diabetic macular edema and diabetic retinopathy.

Just briefly, what are those conditions?

A. These are very related but different disease in which it's the diabetes and the bones of diabetes that results in upregulation of VEGF in the back of the eye and a different kind of blood vessel growth and abnormality, which also results in distortion of the retina, resulting in fuzzy vision and, ultimately, potentially blindness.

Q. Okay. And did you intend that the methods of treatment that you came up with for Eylea could be used for

angiogenic eye disorders other than AMD?

A. Yes.

Q. And before we get into the development work on DME and DR, let's take a look at the original provisional patent application, which we have marked as PTX 304.

Dr. Yancopoulos, we have the title page pulled up here. If you take a look at the title, "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders," do you recognize this document?

A. Yes.

Q. And what do you recognize this document to be?

A. It's a provisional application for a patent on the use of a VEGF antagonist to treat angiogenic eye disorders.

Q. And if we take a look at the second page of this document, what is the date of this provisional filing?

A. January 13th, 2011.

Q. And there's a name there. Who is Frank Cottingham?

A. Frank Cottingham. He's an in-house attorney working on patents at Regeneron.

Q. I'd like to advance through the document a little bit to paragraph 24, which is at PTX 3040009. There's a sentence here -- there's a couple sentences here that say "Nonlimiting examples of angiogenic eye disorders that are treatable using the methods of the present invention," and then there is a list there.

Do you see that?

A. Yes.

Q. And that list, if we can highlight in particular, included diabetic retinopathies and diabetic macular edema, correct?

A. Yes.

Q. Why did you disclose that your methods could be used to treat angiogenic eye disorders?

A. Because we believe that all these disorders shared a common mechanism, that is, VEGF driving abnormal blood vessel growth and leak. And since they all had the same mechanism and we had a VEGF blocker, we thought that we could perhaps treat all of these diseases.

Q. Okay. And let's take a look back at page 1 of the provisional application, and in particular we're looking at paragraph 2, and it says PTX 3040004. Under the section called "Background," it says, "Diabetic macular edema is another eye disorder with an angiogenic component."

Do you see that?

A. Yes.

Q. And then it goes on to say, "DME is the most prevalent cause of moderate vision loss in patients with diabetes and is a common complication of diabetic retinopathy," and then it continues.

Why did you call out diabetic macular edema and

diabetic retinopathy specifically?

A. Because these were two diseases that the science said were likely driven by too much VEGF.

Q. Okay. And let's take a look at page 7 of the document, which is also paragraph 18. And there's a discussion here of secondary and/or tertiary doses of the VEGF antagonist. And in particular I'm going to direct your attention to a sentence that says, "In other embodiments, two or more (e.g., two, three, four, five, six, seven, eight, or more) secondary doses are administered to the patient."

Did you envision a method of treatment that would use four secondary doses?

A. We listed it here; so yes.

Q. And we can take that document down.

When Regeneron began its Phase II clinical trial for DME, were there any other FDA-approved anti-VEGF treatments for DME?

A. No.

Q. And what were physicians primarily using at that point in time?

A. What's known as laser, where you use laser to literally kill parts of the retina to try to save the remaining parts of the retina.

Q. Okay. Why were separate clinical trials then eventually needed for diabetic macular edema instead of just

relying on the wet AMD trials?

A. Because it's a different disease with a shared mechanism. It's sort of like treating two different types of cancers. You can get an approval for your drug that might work in lung cancer, but you might need a whole different regimen, a whole different treatment regimen to treat breast cancer.

So just like two cancers might have the same basic mechanism, can be treated by the same thing, you need different studies for both of them.

Q. Okay. I'd like to take a look at a document that's been marked as PTX 3216 -- if we can pull that up -- which has both an email and an attachment.

And, Dr. Yancopoulos, can you please tell us what these email -- what this email and what this attachment are.

A. This is an email from Peter Powchik, one of our leaders in our clinical group, to myself and our CEO, Len Schleifer.

Q. There's a PowerPoint -- first of all, the date of this document is August 15, 2007.

Do you see that?

A. Yes.

Q. And there's an attachment called "DME Expert Impressions Meeting," correct?

A. Yes.

Q. And were there sometimes slide decks sent around of

the meetings that were conducted with outside key opinion leaders and the like?

A. Yes.

Q. Let's take a look at page -- the page that is marked as 0005. The header at the top says "Impressions."

If we can pull out that middle couple of bullets on this page, both of those.

There's a reference here to "Detailed discussion of direct-to-Phase III plan not held."

Do you see that?

A. Yes.

Q. And some additional verbiage between that.

What was being conveyed about the DME program in this section of this slide?

A. Well, there was some discussion that could we use exactly the same treatment regimen for DME that we had used for AMD? And basically everybody agreed that you couldn't necessarily.

Q. Okay. And there's a reference in that second bullet to possible safety concerns in diabetic population not seen in AMD patients.

What is that a reference to?

A. Yeah. In some ways diabetic patients, they suffer higher risks of heart attacks, strokes, problems like that. And the concern was there was a possible link even at that time

between VEGF inhibitors and increasing the risks of heart attacks and strokes and so forth.

And so the concern was too much dosing or too high a dose might have a different kind of side effects, might cause more problems either systemically, in terms of heart attacks and strokes, or even maybe locally in the eye so that you couldn't predict not only the efficacy but you also couldn't predict the safety profile and whether the same regimen would behave the same way for either safety or efficacy in DME patients compared to AMD patients.

Q. I'd like to talk briefly about the Phase II study that Regeneron conducted for DME.

And if we can pull up PDX 3.004.

Dr. Yancopoulos, is this another slide that you had an opportunity to review for today's testimony?

A. Yes.

Q. And can you please walk us through, briefly, the study arms that were used in the Phase II Da Vinci trial for DME.

A. Well, in some ways they look very similar to what we tried in AMD in that we had a monthly regimen for 2 milligrams, a monthly regimen for 0.5 milligrams; then we had a three loading doses followed by eight-week regimen for 2 milligrams; and then we had three lowering doses followed by prn. And we were comparing them to the fifth arm, which was the standard

laser control.

Q. Okay. In the Phase II trial for DME, did Regeneron even test a regimen that had five loading doses?

A. No.

Q. Okay. Were you aware of any other VEGF drugs under development at the time that were using five loading doses?

A. No.

Q. Okay. We can take that document down.

Do you recall approximately when the one-year data for the Phase II Da Vinci trial became available to Regeneron?

A. No.

Q. And we'll take a look at a couple of documents that may refresh your recollection.

Let's start first with a couple of documents in your binder that are grouped together as PTX 3187 and PTX 3188.

A. Yes.

Q. And can you please identify what these documents are.

A. This is a email about an agenda and a presentation for a Bayer-Regeneron joint steering committee meeting to discuss utilization of VEGF Trap-Eye, or aflibercept, in diabetic macular edema.

Q. And what is the date of the email here?

A. October 19, 2010.

MS. MAZZOCHI: Your Honor, I'd just like to renew our objection as well that this is also to the extent they're

trying to do this to establish a prior conception type date. This was also not disclosed in their discovery responses. We'd like to brief that as well.

THE COURT: Understood. Posttrial briefing and proposed findings and conclusions will be an outstanding avenue for those arguments to be made. Understood.

Counsel, you may proceed.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, what is that? The PowerPoint is titled "JDC Presentation for JSC October 21, 2010."

Can you explain just briefly, what is the JDC and the JSC?

A. The JDC, joint development committee, is a collection of the team members at lower levels who are directly working on things. And they prepare things for these meetings, and they prepare a lot of the -- they do a lot of the work.

And the joint steering committee are the senior-level meetings that the -- senior-level individuals that JDC team members report to.

Q. Okay. And were you on one of these committees?

A. Yes. I was on the joint steering committee.

Q. I'd like to advance through the document a little bit to page 3, and there's a page called "Health Authority Feedback" on PTX 3188.0003.

There's a part near the top of that page called

"Study Design," if we could please pull that out.

And there's a reference to "Study design proposed dosing arms 2 milligrams q4, 2 milligrams q8 after three loading doses," and then "Control: Acceptable."

Do you see that?

A. Yes.

Q. As of October 2010, what number of loading doses were being contemplated for the forthcoming Phase III trial?

A. Three loading doses.

Q. There's a sentence right under that one that starts with "final one-year data."

Do you see that one?

A. Yes.

Q. Can you please explain what that sentence is in reference to.

A. That we were still awaiting some more data, and that might provide additional guidance on number of loading doses.

The reason we were so concerned is the number of loading doses is critical because you want to gain vision and then maintain it when you shift to the every-two-month dosing because you don't think you're going to be gained during the two months. So if you're off by the number of loading doses, you may never get to the same level, the equivalent level, that, for example, monthly Lucentis gets to.

On the other hand, there's also enormous pushback

from a variety of people, including commercial. They want the least number of doses. So you're playing a very tight -- you're walking a tightrope here.

Q. Okay. We can take this document down.

Did you eventually review the data that came out -- the one-year data that came out from the Da Vinci trial?

A. Yes.

Q. And let's look at two documents together. These are PTX 80 and PTX 1028C.

MS. OBERWETTER: And, Your Honor, there's a third exhibit that goes with this that we have in hard copy, if I may approach the witness.

THE COURT: You may.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, if we go back to the email which we have up as PTX 80, there's two attachments to this document, correct?

A. Yes.

Q. Okay. And what was the date of this document?

A. December 8, 2010.

Q. All right. And you were one of the recipients of this, correct?

A. Yes.

Q. There's an email from Caroline Saxton.

What is she referring to there in her email?

A. She's referring to the data that we now have in front of us, which is the short presentation on the one-year data and then the complete data set in this bigger binder.

Q. And why don't we take -- we'll walk through some of this in order, and I assure everyone we're not going to get through every page of PTX 1170 which we've handed up to the witness.

But if we can start with PTX 1028C, what is this document that we're looking at?

A. This is a summary of the results from the one-year data from the Phase II trial in diabetic macular edema.

Q. And were these -- was this an internal presentation or an external presentation?

A. Internal presentation.

Q. And if we advance forward just to page 3 of this document briefly and pull out the upper left-hand.

This was marked, at least in part, with a confidential ledger, correct?

A. Right.

Q. Had Regeneron published the details of its one-year Phase II Da Vinci trial at this point in time?

A. No.

Q. And was it keeping that data confidential?

A. Yes.

Q. Did you have additional data above and beyond even

what was in this PowerPoint?

A. Yes.

Q. And if we just take a look for a moment at PTX 1170, what is PTX 1170 that I have handed you?

A. Well, it's the full data set from the trial that's summarized in this shorter PowerPoint.

Q. And at a high level, can you describe what kind of data is contained in PTX 1170?

A. Well, it gives detail efficacy and safety results on a group level as well as on a patient level.

Q. And did you have that data set available to you when you were deciding what to do for the DME Phase III trial?

A. Evidently, from the email, yes.

Q. Yes. Okay.

And let's take a look at the PowerPoint for a moment. If we can please take a look at page 11 of PTX 1028-C.

Can you please explain what kind of data is presented on this page.

A. Once again, this is visual acuity data, as we said. So on the vertical axis is gain or loss in vision. The white line is the current standard of care at the time because, remember, Lucentis hadn't been approved for this indication at the time; so it was laser. And you see laser; they gain a little vision, it goes up above the zero, and then by the end they've lost vision. And then the four other curves are the

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four arms, the experimental arms that are trying various dosing schedules of -- dosing schedules and doses of aflibercept.

Q. Okay. And this data that we're looking at on this page, if we zoom back out, this is, again, the Phase II Da Vinci data, correct?

A. Right.

Q. Were there aspects of this data set in the visual acuity data from Da Vinci that limited its utility to you?

A. Yeah. As one can see, this is why the experts, as we talked about before, in the other slides that we went through, agreed that you can't really count on Phase II data because the data sets are so small and why the FDA doesn't accept this sort of data.

If you just look up there, these top three curves, see the dark green one, the light blue one, and this purplish one. Okay. At least through 12 weeks, these groups are all treated the same. So in a perfect world or if you had, for example, hundreds or thousands of patients per arm, those three groups would have been right on top of each other. They literally should be identical.

And it just shows that you can't count on the results. These things are bouncy. They're bouncing around. They don't look like the Phase III data, and arms that should be identical can look -- as you can see the green from the other ones -- very different.

So even before you get the different treatments for these three curves started at the 12-week time point, but you can see by then they're already different.

So these are important directionally. We do these studies -- first of all what you can see is every single one of these arms definitely looks like it's better than laser. So it made us feel that, frankly, many of these regimens would be better than laser. But the question is which regimen might actually be better -- or which regimen might actually work with a lower treatment burden compared, for example, to monthly Lucentis and so forth.

These are things that are, frankly, almost impossible to tell from these small studies. So you incorporate -- as I was saying before, those of us who have managed to figure out how to get successful in the business, you incorporate millions of points of data, including things like this, including data that you're seeing there, and many other pieces of data to try to make your best judgments as to which regimens are you going to bet on in these Phase III trials.

Q. Okay. And was this data on this page of PTX 1028-C sufficient to decide on a five loading dose regimen?

A. No. It would be very hard for anybody to definitively come up with any definitive regimen based on this data based on the noise that you're just seeing right here.

Q. And how is it that you decided ultimately on a five

loading dose regimen for DME?

A. Well, like I said, it's a matter of integrating a million pieces of data. I mean, these are questions that sometimes are unanswerable. I mean, how did I come up with the idea to invent the VEGF Trap in the first place? It sort of just came to me, but I incorporated a million pieces of information that I had -- I had integrated over the years.

And the same thing here. I realized that we had to maximize the -- so the whole notion -- the basic notion, the basic thing that we described is you want intense dosing, and then you back off to go to the every-other-month dosing.

And how long you do the intense dosing, we reasoned, or I reasoned, should be different for diabetic macular edema based on, like I said, many points of data. There were many others who thought that VEGF signal was higher in DME than it might be in AMD. We had reason to think that in dosing, division continued to improve as you dosed with monthly treatment.

So there was a lot of things that went into it. It's impossible to point to one thing. But this is why some people are successful in this business, because they guess right more often than not.

Q. Okay. Thank you.

We can take that document down.

I want to turn to talking briefly about the results

of the Phase III VIVID and VISTA trials.

THE COURT: Counsel, before we transition topics, is that a good point to take a brief break or --

MS. OBERWETTER: We could, Your Honor. I have a little bit more; so yes.

THE COURT: Okay. Why don't we do that.

Doctor, we're going to take an afternoon break at this point. We're going to take 15, given the crowd numbers we have and our limited restroom facilities here in the building.

During this break, because you're midstream on your testimony, no one can talk with you. I don't want you to think anyone here is being rude or discourteous, but it's part of the rules that govern this proceeding. So you're a little bit of a man without a country, for lack of a better term, during the next 15 minutes. So if you see folks turn and scatter from you, that's why. It doesn't have anything to do with the PowerPoints we talked about earlier.

But you can go ahead and step down if you'd like, and you can leave all those materials there. We'll deal with those. Thank you very much, sir.

Otherwise we'll take 15 and resume at that point. Thank you all very much.

(A recess was taken from 3:04 p.m. to 3:19 p.m.)

THE COURT: Are you ready, Doctor?

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Counsel?

BY MS. OBERWETTER:

Q. All right. Dr. Yancopoulos, we were turning to the Phase III results for Regeneron's VIVID and VISTA trials. If we take a look at PTX 932. And can you please identify this document for us.

A. Yes. This is the published manuscript that describes the two Phase III trials for aflibercept in diabetic macular edema.

Q. And you are listed on this paper?

A. Yes, I am.

Q. Okay. If we take a look again -- if we go to the data page of this document, which is at page -- advancing forward to Figure 1A, which we've marked for convenience as PDX 932-C, could you please describe the results that Regeneron obtained from its Phase III VIVID and VISTA trials with reference to this figure.

A. So once again, the vertical axis, the Y axis, is vision gained or lost in letters. The red line is the standard of care at the time, which was laser, which is keeping the patients stable.

And what you can see here is that both of the aflibercept treatment arms do almost identically in terms of gaining and maintaining the vision. And once again, the key thing about this is that the 2q8 arm -- that is after five

loads, then going on to every-other-month dosing -- maintains the vision as well as monthly.

Once again, that was the big take-home message and the big advance here that allowed Eylea to become such an important drug for this disease.

Q. Okay. Going into these trials, the VIVID and VISTA trials, did you have an expectation as to the five loading dose eight-week arm would perform?

A. Did I have a what?

Q. An expectation.

A. I had hope, for sure. I mean, I was hoping that it would work. But that's, of course, why we had the two arms because we were, once again, taking the higher likelihood thing which would be monthly, and then we were hoping beyond hope that the every-other-month would behave as well as it did.

Q. Okay. After the completion of the VIVID and VISTA trials, did Regeneron ask the FDA to approve this regimen for patients?

A. Yes.

Q. And why?

A. Because, clearly, it was an advance over the standard of care at the time which was laser, but the results resulted in impressive safety and efficacy, and the regimen that the FDA approved was the every-other-month regimen.

Q. We can take that document down.

Was Regeneron also ultimately able to get an indication for diabetic retinopathy?

A. Yes, we were.

Q. And at a high level, how did that indication come about?

A. Well, we had some evidence from this trial, but the FDA felt that we hadn't prospectively identified all of our end points and so forth, and so it wanted us to confirm it; so we had to do a separate single Phase III trial.

Q. Okay. And that was the PANORAMA trial?

A. Yes.

Q. Have there been other significant -- I'm going to change topics a little bit.

Have there been other significant treatments for wet AMD that have come onto the market since Eylea?

A. Well, for those of us in the field, it almost seemed like back to back to back. I mean, there was the big advance of the Macugen, the first drug. Then that was rapidly displaced by Lucentis. And then Eylea came along and became the new gold standard of care. And it seemed like it was really easy.

In the following ten years, the field was littered with many, many failures, including our own. We had several studies, several attempts to improve on Eylea.

So as I said, Lucentis had set a high bar, which we

were able to meet and exceed. But after that, the Eylea set such a high bar that none of us, including for ten years our own efforts, were able to exceed it. Only in the last year there was an approval of another anti-VEGF agent, but it did not seem to really distinguish itself or exceed in any way Eylea. It was only as good more than ten years later.

And it just shows how hard this field is, how hard it is to get everything right from the drug to the formulation to the regimen and so forth, to get success, let alone success that exceeds what the bar is in the field right now.

And so the whole field failed for more than ten years, many, many, many failures, and the one recent success just matched Eylea, did not in any way surpass it.

Q. And in your view, what has accounted for Eylea being as successful as it has been for as long as it has been?

A. Well, the impressive safety and efficacy profile. It's very hard. Some of the drugs that I talked about failed because of safety problems. Some of them failed because of efficacy problems. So having the safety and efficacy and what is now acknowledged as the longer duration of action really made such a difference, and it became adopted as the standard of care.

MS. OBERWETTER: Thank you. No further questions.

And I pass the witness.

THE COURT: Thank you.

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Counsel.

MS. MAZZOCHI: Thank you, Your Honor. We have some binders for the Court and for the witness.

THE COURT: Everyone may approach.

Counsel, go right ahead.

CROSS-EXAMINATION

BY MS. MAZZOCHI:

Q. Do you have your binders, Dr. Yancopoulos?

A. One binder.

Q. Yeah, one binder.

Dr. Yancopoulos, you talked quite a bit about some of your patents in your direct examination.

Do you recall why you decided to file for these patents?

A. Why I decided to file for these two patents?

Q. Right.

A. Because they were demonstrating a new approach to treating angiogenic eye disorders that we thought could have value that we wanted to protect.

Q. I'd like you to take a look in your binder at an exhibit that is numbered DTX 3196. And these are going to be exhibit pages 7 and 8. And I'm going to pull some information from them up on the screen, specifically your deposition transcript pages 25, line 24, through deposition transcript page 26, line 2.

If we could just pull that up on the screen, please.

A. Could you repeat the numbers again, please.

Q. Yes. DTX 3196. I'll put these specific lines up on the page. They're on exhibit pages 7 and 8. If you see in the lower right-hand corner 001, 002. And actually we're going to take a look at line -- transcript page 25, line 24 and 25, over to page 26, line 1.

Do you recall giving a deposition in this case?

A. Yes.

Q. All right. Can you confirm that at that deposition I asked you the question, "Do you recall why you decided to file for these patents?" and you gave the answer, "I don't recall"?

A. I may have said that. I don't recall.

Q. Do you know how many of your patents over the years have been held invalid?

A. No, I do not.

Q. Do you know how many have been held unenforceable for inequitable conduct?

A. No, I do not.

Q. Are you aware -- do you know that at least one of your patents has been held invalid for inequitable conduct?

A. I guess 1 out of 150? I can understand that.

Q. You can understand that?

A. I can understand that. Sometimes something happens that something invalidates a patent. I don't know much about

the patent business. Sorry.

Q. Well, are you aware that one of the reasons why your patent was held unenforceable for inequitable conduct is because the court found that you made material misrepresentations regarding unexpected results to the PTO that were false?

A. I thought it was because we failed to cite what was considered one citation that was prior art. So we missed one citation. That was my understanding.

Q. Tell you what. Let me pull up for you.

MS. MAZZOCHI: Tom, this is in --

THE WITNESS: Are you trying to imply that I tried to misrepresent something in one of my patents?

THE COURT: Doctor, your role here is simply to answer questions.

Counsel, next question, please.

BY MS. MAZZOCHI:

Q. If it would be helpful to you, I can refresh your recollection on some of the details. If we can turn to page --

MS. OBERWETTER: Objection, Your Honor. I don't understand the relevance of this as it relates to any of the patents at issue in this case, and there has been a prehearing ruling on their motion to amend to add inequitable conduct.

THE COURT: Correct. But I assume this is aimed at the witness's credibility. Is that correct?

MS. MAZZOCHI: Correct.

THE COURT: Understood, but the exhibit that's displayed currently on the Court's screen is a case. I can barely read it. But we need to ask the witness about things he has personal knowledge about, including -- and that includes impeachment or credibility.

Objection overruled at this point.

BY MS. MAZZOCHI:

Q. And if we can -- we're going to page 1349.

A. Which document are we in?

Q. This is a court decision entitled "Regeneron Pharmaceuticals Inc."

A. What number? What am I looking for?

Q. We're going to put it up on the screen because I have to actually see if this is going to help refresh your recollection. Then if it does, we can talk more about it.

A. Okay. Couldn't I just turn to it? Could you just tell me which document it is?

THE COURT: It's not in the binder, Doctor.

THE WITNESS: It's not in the binder.

THE COURT: Use the screen there. Thank you.

Go ahead, Counsel.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, you indicated that you thought that all that was at issue was that you didn't cite a reference.

According to the court decision, one of the things it said Regeneron did was that "Regeneron sent -- also sent a presentation to the PTO with the reply. In that presentation, Regeneron asserted that it had developed a commercial embodiment of the claimed mouse with surprising results. It is undisputed that that assertion was false. Regeneron had not developed any such mouse at the time."

Does that help to refresh your recollection as to one of the reasons why one of your patents was held unenforceable for inequitable conduct?

A. You know, I am not involved in these sorts of patent disputes and I was not present. I didn't testify in that case. I know very little about it. And I somehow had thought that it had to do with citations. I don't know exactly what this is referring to.

Q. Okay. Well, Dr. Yancopoulos, given the fact that Regeneron had been -- had one of their patents, one that you were on, held invalid for inequitable conduct based on -- based on a false statement to the PTO, did you after that point make sure that your scientific representations and specifications were reviewed for scientific truth and accuracy?

MS. OBERWETTER: Objection, Your Honor. The question is lacking foundation in multiple respects at this point, both with respect to what the ultimate conclusion of the court was, the reasons for it, and this witness's lack of knowledge.

THE COURT: The witness indicated he's not familiar with this background, Counsel. I think if you want to ask about any changes in business practices, that's appropriate, but he's not expressed any personal knowledge about this at this point.

MS. MAZZOCHI: Right. And that was exactly what I believe I just asked, is that given --

THE COURT: I disagree. Objection sustained. Rephrase.

MS. MAZZOCHI: Okay.

BY MS. MAZZOCHI:

Q. Did you implement any business practices to ensure that the accuracy of all of the scientific representations that your patent applications were making were truthful and accurate?

A. I don't really know how to answer that question. I think that we always endeavor to do everything truthfully and correctly. And I'm sure on occasion some things get missed, no matter how good our due diligence.

So I don't know the details about this. I don't know how -- clearly, we did develop a commercial embodiment of the claimed mouse that was very successful. I don't know whether the timing is what was at issue. I don't know whether that was done deliberately or was somehow a mistake. But I'm sure that we have practices that try to ensure that things happen

correctly and truthfully all the time. Not to say that sometimes mistakes don't happen.

Q. Let's put up on the screen DTX 2745, exhibit page 1. A copy of this should be in your binder.

THE COURT: What number was that, Counsel?

MS. MAZZOCHI: 2745.

THE COURT: Understood. Thank you.

BY MS. MAZZOCHI:

Q. Can you confirm this is a publication by Jocelyn Holash, you, and others, titled "VEGF Trap: A VEGF Blocker with Potent Antitumor Effects," which I believe was published in the proceedings of the National Academy of Sciences in 2002?

A. Yes.

MS. MAZZOCHI: Your Honor, we'll move DTX 2745 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 2745 was admitted.)

MS. MAZZOCHI: Thank you, Your Honor.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, in DTX 2745, pages 1 to 2, I'd like to direct your attention to the "Materials and Methods" section that appears under the subheading "Engineering VEGF Traps." Let me pull that up on the screen for you.

Do you see those on the screen?

A. Yes.

Q. If we look at the last sentence, which appears on the top of exhibit page 2, you reported in your papers that all of your VEGF Trap variants were produced and purified from Chinese hamster ovary cells. True?

A. I know that we produced them using Chinese hamster ovary cells. I assume that this statement is true.

Q. And using CHO cells will cause your VEGF Trap proteins to be glycosylated, right?

A. It depends on which Chinese hamster ovary cells you use. There's some that cause glycosylation, some that don't.

Q. And let's go to the second page of DTX 2745, right-hand column, where you are discussing your injections into mice. It's the text that starts "obtained from American-type culture collection."

Do you have that there on the screen?

A. Yes.

Q. And roughly in the middle of the text we have up on the screen, there's a reference to a vehicle that states PBS plus 0.5 percent glycerol.

PBS stands for phosphate-buffered saline, right?

A. Yes.

Q. And it's an isotonic solution?

A. I'm not sure, actually.

Q. Dr. Yancopoulos, let me call up DTX 8180, exhibit page 1, which is an article titled "The one-year results of the CLEAR-IT 2, a Phase II study of vascular endothelial growth factor Trap-Eye dosed as-needed after 12-week fixed-dosing," from the journal *Ophthalmology*, June 2011, Volume 18, pages 1098 to 1106.

You were a coauthor on this publication, yes?

A. Yes.

MS. MAZZOCHI: Your Honor, we move DTX 8180 into evidence.

THE COURT: Any objection.

MS. OBERWETTER: No objection.

THE COURT: Without objection, so admitted.

(DTX 8180 was admitted.)

MS. MAZZOCHI: Thank you, Your Honor.

BY MS. MAZZOCHI:

Q. Let's go to the second page of DTX 8180, the second full paragraph that starts off "vascular endothelial growth factor Trap-Eye."

Do you have that on the screen?

A. Yes.

Q. I'd like to direct your attention to the second sentence in that paragraph that's talking about VEGF Trap-Eye that says, "It was developed specifically as an ultrapurified iso-osmotic solution for ophthalmologic use."

Do you see that?

A. Yes.

Q. And as support for that statement, do you have a notation there, a citation number 25?

A. Yes.

Q. If we can turn to the DTX 8180, exhibit page 8, can you confirm that citation number 25 in the right-hand column is to Holash, et al., VEGF Trap, a VEGF blocker with potent antitumor effect, proceedings of the National Academy of Sciences USA, 2002, Volume 99, 11393-8, which we were just looking at before as DTX 2745?

A. Can we go back to the previous paragraph that we were looking at?

Q. I'm not sure. Let's start first. Can you just confirm this is the citation, that I read it correctly?

A. It's just that, clearly, a mistake was made in the position of the reference. It should have been after the first sentence of that paragraph as opposed to the second sentence because there was nothing about that point in that reference. So it was -- that reference refers to the wrong sentence.

Q. Let me be clear. It's your testimony here today that the citation support in a journal with your name on it in peer-reviewed literature is wrong?

A. No. I'm saying it was inappropriately moved one sentence. It should have been one sentence earlier.

These things happen. It could have been done in -- at the editorial stage or somebody could have missed it. But clearly the paper is not referring to anything about ophthalmic use, but the previous sentence is the one that describes what the VEGF Trap is.

Q. Again, I just want to be clear. It's your testimony today that you believe that there is a mistake in your journal -- in this journal publication?

A. There was a mistake in the position of -- how many footnotes are in here? Yeah. It was a mistake in the position of one in 50 or so footnotes. I'm sorry. By one position.

Q. Dr. Yancopoulos, I believe we've heard a lot from you earlier today that you believe it was the properties of aflibercept itself that allowed for your eight-week dosing regimen to work where you believe it had failed with other molecules, right?

A. For sure, part of the reason for the success was the molecule. Without a molecule, you have nothing. On the other hand, if it hadn't been delivered to that concentration and purity and so forth, it quite possibly would not have worked either. So it's a combination of many factors that allowed it to actually work. Obviously, if we had given a tiny amount of it, it would never have worked, so -- no matter how good the molecule was.

Q. But ultimately, you believe your eight-week dosing

regimen worked because you had a molecule you thought was a better molecule, which was aflibercept?

A. And for many other reasons as well, including the fact that we were able to concentrate and deliver enough of it so we could last longer. If we gave one molecule of the greatest blocker in the world, it obviously would not have worked for two months.

Q. All right. Now, even though you had found this extremely potent VEGF inhibitor, I believe, in late 1990s, you said you were having some difficulty finding big pharma partners to fund you?

A. Yes.

Q. And the lack of target validation in the clinic, together with that lack of recognition of commercial opportunities, also contributed to that difficult partnering environment for Regeneron, fair?

A. Could you just repeat that.

Q. Sure. The lack of target validation in the clinic, together with a lack of recognition of commercial opportunities, initially led to a difficult partnering environment for Regeneron, right?

A. Yes. Yes.

Q. Now, when it came to finding partners, one of the first game changers, when it came to using VEGF inhibitors for cancer indication, were the Avastin cancer results, right?

A. Yes.
Q. And those came out around 2003?
A. Yes.
Q. And then the next game changer for Regeneron was the clinical trial data that came out for Lucentis. That's what allowed you to partner with Bayer, right?
A. That contributed to the partnership.
Q. That was a game changer, right, the Phase III Lucentis data?
A. It contributed to the interest in the field, yes.
Q. Do you recall whether you called it a game -- the Phase III Lucentis data a game changer that led to the global collaboration with Bayer HealthCare for VEGF Trap-Eye?
A. It would not surprise me if I called the Lucentis results a game changer. I think I referred to them that way today. I don't know if I necessarily publicly linked them to our deal. I couldn't remember whether I did that or not.
Q. Whether you said that publicly, internally you understand that, right? That was what was -- that's what incentivized or enticed Bayer to want to partner with you, true?
A. Well, it was a major reason that the fact that, as you said, it was now clinical validation in the field contributed to somebody wanting to partner with us.
Q. Right. And it was the Phase III Lucentis data that

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was the driver on that for Bayer, right, in terms of wanting to come to you?

A. Like I said, it was one of several things that contributed. You have to ask Bayer if it was the major driver.

Q. By 2010 Lucentis was a 2 to $3 billion market, correct?

A. I don't remember the timing of when it became an important drug in the revenues, but if you say so.

Q. If it would help you out, let's pull up DTX 2053. And do you see that this is titled "RBC Capital Markets, Moderator Phil Rosenfeld, October 1st, 9:00 a.m. Central Time"?

A. Yes.

Q. Do you recall receiving a copy of this transcript?

A. I don't recall. I may have.

Q. If it will help you out, I can give you the document showing that this was attached to your email. Let's go ahead and pull up what I'll designate as DTX 2053A.

Can you confirm that this is an email dated Tuesday, October 19, 2020, from Murray Goldberg to Len Schleifer as well as you and others? It says, "Attachments, transcript.doc."

A. That's what it says.

Q. It says, "Attached is the transcript of the conference call that RBC hosted with Phil Rosenfeld and Quan Nguyen re: Lucentis, Avastin, and VEGF Trap-Eye. Lots of interesting observation."

Do you see that?

A. Just trying to find the document in my book here.

What was the question?

Q. Sure. Just do you see what I just read out from the highlighting?

A. I see it. I see the highlighting here.

Q. So does this help to refresh your recollection that you probably did, in fact, receive a copy of the RBC transcript?

A. This implies that I received it. Whether I read it or not, this doesn't help me.

Q. But, nevertheless, you received a copy of it as part of your ordinary customary business activities at Regeneron, right? Through your email?

A. Yeah, looks like I received an email of this.

MS. MAZZOCHI: Your Honor, we move DTX 2053 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: Depends on the purpose for which it is offered, Your Honor.

THE COURT: Fair enough.

Purpose?

MS. MAZZOCHI: Sure. The relevance is that there's some information in there that they thought was interesting about Lucentis and Avastin. It relates to some of the issues

in the case that we're going to get into in terms of what people were thinking at the time in 2010, which is shortly before the patents were filed in this case.

THE COURT: What specific issues?

MS. MAZZOCHI: I don't know if you want me to say it in front of the witness, Your Honor, but there are certain things in there relating to, as stated here in the covering email, hospital academic centers, Avastin, and private practice, physician reimbursement, as well as -- I was actually going to use it initially just to point out that they acknowledge that the Lucentis market was over $3 billion.

THE COURT: Any objection?

MS. OBERWETTER: Your Honor, it's a long document. So I will reserve on further hearsay objections, but subject to that, no, Your Honor.

THE COURT: So admitted.

(DTX 2053 was admitted.)

MS. MAZZOCHI: Thank you.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, let's go back now to DTX 2053, and let's look at the exhibits page 2, sixth paragraph down. And can you confirm that in this transcript that was attached to your email, it says, "Lucentis dominates the branded-approved market with about 3 billion in sales"?

A. I see that.

Q. Was that consistent with your recollection in that time frame of 2010 that Lucentis had a market that was billions in sales?

A. I probably knew that Lucentis had lots of sales. I probably did not know the exact number.

Q. And did you also have an understanding that Avastin, even though -- let me take a step back.

You understood that physicians in this 2010 time frame were using Avastin off-label to treat wet AMD, right?

A. Yes.

Q. And the formulation that was being injected into patients' eyes was a formulation that had been developed for intravenous cancer use, right?

A. Yes.

Q. And physicians were, to your knowledge, still being reimbursed by CMS, the federal government, in connection with those uses, right?

A. Yes.

Q. All right. Now, one of the other things that this conference call mentions is that in 2010 Lucentis was charging about $2,000 per injection.

Do you recall whether that price point also guided your decision on how to price Eylea?

A. Yes, it did.

Q. Let's move on to DTX 913, exhibit page 1.

Can you confirm that DTX 913 is an email thread that was forwarded to you, your CEO Leonard Schleifer, and others on Monday, February 5th, 2007, from Avner Ingerman about Lucentis labeling that had been approved in Europe?

A. Yes.

Q. And one of the things Mr. Ingerman was forwarding to you by this February 2007 date was the Lucentis labeling that was approved in Europe?

A. Yes.

Q. And one of the things that the European regulatory authorities did do is they approved Lucentis for both monthly dosing in AMD as well as for use with a loading dose of one injection per month for three consecutive months, followed by a maintenance phase or monitoring that was described as being given on a prn basis.

A. This was a highly controversial decision because it was based on absolutely no data. And what we know in Europe, they tend to do things because of cost as opposed to patient benefit. And as has now been largely validated by subsequent studies, that was a really inferior regimen that resulted in lots of vision loss.

So it was a controversial decision for them to approve a regimen that was never tested or studied in Phase III trials and which resulted in worse vision outcome for patients.

Q. Dr. Yancopoulos, let's start first with you don't

dispute that one of the things that the dosing instructions for Lucentis included in the European Lucentis label was a loading phase of one injection per month for three consecutive months?

A. Followed by prn dosing, which I just want to point out was a very controversial decision at the time. It was subsequently realized to be very inferior regimen that led to poor visual outcomes for patients.

Q. I just want -- Dr. Yancopoulos, I just want a clear yes or no. I understand you're going to say you don't like prn dosing regimens. I just want to be clear that your understanding, as of February 2007, is that the European regulatory authorities approved a dosing regimen that had three monthly loading doses followed by a maintenance phase that would allow for an extended dosing interval beyond one month.

A. It was followed by prn dosing, which was a highly controversial decision at that point in time, which resulted in worse visual outcomes.

Q. Prn dosing allows for a regimen or a dosing interval to go beyond one month, right?

A. Prn dosing is dosing as needed. That's what it stands for.

Q. Right. And if the patient does not need the dose at the next month, they can extend until the next office visit, right?

A. The problem is, is how do you determine "as needed"?

And the problem with prn dosing is it depends. "As needed" means the patient starts to fail and that you treat them when the patient fails. And what that has resulted in is in systematic underdosing of patients and poor visual outcomes, which is why it is no longer used.

Q. Well, with the DME data that you saw that was coming out of Phase II when the doctors were allowed to dose the patients as needed in a prn regimen, they actually got better letter gains relative to what happened for the three loading doses followed by the fixed eight-week dosing interval, right?

A. Well, as you said, in Phase II studies, prn at times appeared like an attractive dosing regimen. When prn was studied in large Phase III trials, such as CATT and HARBOR, it resulted in the realization that the prn dosing regimen was a very inferior regimen that resulted in worse visual outcomes, which is why sophisticated drug developers don't focus and count all their data just on Phase II. That's why you need large Phase III trials, which have invalidated prn, which is why prn is no longer utilized.

Q. That's your opinion, right? You haven't done any surveys or anything in that regard that you've presented in court today?

A. Well, I can tell you that prn is no longer utilized by the community.

MS. MAZZOCHI: Your Honor, I'd just like a very, what

I think, is a yes-or-no answer. Did he know that the European labeling would allow for three loading doses followed by a maintenance phase that would permit an extended dosing interval? It either did or it didn't.

A. I think I've answered that question.

THE COURT: Try one more time, Doctor. Were you aware that's what the label says?

THE WITNESS: Well, I think a yes-or-no answer can be used in a misleading way, and I don't want to mislead anybody. I think that there was -- as I described it, the full answer is that this was a controversial decision, which has subsequently been realized to have resulted in poor vision outcomes and is a regimen that's no longer utilized.

BY MS. MAZZOCHI:

Q. But it's a regimen that you utilized in your own clinical studies, right?

A. It was one of the many regimens that we included in our various clinical trials.

Q. You were also, in the 2006 to 2007 time period, tracking what was happening with Lucentis for the DME indication, true?

A. State that again.

Q. You, in the 2006 to 2007 time period, were tracking what was happening with Lucentis for the DME indication, true?

A. Yes.

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Q. Let's take a look at DTX 4070, a publication titled "Vascular Endothelial Growth Factor is a Critical Stimulus for Diabetic Macular Edema" by Quan Dong Nguyen, et al., from 2006.

You've seen this paper before, haven't you?

A. Folder just completely fell apart.

THE COURT: It's 4070.

MS. MAZZOCHI: The title is up on the screen for you as well, Dr. Yancopoulos.

THE COURT: Just one second, Counsel. We're reassembling the exhibit notebook.

THE WITNESS: Yes.

MS. MAZZOCHI: Your Honor, we move DTX 4070 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 4070 was admitted.)

BY MS. MAZZOCHI:

Q. Now, Dr. Yancopoulos, back in 2006 when you first reviewed this paper directed to the use of Lucentis for diabetic macular edema, you believed that this study had a lot of important implications, right?

A. Yes, I did.

Q. And one of the reasons why you believed the study had very important implications is because it showed patients had

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substantial visual gain, right?

A. Can you keep going?

Q. I'm just saying, do you recall stating --

A. I actually showed Figure 4 from this paper in the Bayer presentation. That was what we spent time on in the previous discussion, and that figure summarized why I thought this paper important because in Figure 4 it clearly shows that Lucentis did not appear to last for two months. It only lasts for one month. That's why I thought this paper was important, as we summarized in the Bayer presentation that I showed, if you want to go to Figure 4.

Q. I'm asking a different question, sir, and I'd appreciate it if you just try focusing on what I'm asking you.

You characterized the results of this paper as showing that these patients have substantial visual gain, right?

A. I don't know if I characterized, but I would characterize that they had substantial vision gain, yes.

Q. Let's pull up DTX 8127, exhibit page number 1.

Can you confirm that this is an email from you to Peter Powchik and Neil Stahl and others dated Thursday, December 7, 2006, subject line, "Lucentis pH 1 in DME and implications, attachments, read Lucentis pH 1 DME."

Is that your email?

A. Yes.

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Q. And if you take a look at the second point that you put in your email, did you indicate that these patients have substantial visual gain?

A. Yes.

Q. Okay. Did you say yes?

A. Yes.

Q. Thank you.

All right. Attached to this particular exhibit -- so let's just stay in this one since you had the paper -- a version of the article attached.

A. What was the DTX for that email?

Q. 8127.

A. Could you put that back up for a second?

Q. We've got your -- oh, you want the email back up?

A. Yeah.

Q. Sure.

A. Because like I said, the most important point is Point 1, which says that "Lucentis clearly does not last past four weeks, according to this study."

So as I said, that was the major point to me of this paper, Point 1, as I summarized in this email, and as was detailed in the Bayer presentation that we showed before. That was the major take-home message from this paper.

Q. Let's go to DTX 8127, the actual paper itself, and let's go to the "Methods" section that appears on the second

page of the exhibit.

Can we agree that ten patients with chronic DME received, as of this publication date, intraocular injections of 0.5 milligrams of ranibizumab at baseline, and at one, two, four, and six months.

A. That's what it says.

Q. And if they -- the patients received a dose at baseline and at one, two months, those would be three loading doses spaced a month apart, right?

A. Yes.

Q. And then the next dosing interval was eight weeks later at month four?

A. Where does it say that here?

Q. Where it says at baseline and at one, two, four, and six months, right?

A. Yes.

Q. All right. So the fourth dose in the regimen would have been eight weeks after the third dose in the regimen, right?

A. This is exactly the data that we went over, which actually showed that Lucentis at eight weeks didn't last, the one with the red arrows and the bracket that said Lucentis doesn't last eight weeks.

MS. MAZZOCHI: Your Honor, I'm really trying to move things along here. It's not going to go very well if the

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witness argues with me at every single opportunity.

THE COURT: Repeat your question, Counsel.

MS. MAZZOCHI: Sure.

BY MS. MAZZOCHI:

Q. My question, Dr. Yancopoulos, is was there an eight-week, or two-month, separation between the third dose in the regimen and the fourth dose in the regimen? Yes or no.

A. There was an eight-week separation that resulted in lack of vision gain.

Q. I'm just -- I'm not asking for additional commentary. I just want to know --

A. I'm providing useful context. I don't want to say something out of context.

THE COURT: Everybody, questions are asked, Doctor. You may answer them and provide context within reason.

Next question.

BY MS. MAZZOCHI:

Q. Can you confirm that the next -- that the -- there were then also -- there was a second eight-week dosing interval between four and six months?

A. Yes. There was another eight-week interval that also failed to result in visual gain.

Q. Dr. Yancopoulos, nevertheless, in your covering email, you did note that, overall, at the end of this regimen, patients did, in fact, experience gains in visual acuity and

improvements -- I'm sorry -- gains in visual acuity.

A. Well, we had a context, because the most important point was Point 1 which says, "Lucentis, which clearly does not last past four weeks, according to the study." That's the take-home message. That was why I made that whole figure for the Bayer presentation, not what you're trying to seemingly imply, that eight-week dosing worked. The whole point of my email says Lucentis clearly does not last past four weeks. Clearly, eight-week intervals did not work.

Q. I am asking at the conclusion of the study, did the patients experience an improvement in visual acuity?

A. From their baseline levels.

Q. Yes. And --

A. That's not what Point 2 says, though, in the email.

Q. And compared to their baseline levels, by the end of the dosing regimen, patients did, in fact, experience an improvement in macular volume?

A. I'm really confused here because, if what you're trying to imply is that Lucentis every two months would have worked, clearly, that's not the case.

So is that what you're trying to imply?

Q. All I'm asking, Dr. Yancopoulos, is did patients overall at the end of the regimen experience an improvement in their vision compared to baseline?

A. As they did in the PIER regimen, which is

every-three-month dosing.

Q. And they also experienced an improvement in macular volume at the end of the dosing regimen compared to baseline, right?

A. The question is were they achieved as good --

THE COURT: Doctor, Doctor, you need to answer the question that's asked.

Will you repeat that question, Counsel.

BY MS. MAZZOCHI:

Q. Yes. Dr. Yancopoulos, can you confirm that the patients in this study at the end of the regimen did, in fact, experience an improvement in macular volume?

A. For context, they achieved improvements. Nowhere in this study does it show that they improved -- achieved improvements that would be equivalent to that to monthly ranibizumab.

Q. I wasn't asking you that question, sir.

A. That is the relevant question.

THE COURT: Doctor, with all due respect, that's my decision as to what questions are relevant or not.

The question was answered. Move on, Counsel.

BY MS. MAZZOCHI:

Q. Let's take a look at Example 5 of your '572 patent, which is in PTX 3. I believe it's around page 22 of the exhibit in Column 14.

A. Is this in your book or in my prior book?

Q. It's in your prior book, PTX 3. Lawyers kill a lot of trees, but we do try to not repeat exhibits if we don't have to.

THE COURT: What page in that exhibit, Counsel?

MS. MAZZOCHI: It is exhibit page 20, Column 14, starting at lines -- around 30 to 50. We've got it up here on the screen for you as well.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, can you confirm that the dosing regimen set forth in Example 5 of your '572 patent is described -- one of the arms is described as giving three initial doses of 2 milligrams VEGFT once every four weeks, i.e., at baseline and weeks 4 to 8, followed through week 52 by either once every eight weeks dosing or as-needed dosing with a very strict repeat dosing criteria, prn.

A. Yes.

Q. And the dosing regimen that was described as three initial doses, i.e., at baseline and weeks four and eight, every four weeks, followed by every eight weeks dosing, at least for the first six months, tracked the Lucentis DME study we were just looking at in terms of the steps of the regimen being the same?

A. The steps of the regimen but not the visual acuity outcomes, which track very differently.

Q. Dr. Yancopoulos, the name that Regeneron gave to the clinical trial that corresponds to your patent's Example 5 was the Da Vinci trial, right?

A. Yes.

Q. Do you recall who made the decision to use three monthly loading doses?

A. The ultimate decision would have probably been on me, after consultation with our team, though I can't specifically remember that at this point in time, 10 to 15 years later.

Q. Well, you do remember it or you don't remember it. Do you not remember?

A. I don't specifically remember it, but I assume that that was probably the case.

Q. Let's go with what you actually do or don't remember.

Now, even though -- well, you were not listed as a coauthor for the publication about this clinical trial, right?

A. If you can point me to the paper.

Q. Sure. Let's pull up PTX 686, first page. This is the Diana Do, reporting on the outcomes of the Da Vinci study.

Can you confirm that you are not even listed as a coauthor on the article reporting on this study?

A. I can see that I'm not listed on the list.

Q. Now, you talked a bit about this decision to move from three to five loading doses for the Phase III clinical trials. Is there data that you put into your '572 and '601

patent specifications for any rationale, such as about reaching a plateau in the context of DME therapy, that would justify increasing the number of loading doses before switching to the eight-week dosing?

A. I can't say right now without reading the patent whether there's anything in there; but as I said before, that decision was based on a million points of data, as we saw before in this book and in the presentations and so forth. How much of it might be in the patent, I couldn't tell you without reading the whole patent right now.

Q. All right. Again, do you remember that I asked you this question at your deposition?

A. Do I remember that you asked me this specific question at the deposition?

Q. Right.

A. No.

Q. All right. Well, let's put up DTX 3196, exhibit page 11, which is your deposition transcript.

THE COURT: I'm sorry, Counsel. What exhibit number is that again?

MS. MAZZOCHI: 3196.

THE COURT: Thank you.

MS. MAZZOCHI: Exhibit page 11, transcript lines 40:24 through 41:14.

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BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, did I ask you, "Well, is there any data that you put in your '601 patent or any rationale about reaching this plateau in the context of DME's therapy that would justify increasing the number of loading doses before switching to the eight-week dosing?"

And did you give the answer, "In my attempt to read the whole patent very quickly earlier, I'm not aware of seeing that data shown, though it could well be in some of the many references that are included."

Was that the question you were asked and the answer you gave?

A. If that's what the transcript says, I guess that's what I said.

Q. Okay. Let me take you back to your -- well, actually, let's try to move along.

Let's actually switch gears for a minute and talk a little bit more about some of these formulation issues.

If you could take a look -- we'll go back to PTX 3 again, and now we're going to go to exhibit page 16, which corresponds to Column 5. And I'd like to direct your attention to lines 64 to 67 in your '572 patent.

Do you have those lines on the screen?

A. This is Column 6?

Q. Column 5, lines 64 to 67 in your '572 patent.

A. Yes.

Q. Did you state there, "A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists, Remington's Pharmaceutical Sciences," and then gives the citation.

A. Yes.

Q. Was this a true statement you made in your patent there?

I'm just asking if it's a true statement, Dr. Yancopoulos, that you put in your patent.

A. Right. It's caveated right below, "Provided that the VEGF antagonist is not inactivated by the formulation, the formulation is physiologically compatible and tolerable with the route of administration." Yes.

Q. Dr. Yancopoulos, I'd like to now direct your attention to one of your other VEGF patents, which is DTX 2730, and we'll start with exhibit page 1. U.S. Patent Number 7,303,747, which issued on December 4th, 2007.

Do you see that?

A. Yes.

Q. And you're a named inventor on this patent?

A. Yes.

Q. Do you remember if this patent actually covers your aflibercept molecule?

A. I'd have to look at this patent. Was it in my --

your book?

Q. Oh, yeah. You've got a copy of it in the binder that we gave you.

A. Under --

THE COURT: 2730.

MS. MAZZOCHI: 2730.

Your Honor, while Dr. Yancopoulos is looking for that, we'd like to move DTX 2730 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 2730 was admitted.)

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, to try to move things along, I'd like to direct your attention to exhibit page 13 of DTX 2730, specifically Column 1, the brief summary of the invention of your '747 patent at lines 46 to 55.

Do you see that on the screen?

A. Yes.

Q. One of the things your invention in this patent was about involved ameliorating an eye disorder, right?

A. Yes.

Q. And if we take a look here -- or starting around line 50, one of the eye disorders you listed included age-related macular degeneration? It's right there on the

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screen, sir.

A. Yes.

Q. And another embodiment you listed there was the eye disorder to treat diabetic retinopathy?

A. Yes.

Q. Now let's go to the 15th page of this exhibit, which is your '747 patent at Column 5, lines 3 to 26. And we've got that up on the screen there for you.

Do you see that?

A. Yes.

Q. And do you see the text that is highlighted that starts at line 25, over to line 26, that reads, sequence -- "SEQ ID" -- meaning sequence ID -- "and then VEGFR1R2-Fc delta C1(a)."

Do you see that?

A. Yes.

Q. That's the sequence ID for aflibercept, right?

A. That, I'm not sure of.

Q. You're not sure?

A. I don't know.

Q. All right. Well, let's pull up PTX 3, which uses your '572 patent we were looking at earlier. Let's go to -- I think it's around exhibit page 11. Let's try 14. There we go. Column 2, lines 51 to 56.

Isn't it true that you stated here that

VEGFR1R2-Fc delta C1(a) was aflibercept?

A. It says here that that name refers to aflibercept, yes.

Q. Okay. And --

A. I don't know that sequence corresponds to aflibercept, but yes, the name here says it's otherwise known as aflibercept.

Q. Okay. And that was a true statement you made in your '572 patent asserted here, right?

A. I believe so.

Q. All right. Let's go back then to DTX 2730, which is your '747 patent, exhibit page 16.

A. Which patent is this?

Q. This is your '747 patent, which is DTX 2730. And we'll go to exhibit page 16, and I'd like to direct your attention to Column 7, lines 5 through 28.

Do you see there there's a heading that's titled "Methods of Administration and Compositions"?

A. Yes.

Q. And does it also say, starting at line 13, that compositions -- strike that.

I'm sorry. I wanted to direct your attention to the last part of this. It says -- starting at line 26, it says, "Aqueous compositions of the invention have ophthalmically compatible pH and osmolality." Do you see that?

A. I see that.

Q. Can we agree that your '747 patent taught to put VEGF inhibitor compounds, like aflibercept, into pharmaceutical formulations that had ophthalmically compatible pH and osmolality?

A. I don't know -- you're using certain legal terms, and I'm not the guy who writes the patents. I don't know what you mean by "taught." So I can't -- I can't comment on that. It sounds like that means something that I don't understand.

Q. Okay. We'll phrase it this way for you.

Can we agree that on exhibit page 16 of DTX 2730, your 2007, '747 patent at Column 7, lines 26 to 28, you wrote that "Aqueous compositions of the invention have ophthalmically compatible pH and osmolality"?

A. Yeah. And let me also clarify. I didn't write this patent, but -- we have patent attorneys who write these patents. But it says in here, "Aqueous compositions of the invention have ophthalmically compatible pH and osmolality." Yes, that's what it says.

Q. Do you have an understanding that an aqueous composition with an ophthalmically compatible pH and osmolality, as you use that phrase in your '747 patent, will be isotonic?

A. Ophthalmologically compatible could or could not include isotonic.

Q. But if it's ophthalmically compatible osmolality, because that's the particular metric, right? pH plus osmolality will determine whether it's isotonic?

A. Compatible means compatible. It doesn't mean the same. Isotonic means, by definition, the same. Compatible means something that would be compatible, which does not have to be the same.

Q. Let me ask you this: When you used the term "isotonic" in your '572 patent, did you intend for it to just mean the same as what we get in the eye?

A. Well, isotonic, by definition, means the same tonicity. So, yes, I intended it to mean the same tonicity.

Q. Do you know whether there's any range that is permitted for that tonicity within the eye?

A. For compatibility? For what purpose? For compatibility?

Q. Any purpose.

A. Well, yes, there can be -- compatibility has to be tested, and presumably a range of tonicities have been used and can be used that would be compatible with research in the eye. It doesn't mean they have the same tonicity. That's a chemical term, "same tonicity." "Iso" means same tonicity.

Q. And if it is iso-osmolar, will it also be isotonic based on your understanding of how you use the term isotonic and osmolality in your patents?

A. Now we're going back to chemistry 101. I believe that iso-osmolar would be the same as isotonic, but this is not something that I'm an expert on.

Q. If we can compare what you said in your '747 patent about some of these formulations with what you have in your '572 patent, do you believe that your '747 patent's description of pharmaceutical formulations in the context of isotonic added anything different beyond what we saw in your '747 patent about requirements for the isotonic solution?

A. I think you said '747 twice; so I'm a little confused.

Q. I'm sorry '747 patent versus '572 patent. Let me start over because I don't want you to be confused.

Did you add anything conceptually that you considered to be new in terms of describing an aqueous composition of the invention that has an ophthalmically compatible pH and osmolality that we saw in the '747 patent as compared to what you talked about for pharmaceutical formulations that were isotonic in your '572 patent when we were looking at Column 6, starting around lines 18 to 34?

A. Ophthalmically compatible pH and osmolality would include, as we said, a range that could, for example, be hypertonic, hypotonic, or isotonic. We specifically highlighted the isotonic solution in the '572 patent.

Q. Now, the description of isotonic solution that you

provide here in your '572 patent, that's not something that you actually came up with, right?

A. No, I did not.

Q. And you did not actually come up with this idea of a formulation that has the isotonic solution containing glucose that may be used in combination with an appropriate solublizing agent, such as an alcohol, right?

A. As I said before, I relied on our formulation experts to develop and recommend and show me data as to which was the best formulation that they had recommended.

Q. And just to be clear, when we're looking at this isotonic solution in your '572 patent, you did not actually come up with the idea of a formulation that was isotonic and also had a solublizing agent, right?

A. I did not come up with the formulation. As I said, I relied on my experts and chose between the choices that they gave me and the recommendations at the time.

Q. Sure. I'm talking more specifically about what you actually wrote here in -- or what is written here in your patent.

Do you believe you came up with an idea of an isotonic solution that may be used in combination with an appropriate solublizing agent?

A. No, I did not come up with that idea.

Q. All right. Did you come up with the idea of an

isotonic solution that might also be combined with a nonionic surfactant?

A. No, I did not come up with that idea.

Q. Let's go ahead and jump ahead to exhibit -- let's go ahead and pull up DTX 5073.0001. So, Dr. Yancopoulos, let's go through a little bit with the Court about what the Eylea formulation was that was used in your clinical trials.

Dr. Yancopoulos, do you dispute that the ingredients of the 2-milligram Eylea formulation that the FDA approved in November 2011 were also the same ingredient list for the 2-milligram formulation that was actually given to the doctors performing the VIEW 1-VIEW 2 clinical trials with aflibercept?

A. Do I dispute?

Q. Right.

A. Can you ask that again?

Q. Sure. Maybe I'll -- since you don't like the word "dispute," I'll rephrase it this way.

Do you agree that the Eylea formulation that the FDA -- the ingredient list for the Eylea formulation that the FDA approved in November of 2011 was the same formulation ingredient list for the 2-milligram formulation that was actually given to the doctors performing the VIEW 1 and VIEW 2 clinical studies?

A. I believe it was.

Q. Okay. And if we can take a look at the first page of

DTX 5073, can you see that this is titled 2.7.1, "Summary of Biopharmaceutic Studies and Associated Analytical Methods"?

A. Yes.

Q. And do you have an understanding that these are the types of things that are submitted by Regeneron in connection with its BLA with the FDA?

A. Yes.

Q. Is this work that you, as president and chief scientific officer, ultimately were responsible for overseeing?

A. These functionalities reported up to me. I did not directly oversee them.

Q. That's fine.

MS. MAZZOCHI: Your Honor, we move DTX 5073 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection.

THE COURT: Without objection, so admitted.

(DTX 5073 was admitted.)

BY MS. MAZZOCHI:

Q. And let's go ahead and move along to -- let's have you take a look at DTX 5082, and we'll start again with exhibit page number 1. This is a part of the Regeneron BLA that is titled "2.3.P Drug Product."

Do you see that?

A. Yes.

Q. And is this also work that you, as president and chief scientific officer, were ultimately responsible for overseeing?

A. When you said formulation development, that did report up to me. If we're talking about some of the aspects that are under here -- you know, the manufacturing, the drug process, and so forth -- that reports up to our head of manufacturing.

Q. And does your head of manufacturing report to you, or do they just report to your CEO?

A. They report to our CEO.

Q. Let's go ahead, and we'll move along.

Now, ultimately, though, Dr. Yancopoulos, you would agree that pharmaceutical formulations is not an area of expertise for you, right?

A. Yes, I would agree.

Q. Dr. Yancopoulos, we did look earlier -- I think it was PTX 311. Let's go ahead and call that up.

This was your 2012 article titled "Intravitreal Aflibercept VEGF Trap-Eye in Wet Age-Related Macular Degeneration."

Do you have that?

A. Yes.

Q. Let's take a look as well at the exhibit that you had pulled up. I believe it was PDX 3-0311-B. See if we can pull

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that up on the screen. I think it was the one that had what you called the integrated data on it.

MS. MAZZOCHI: Pardon me, Your Honor, with a lot of these exhibits going on.

BY MS. MAZZOCHI:

Q. All right. There we go. Dr. Yancopoulos, is this the slide -- can you confirm that up on the screen you have PDX 3-0311-B?

A. Yes.

Q. And this is one of the slides you testified about in your direct examination?

A. Yes.

Q. Can you confirm that, if we take a look at the integrative data, the dose that performed the best in terms of letter ranking was the 2q4 regimen in yellow, yellow-orange?

A. Numerically, it had a higher number at the end; statistically, these were all no different from each other.

Q. Right. And my questions are just going to be at the end of the dosing regimen. So can we agree, then, that the 9.3 2q4 aflibercept monthly dosing regimen was the best numerically in terms of number of letters gained?

A. Well, in VIEW 1 it was numerically better; in VIEW 2 it was actually numerically worse. They were reversed to the point that I made before, and then they were within less than a letter difference at the end of the trial.

Q. That's why I asked you about the integrated data. So can you confirm that at Week 52 the integrated data curve from the VIEW 1-VIEW 2 study put the monthly aflibercept dosing regimen numerically at the top with 9.3 letters gained?

A. There was not statistically significant difference of 0.9 letters, in which the 2q4 was 0.9 letters numerically different from the 2q8, but not statistically different.

THE COURT: Yes or no, Doctor.

BY MS. MAZZOCHI:

Q. Do you need me to repeat the question?

A. Yes.

Q. Can you confirm that in the integrated data set for the VIEW 1-VIEW 2 clinical studies, the aflibercept 2q4 dosing regimen numerically performed the best with 9.3 letters?

A. It was numerically higher.

Q. Right. And then the next numerically higher number, at 8.7 letters, was ranibizumab dosed monthly, right, with 8.7 letters gained?

A. I think this was a misrepresentation of the data. I can't -- I can't in good conscience say yes to things that are misrepresentations. You're making -- trying to make a point about .3-letter differences that are statistically insignificant, that didn't repeat in the two studies.

Q. All I'm asking you, Dr. Yancopoulos -- this is your slide --

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A. Right.

Q. -- can you confirm that the integrated data set you presented here had ranibizumab monthly, R q4, at 8.7 letters?

A. It had it at 8.7.

Q. All right. And, likewise, right below that, at 8.4 letters, was your aflibercept 2q8 regimen, which was three monthly loading doses followed by every-eight-week dosing?

A. At 8.4 for 2q8.

Q. And your -- that at 8.3 letters was your 0.5-milligram dose given monthly, right?

A. Those are the numbers.

Q. And if we look at your VIEW 1-VIEW 2ETDRS letters in A and B, even -- can we agree that the letter range variation for the monthly Eylea dosing was from 7.6 to 10.9?

A. Yes.

Q. And can we agree that for the ranibizumab, the ultimate letter range in VIEW 1 and VIEW 2 ranged from 8.1 to 9.4?

A. Yes.

Q. And can we agree that for the 2q8 dosing -- so the three loading doses followed by eight-week dosing with aflibercept -- that dosing range was from 7.9 to, I believe, 8.9?

A. Yes.

Q. And for the 0.5 dose of aflibercept given monthly,

your letter variation range was from 6.9 to 9.7 across those trials?

A. Yes.

Q. Now, when it comes to this Heier -- oh, I'm sorry. When it comes to the Heier publication that you're a coauthor on, PTX 311.001, you did at some point submit a version of this publication to the *New England Journal of Medicine*, right?

A. Yes.

Q. And the *New England Journal of Medicine* rejected your manuscript?

A. Yes.

Q. All right. Let me put before you DTX 915. It's also in your binder, and I'd like to go to the first page of the exhibit.

Can you confirm that DTX 915, the first page includes an email from you to Bala Dass and others dated Thursday, January 19, 2012?

A. Yes.

Q. And did you write the commentary in this email? "I would agree with Peter and Dave and do whatever is necessary to get the first paper out in NEJN," meaning *New England Journal of Medicine*.

A. Whatever is necessary refers to the line below that says "withdraw a related paper from consideration in another journal."

Q. By the way, that was -- you did write commentary in this email, right?

A. Right.

MS. MAZZOCHI: Your Honor, we move DTX 915 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection.

THE COURT: Without objection, so admitted.

(DTX 915 was admitted.)

MS. MAZZOCHI: Thank you, Your Honor.

BY MS. MAZZOCHI:

Q. If we go to the second page of this exhibit within the email string, did you receive various reviewer comments about your manuscript from the *New England Journal of Medicine*?

A. Yes.

Q. All right. Let's take a look at a few of them.

If we can go to exhibit page 6 in DTX 915.

I'd like to go through a couple of the comments from Reviewer Number 1, particularly Item 18, which was commenting on your manuscript page number 11. Let's pull that up for you on the screen.

Do you have it?

A. Yes.

Q. And did they -- if we go to the -- three, four, five, six -- seventh line down in terms of talking about the CATT

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study, did the reviewers tell you that the -- I'm sorry -- in talking about your study, that the average number of injections in your VTE, meaning VEGF Trap-Eye, 2q8 group was 7.6 and the average number of injections -- average number for the ranibizumab prn group equivalent in efficacy to ranibizumab monthly was 6.9.

Is that what the reviewer wrote to you?

A. I see that. I'm not sure it's correct, though.

Oh, this is the ranibizumab prn group. I'm sorry. This is not in our study. This is comparing cross-study comparisons. Sorry. I didn't understand comparing our study from the study from CATT, yes.

Q. Yup. And then the reviewer took that data and said, "While the argument of decreased burden for the patient by eliminating five monthly monitoring visits in the first year is solid, the argument for increased patient safety is overstated, particularly relative to ranibizumab prn."

Is that one of the comments you received?

A. Yeah. This is comparing our regimen to a regimen that is now obsolete because it's considered not as effective, yes.

Q. Sir, I just wanted confirmation that these are the comments you received. Because you're not an expert, I'm actually trying to not invite commentary. I'm just trying to confirm the commentary you received.

A. I'm just putting it into context.

Q. Let's take a look at exhibit pages 6 and 7, the text that goes from the bottom of page 6 in DTX 915 and over to the top of page 7, which are some of the comments from Reviewer Number 2.

If we look at the top paragraph of the text on DTX 915, exhibit page 7, Reviewer 2 gave you the feedback that "The primary finding that may differentiate VEGF Trap as compared to the many prior reports is an apparently noninferior semimonthly dosing schedule as opposed to monthly dosing. Although clearly of burden -- benefit to patients and physicians, this is not a major conceptual advance."

That was the feedback you got from Reviewer Number 2, right?

A. That was.

Q. Okay. Now let's go a little bit more than halfway down, exhibit page 7 in DTX 915. We now have comments for the author from Reviewer Number 3 that I'd like to pull up on the screen.

And let's take a look at Reviewer Number 3's first full paragraph of text and the second-to-last sentence.

Reviewer Number 3 said of your manuscript, "The paper also lacks balance and is much too heavy-handed in its treatment of every-two-month dosing, so much so that it comes off as the beginning of a marketing campaign."

Was that feedback that you received from Reviewer Number 3?

A. That is what he wrote.

Q. Let's go to exhibit page 11 in DTX 915 and look at some more feedback you received from Reviewer Number 3. And this time I'll ask that the top paragraph be put up on the screen. So we're in exhibit page 11. Let's pull up the top paragraph. It's pretty lengthy. We'll scroll on through it.

Let's begin around the fifth line down on DTX 915, page 11. It says -- actually, to be fair, let me do the whole sentence.

So do you see starting in the third line down there's a reference to the CATT and HARBOR clinical trials?

A. Yes.

Q. And in the CATT clinical study, ranibizumab, Lucentis, was tested head to head against Avastin, bevacizumab, in connection with wet AMD, right?

A. Yes.

Q. And they found that there was really no clinical difference in that class -- in that CATT study between the two drugs, right?

A. No. That's incorrect.

So as I said, at this time, prn was very much in favor. And particularly with the early results from CATT and HARBOR, some people were failing to see the problems with prn.

Once the field evolved, probably a year or two after this, especially when they had the subsequent year's data, it became very clear that these prn regimens were just not delivering the visual acuity outcomes. And the evidence for this is they rapidly dropped out of favor and were no longer being utilized to this day. So these experts are among the experts at the time that had it wrong in terms of favoring at that time based on early data prn regimens.

So I don't want to be -- I had publicly at that time pointed out the difficulties with prn dosing which have since been validated, though, as I said, people at the time were still stuck in that regimen. But history has proven these ineffectual and obsolete now.

MS. MAZZOCHI: Your Honor, I'd like to move to strike because my question --

THE COURT: Denied. That motion is denied. We're reviewing random comments from reviewers for a medical journal. I'm about to ask the question what is the relevance of this line of questioning anyway, Counsel?

MS. MAZZOCHI: Your Honor, the relevance of this line of questioning is that many of the arguments that we're going to hear from Regeneron's witnesses in connection with unexpected results are making exactly the type of arguments that were made in that Heier paper that the -- that Regeneron's going to rely on.

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And they're trying to treat those comments that are in the Heier paper as if they are gospel and uncontested. And our point is that no, in fact, there were people who disagreed with some of the premises that you put into that paper; therefore, it shouldn't be accepted as truth in this case.

THE COURT: This is getting to one of the many reasons the Court denied all the motions for summary judgment. I think there's a genuine dispute that the doctor just articulated on that. So the motion to strike is denied. You may ask your next question.

BY MS. MAZZOCHI:

Q. The question with regard to CATT is did they discover any differences between the number of letters gained between bevacizumab versus -- versus ranibizumab for comparable dosing regimens?

A. I think it's hard for me to remember all the details now, but the ultimate conclusion after looking at the follow-up data of CATT was that prn regimens were not as effective. And that largely explains why they are no longer being followed. Also, that Avastin was not as effective and, even under prn regimens, had to be dosed more frequently than Lucentis.

Q. In a way that was statistically significant, to your recollection?

A. I don't remember all the details, but clearly the field had -- has come to the conclusion that prn dosing is

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suboptimal and that Avastin is suboptimal to Lucentis when given the same way.

Q. If we carry on with the reviewer comments, one of the reviewer comments back to your manuscript was that you state that CATT and HARBOR still required mandatory monthly visits. In the next line you refer to the CATT prn treatments as difficult treatment decisions. "I would not characterize these as difficult since they are what clinicians do every day in their practice."

Was that also feedback that you received?

MS. OBERWETTER: Your Honor, I am going to object at this point to the continuation of this line as to the series of unidentified reviewers as to the relevance and probative value.

THE COURT: Overruled for the reasons counsel previously articulated.

BY MS. MAZZOCHI:

A. So we can talk about subjective judgments. I don't think anybody would disagree that bringing an elderly patient in once a month or once every two months is not more difficult and much more burdensome on the patient, no matter what characterizations your treatment is on. I think everybody would agree, if you've ever had an elderly parent, bring him to the doctor once a month or once every two months is twice as burdensome.

Q. But in your clinical trials, the VIEW 1-VIEW 2

clinical trials, even in the every-eight-week dosing regimen you still required the patients to show up every month, right?

A. The FDA deemed that that was what was conducted in the trial, but the data clearly showed that there was no need to be bringing them in. So the label did not require any of those monitoring issues. So the FDA, which is the ultimate arbiter, said that there is no need for these burdensome monitoring visits.

They were required for the protocol to make sure that there would be no need. And the studies showed to the FDA's satisfaction that there was no need for monthly monitoring visiting, thus cutting the number of burdensome visits by half and also taking all need to do these various testings, whether you think they're difficult or not -- I mean, physicians may like to do them because they are compensated for doing these assessments, but what the FDA agreed was there was no need for the patients to come in, and there was no need for the doctors to do these assessments if you used their approved regimen.

Q. Didn't the FDA require you in the Eylea label to include language that said patients should be assessed regularly?

A. And regularly would be consistent with coming in every two months for their dose.

Q. Let's go to the last eight lines on exhibit page 11 in DTX 915, first paragraph. I'd like to direct your attention

to some additional text that says, "Lastly, you say that aflibercept will decrease treatment burden."

Did *New England Journal of Medicine* Reviewer Number 3 give you feedback that said, "Lastly, you say that aflibercept will decrease treatment burden. So does prn dosing, which is the primary way Lucentis and Avastin are used, and maybe to a greater degree in the first year and maybe with an equivalent result"?

Do you see that?

A. Once again, the field at the time, which we've already acknowledged, believed that prn dosing was the way to dose. It has been almost completely abandoned now because it was realized that it was not a way to get the best visual outcomes. So they're comparing us.

So the whole point of prn was to decrease treatment burden. Everybody says treatment burden was so important. Prn was devised to try to decrease treatment burden. It's now been abandoned because it did not lead to equivalent visual outcomes. We delivered a way to avoid all that, to decrease the treatment burden by half and deliver the same visual outcomes as the FDA agreed.

So you're trying to say that yes, of course, I could not treat the patients at all and there would be no treatment burden, but of course they would lose their vision. So you're comparing us to a regimen that's no longer being utilized. I'm

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sorry, but the reviewers at the time were trapped in their old paradigm. No matter how expert they were, no matter how utilized they were by the *New England Journal of Medicine*, they've now been proven wrong by history.

Q. In what year do you believe history decided to prove the prn regimens wrong in your understanding?

A. From that period of time, which was --

Q. This was in 2011.

A. -- 2011, over the ensuing five years, prn gradually completely fell out of favor.

Q. Dr. Yancopoulos, let's go back, then, to PTX 3, your '572 patent. And I'd like to start at exhibit pages 21 to 22, which has your Example 7. And we'll pull that up for you on the screen.

Dr. Yancopoulos, let's take a look at the first regimen you put in your Example 7 titled "Dosing Regimen."

It says, "Specific nonlimiting examples of dosing regimens within the scope of the present invention are as follows." And then it says, "VEGF T 2 milligrams, 0.05 milliliters, administered by intravitreal injection once every four weeks, monthly."

Do you consider your '572 patent -- strike that. Let me start over.

Do you believe that you invented a monthly dosing regimen for aflibercept?

A. I don't know what the legal definition of invention is. We were the first to actually utilize this regimen and demonstrate its efficacy in clinical trials.

Q. Now, you've spent a lot of time today saying how much you hate the prn dosing regimen, that you thought it was just the dumbest thing that you could be doing. Well, let's move over in your patent to exhibit page 22 and take a look at the part of your Example 7 dosing regimens that appears in Column 17 of your '572 patent at lines 33 to 37.

Now, this dosing regimen is basically a first injection followed by nothing but a prn dosing regimen, right?

A. Could you direct me again to where we're talking.

Q. It's right here on the screen, but it's at Column 17, lines 33 to 37, exhibit page 2.

A. Yes. It's one of the examples of regimens that could be used.

Q. Okay. So you claimed as your invention a dosing regimen that you called earlier today the dumbest dosing regimen ever?

A. I think the point is that they're within the scope of the present invention. Nowhere am I saying that this is the preferred. This would work and provide some benefit to patients, just not a -- it would not provide the best visual outcomes, as we now know.

Q. Dr. Yancopoulos, you put a whole series of prn dosing

regimens in Example 7 as supposedly within the scope of your present invention, right?

A. Well, once again, I did not write the patent; but yes, these are listed as regimens that are within the scope of the invention, not necessarily highlighting which would be the regimen that resulted in the best visual outcomes for patients. That was what would be determined by our clinical programs and our FDA-validated Phase III clinical program.

Q. Would it be fair to say, then, that in Example 7 you were trying encompass all the ways in which aflibercept was utilized and shown to have some efficacy?

A. Not being an expert in these patents, but I think all these list dosing regimens that would be within the scope of the present invention. And I don't think that we would be saying which would be the best one that would produce the best visual outcomes.

Q. Let's stay in PTX 3, exhibit page 22, and look at the text that's at the end of Example 7, which I believe is near the bottom of Column 17, starting at lines 45 to 53, which then goes over onto the next column, 18, through line 3.

Do you have that on the screen?

A. Yes.

Q. All right. Now, if we look at this list of diseases there which are described -- now, one of them is described as wet AMD, right?

A. Yes.
Q. You have FDA approval for that with aflibercept?
A. Yes.
Q. Do you have FDA approval for an indication that is specifically called exudative AMD?
A. That's another way of saying the same thing.
Q. Now, you do have -- do you have an FDA approval for --
I'm sorry. Can you keep that up, please.
Do you have FDA approval for choroidal neovascularization?
A. Choroidal neovascularization is something that marks a variety of different diseases, including AMD. So if we look at the list, we have an approval, age-related macular degeneration, wet AMD. That's the first one. Retinal vein occlusion, RVO, yes.
(Reporter clarification.)
THE WITNESS: I'm reading the list in order.
So the first one is AMD and particularly wet AMD. Yes, obviously, we have the approval.
Retinal vein occlusions, yes, we have the approval.
Central ventral vein occlusion, yes, which is example macular edema following -- yes.
Branch retinal vein occlusion, BRVO, yes.
Diabetic macular edema, DME, yes.

Choroidal neovascularization, that marks a variety of different diseases, including AMD and DME; so it's not a specific disease.

Iris -- so we did not do Phase III trials in iris neovascularization. So we've knocked off the first whatever it is on the list. We haven't necessarily done all of those things subsequently on the list. It is pretty remarkable that, of the first five or six things that we've tried, there's extraordinary clinical benefit and they're all approved.

BY MS. MAZZOCHI:

Q. Can we agree that one of the things that is not here on the list is diabetic retinopathy?

A. Well, vascular retinopathy, I see is on the list. It's the last thing actually on the list.

Q. I'm talking about specifically diabetic retinopathy.

A. Like I said, vascular retinopathy is the same category. It's just that it occurs in diabetes.

Q. Does this language contain any statement of preference to use a particular dosing regimen from Example 7 for diabetic macular edema?

A. Not in this paragraph.

Q. All right. Let's stay in PTX 3 but go to exhibit page 15, which --

THE COURT: Counsel, before we do that, can I ask you how much longer you anticipate cross taking?

MS. MAZZOCHI: I apologize, Your Honor. I've probably got, I would guess, another maybe 30 minutes. I'll try to move it along. I'd hoped we'd be able to go faster.

BY MS. MAZZOCHI:

Q. Let's stay in PTX 3 but go to exhibit page 15, which is Column 4 of your '572 patent, lines 22 to 31. And this is the paragraph that starts off "The methods of the invention may comprise administering to the patient any number of secondary and/or tertiary doses of a VEGF antagonist."

Are you there on the screen?

A. Yes.

Q. All right. And now let's highlight the next sentence that reads, "For example, in certain embodiments only a single secondary dose is administered to the patient. In other embodiments, two or more -- e.g., two, three, four, five, six, seven, eight, or more -- secondary doses are administered to the patient."

Do you see that?

A. Yes.

Q. You did not put any upper limit on "or more" for the secondary doses, right?

A. That is correct.

Q. And likewise if we take a look at the tertiary dosing description administered to the patient, you did not put any upper limit on the number of tertiary doses, right?

A. Correct. These are intended to be treatments for life for these elderly patients.

Q. Can we agree that, of the options you've listed here, we're going to have at least ten or more options for secondary doses and certainly more than ten different options for tertiary doses in terms of the number given?

A. There is a number of embodiments.

Q. Right. But in terms of the actual number of options that are contemplated here, can we agree there's going to be at least ten or more for the secondary doses and at least ten or more options for the tertiary doses?

A. Yes.

Q. And if we -- and if a patient is going to be taking tertiary doses for a lifetime, that could be as many as 100 or 200 doses, right?

A. It's possible. These are elderly patients, however.

Q. If these doses can be given either on a fixed-dose regimen, a prn-dosing regimen, or a treat-and-extend basis, that's three additional options to impose on the dosing intervals, right?

A. Now I'm totally confused. What do you mean by that?

Q. Sure. Well, you don't specify here that the secondary dose is going to -- I'm sorry. Let me strike that and take a step back.

You don't specify that the tertiary doses are going

to be administered either on a fixed monthly basis, a prn basis, or a treat-and-extend basis, right?

A. I'd have to go over this, but I thought that the secondary doses would be given monthly. Okay? So let me just read what it says here.

"In one exemplary embodiment of the present invention, a single initial dose is administered to a patient on the first day followed by two secondary doses, each administered four weeks after the immediately preceding dose, i.e., at week four and eight, followed by at least tertiary doses each administered eight weeks after the immediately preceding dose, i.e., weeks 16, 24, 32, 40, and 48. The tertiary doses may continue at intervals of eight weeks indefinitely during the course of the treatment regimen. This exemplary administration is depicted graphically in Figure 1."

So I think the embodiments, yes, they cover a variety of ways to do it. But we specifically give exemplary examples that the secondary doses, for example, are intended to be given monthly. So the whole notion -- the whole idea was a short period of intense dosing monthly and then switching to an every-eight-week regimen, which is obviously eventually what we studied in the clinic. But that's, for example, what is in Figure 1, a single exemplary embodiment. But I agree, the embodiments, you could try to do some math and say that there's a lot of them.

Q. Okay. Well, let's stay on this exhibit page and look at your '572 patent at the text that appears at Column 3, starting at line 66, and which then runs over to Column 4, line 1. Now, I understand you said that you gave an example of monthly dosing, but your specification says here that the secondary dose can be administered on an interval of two, two and a half, three, three and a half, or four weeks, right?

A. Right. Once again, my expertise is not in writing these patents. My understanding is that they give embodiments that will cover a lot of possibilities. But in the key exemplary embodiments, we highlight what ends up being relevant to the particular examples and -- including the ones that ultimately were the ones that we tested in Phase III and got approved by the FDA.

Q. Sir, did you give the possibilities of two, two and a half, three, three and a half, or four weeks for your secondary dose interval?

A. Right. There are a listing of many numbers that you just listed, yes.

Q. Right. And, likewise, for the dosing range on the tertiary dose, did you also give an interval option of 8, 8 and a half, 9, 9 and a half, 10, 10 and a half, 11, 11 and a half, 12, 12 and a half, 13, 13 and a half, 14, 14 and a half, or more weeks after the immediately preceding dose?

A. Yeah, that's what's written in the patent.

Q. All right. And that's an additional -- that's at least 13 different tertiary interval options, right?

A. Yes. I mean, if you multiply these, you can get all sorts of possibilities. But like I highlighted, the ones that we put into a figure and ended up utilizing are just specific ones. You couldn't possibly test all of these.

Q. Now let's jump over to page 15 of Exhibit PTX 3 to Column 7 of your '572 patent, top of the column, from lines 1 down to 28.

Do you have that on your screen?

A. Yes.

Q. This is where you're listing all the possible doses to include in your dosing regimens, right?

A. Yes.

Q. And because the hour is late and our court reporter is heroic, I'm just going to ask if you'll accept my representation that there are at least 60 different dosing possibilities listed there.

A. Yes.

Q. Thank you.

And, likewise, you do not require -- or your regimens did not require using the same dose for the secondary and tertiary doses; you contemplated also having one dose for the secondary doses and a different dose for the tertiary doses, right?

A. Yes.

Q. All right. Now, let's go to -- let's pull up, if we can, PTX 3333. I believe on one of these pages you said that there was some data that you relied on. Let's see if I can get the exact exhibit page number.

A. Are you looking for Slide 47, the one that we were talking about during the prior --

Q. Well, unfortunately, the versions that we got from plaintiff's counsel didn't have an exhibit number on them. It's the one that ends in page 3752. So it looks like it's about ten pages from the end of the exhibit.

Let's go four more pages forward, please. 372 are the last four Bates numbers -- I'm sorry -- the last three Bates numbers. There we go.

The data, particularly this idea of the three month, three month, three month, and the arrows that you put on here that you said represented your great insight as to what needed to happen with these dosing regimens, did you put any of that data in your '572 or '601 patent?

A. Did we put the data from the PIER study into the patent?

Q. Right.

A. I would have to read the patent to know, but you can tell me, I'm sure.

Q. I didn't see it. Did you put your insight that you

needed to make sure that you weren't getting any vision loss before you did your next dose interval anywhere in your patent?

A. Say that again.

Q. Whatever you called your great insight as to why Lucentis failed, did you put that guidance anywhere in your patent specifications?

A. The thought processes about when Lucentis would fail, okay, I think, as we summarized in this slide and the very next slide, was the basis of deciding for us what design to do in our Phase III program. I do not think that we put in when Lucentis failed in our patent.

Q. And you didn't put in your reasoning as to why you believed Lucentis, as you put it, failed in your patent, right?

A. Yeah. I didn't say that this was any great insight, by the way. I think it's obvious that, after the first three injections, you lose vision. I just pointed it out. I didn't say it was a great insight. But it's right there. It was in the Genentech FDA label. We probably cited the Genentech label as a reference in our patent. We should look at that.

Q. You also talk --

A. Can you check to see -- I mean -- so before I say we didn't, we probably had the Lucentis label as a reference in our patent. So this data was in there then.

Q. Did you provide your reasoning or explanation? That was the point, sir. Your reasoning, your explanation, your

insight.

A. I'd have to read the patent in detail, but I don't know.

Q. It's not there.

All right. You also talked about how you needed to have some meaningful Phase III data. Can we agree that, in your '572 and '601 patents, there is no Phase III data for DME?

A. That is probably the case. We did not have Phase III data at that time.

Q. And, likewise, there was no clinical diabetic retinopathy data from any phase, Phase I, II, or III, in your '601 or '572 patent, right?

A. It's hard to remember all the timelines, but I think in general we create these patents and you try to cover the embodiments that you will try in the future as in your Phase III trials.

Q. Dr. Yancopoulos, you're not a board-certified ophthalmologist, right?

A. No, I'm not.

Q. And at some point do you recall the situation where patients were being denied Eylea monthly treatments when they needed them and prescribers were being denied payments for monthly administration of Eylea?

A. Yes.

Q. And in response, Regeneron prepared a labeling

submission to the FDA to allow for a change in the label, right?

A. Yes.

MS. MAZZOCHI: Your Honor, we'd like to call up DTX 902.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, can you confirm this is an email on which you were copied on this issue?

A. Yes.

Q. And one of the reasons Regeneron was willing to make these changes for the label for AMD and make a similar change for DME was to allow for patients who were being denied their physician-recommended treatment to actually get insurance coverage for the monthly dosing treatments they were being denied, right?

A. Yes.

Q. Dr. Yancopoulos, you would agree that, while clinical trial results may show results for the overall population or an average patient, we all know that individual results for almost any drug for any disease are going to vary for each individual, right?

A. That is quite possible, yes.

Q. And, Dr. Yancopoulos, you also know that the FDA and current practice allows physicians the individual freedom to treat individuals differently for various reasons, right?

A. Yes.

Q. And while a doctor may have to defend their decision if they prescribe off-label, you know that they do have the freedom to prescribe Eylea, or aflibercept, off-label, right?

A. Yes.

Q. And while you talked about your current Eylea product here today, Regeneron is planning on launching a new version of its aflibercept intravitreal product, right?

A. Yes.

Q. You're trying to get FDA approval for an extended dosing interval that is as long as 16 weeks, right?

A. Right, with a different, more concentrated formulation of aflibercept.

Q. Because from your perspective, there remains a need to alleviate treatment burdens with intravitreal VEGF inhibitors, right?

A. Yes. We would agree that, even treating patients every eight weeks, and as you said some people might require more frequent treatment, alleviating treatment burden further would have more advantages, yes.

Q. Let's pull up DTX 228.0002 that counsel asked you about.

A. Which book am I in?

Q. This is in the ones that your attorneys used with you. And let's look particularly at the -- what was described

as Lucentis control VT 0.5 q4w, VT 0.2 4qw, and then VT 2.0 q8w, dose somewhat still undecided.

Do you see that?

A. Yes.

Q. You testified that this reference to VT 2.0 q8w actually referred to not just an eight-week dosing regimen but one with three loading doses.

Do you have any documents that you're aware of that corroborate that statement.

A. It's hard to remember any documents from 15 years ago.

Q. Okay. But somehow you're remembering that that actually meant three loading doses even though three loading doses aren't written there?

A. Yes. I distinctly remember that because that was exactly what we were planning on designing.

Q. Let's take a look at PTX 3216. This is the key opinion leader discussion.

You said that some unnamed key opinion leader told you that there were safety concerns with DME dosing. Who was that key opinion leader?

I believe it was in the slide presentation.

A. Can you say again? What is it that you're referring to that an expert said?

Q. Yeah. If we take a look at -- it's the page of the

exhibit that ends in 5555; so second-to-last page of the exhibit.

You said that there were key opinion leaders who told you that there were possible safety concerns with the diabetic population.

Who do you contend told you that?

A. Well, I think there were already in the label, the original label for Lucentis, there was a possible association with what they called ATPC events or events related to heart attacks and strokes and so forth. And I think the concern was that the diabetic population might be more prone to the same safety concerns that were seen with AMD because, as we all know, if you have diabetes, it increases your risk of heart attacks and strokes.

So there was already the concern with the class, and that was in the Lucentis label, that it might be associated with an increased risk of heart attacks and strokes for AMD, and the possible safety concern in the diabetic population was that perhaps anti-VEGFs would have even more of a risk, which caused us to be concerned about going to even higher doses.

Q. Doctor, I'm not asking you what the basis was. I'm asking you who offered that opinion at your key opinion leader meeting.

A. I would not remember an individual, but I think that a lot of individuals were concerned about that, both internally

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and externally.

Q. Can you give me the name of any one of your key opinion leaders who attended that meeting who you believe expressed that concern?

A. I'm sorry, but at this point I can't give you the name of any key opinion leader who even attended the meeting.

Q. Okay. This brick of an exhibit, PTX 1170 -- it's about 4 inches thick -- did any of this data, to your knowledge, make its way into your '572 or '601 patent?

A. I have no recollection.

Q. Do you recall whether you even put any DME monthly visual -- I'm sorry.

Do you recall whether you put any monthly visual acuity data results for DME anywhere in your patent specification?

A. We could review the patent. I don't remember off --

Q. Well, the only place where you have any actual DME data is in Example 5. So let's go ahead and pull that one back up, PTX 3. I believe it's exhibit page 22.

I'm sorry. Let's go to Example 5. It's one or two pages earlier. And let's go down to Table 2.

Did you provide any monthly data showing mean change in visual acuity?

A. Apparently, yes.

Q. Sorry. Did you say yes?

A. Apparently, yes, in this table.

Q. On a month-by-month basis?

A. It says here "VEGF Trap .5 milligram monthly, .2-milligram monthly."

Q. Then my question was too confusing. I apologize. I don't mean did you have a monthly dosing? I mean did you provide the letter results each and every month?

So you had that graph that you were pointing us to earlier where you showed the drop-off for the Phase II DME data.

A. Right. You're saying the -- is this the Da Vinci study that we're talking about?

Q. Yes. It's Example 5.

A. So you're saying that we previously saw the graphs over time, and here we have the table of the results at Week 24.

Q. Right.

A. So we did not show the data between months zero and 24, yes.

Q. But it was the data that you saw in those -- at each of those intervening months that caused you to realize you wanted to have more loading doses, right?

A. Well, I think, as I said before, there was a lot of data, from here to the data that you're referring to to much other data that I used to come up with that decision to use

five loading doses, yes. So there's a lot more data that was utilized than is in this patent.

Q. Just so the record is clear, let's pull up PTX 1028-C.0011.

A. Which book is that in?

Q. That's your plaintiff's counsel's book, I believe.

A. PTX --

Q. 1028-C.0011, the Da Vinci mean change in visual acuity data that was set forth on the month -- I'm sorry -- the every-four-week basis.

Can you confirm you did not put that data into your patent?

A. Yes. As we just reviewed, this graph does not appear in the patent.

Q. But can you also confirm that, if we take a look at the 16-week mark, that is where the three loading doses followed by every-eight-week dosing dropped off, right?

A. Yeah. I don't think -- as I said before, we consider a lot of these changes in these very small number of patients noise. So if -- let me just use my laser pointer.

If you're trying to make the point that this line here meant anything different than this line here or this line here, it did not. So, no, I don't think you can make any conclusions because I think we all agree the change here looks just like the change here looks just like the change here. So

you could draw no conclusions from these small numbers of patients and the extreme variability seen in these small numbers.

Q. Let's take a look at PTX 1028-C.0016, the mean change in retinal thickness. Can we agree that, numerically, according to this graph, your 2q8 dosing regimen, which was three loading doses followed by every-eight-week dosing, numerically had performed the worst by Week 16 for mean change in retinal thickness?

A. Yes.

Q. And that was the fifth dose day, right? The fifth dose given within the context of that regimen?

A. I'm not sure that's correct.

Q. Well, there was a dose given at baseline at week zero, right?

A. Yeah. It was not the fifth dose.

Q. For the 2q8 regimen, was the first dose given at time equals zero?

A. Yes.

Q. The second dose was given at time equals 4?

A. Yes.

Q. And the next one was given at time equals 8?

A. Yes.

Q. Then skip the dose on week -- on Week 12?

A. Yes.

Q. All right. And then a dose was given at Week 16?
A. Yes. That would be the fourth dose.
Q. Now, for the prn dose at Week 16, those patients performed better numerically, right?
A. Yeah. The prn, I think at that point, was monthly dosing at that point.
Q. All right. Your understanding is that the prn was still doing monthly dosing in the Da Vinci study at the 16-week mark?
A. Let's go to it.
Q. That's fine. I'll withdraw it. Let's move along.
A. Yes.
THE COURT: How much longer do we have, Counsel?
MS. MAZZOCHI: Sorry?
THE COURT: How much longer do we have?
MS. MAZZOCHI: Your Honor, let me just wrap this up here, and I'll warn my colleagues that, if there's anything further they think I need to do, then they can start gesticulating frantically.
THE COURT: They're your sticky notes.
Go ahead, Counsel.
BY MS. MAZZOCHI:
Q. Dr. Yancopoulos, is it true that your net worth has been pegged at over $1 billion because of the value of Regeneron's stock that you own?

A. I honestly have no idea what my net worth is. I don't follow those sorts of things.

Q. We can at least agree, Dr. Yancopoulos, that your current stake in Regeneron is worth over $100 million, right?

A. Probably for sure, yes.

Q. All right. And, finally, you have not actually been treating patients for the many conditions that we've discussed today any time in the last 10 to 15 years; is that fair?

A. No, I have not been a practicing physician.

MS. MAZZOCHI: Thank you, Your Honor. We'll pass the witness.

THE COURT: We're going to take up recross tomorrow, assuming it's longer than five minutes.

MS. OBERWETTER: This will be very short, Your Honor.

Would you like a break? Your Honor, as long as we're coming back to finish this, then I'm happy to have a break.

THE COURT: I was going to come back tomorrow morning to finish it. What's your definition of very short, Counsel? Let me ask that.

MS. OBERWETTER: Five minutes, plus moving in the exhibits that I identified earlier.

THE COURT: I've fallen for that trick before.

MS. OBERWETTER: I'm pretty sure it's not a trick, Your Honor.

THE COURT: I didn't mean -- that was nothing

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personal.

REDIRECT EXAMINATION

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, just a few more questions for you today.

First of all, Ms. Mazzochi had some questions for you about DTX 4070, which was an article by Dr. Nguyen, if we could pull that up briefly.

And, Dr. Yancopoulos, do you recall the questions about this exhibit generally?

A. Yes.

Q. Okay. If we could actually take a look at the last page of text of this document, which appears at the top of DTX 40700009, and if we could actually hone in on just the top five lines there.

Dr. Yancopoulos, this is an article that you included in that Bayer 2007 PowerPoint that we looked at earlier today, correct?

A. Correct.

Q. How did Dr. Nguyen conclude his article?

A. In terms of you want me to read this or --

Q. Yes. Yes. What were the questions that he was posing after the data he presented?

A. Whether the different patterns of response to the Lucentis in different patients was because of different levels

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of VEGF production in these patients and what was the optimal timing for injections.

Q. Okay. And that is where he ended in terms of identifying regimens, correct?

A. Yes.

Q. We can take that document down.

If we could put back up PDX 3-0311-B, which was that colorized excerpt from the Heier 2012 reference.

And you recall Ms. Mazzochi had some questions for you about the numeric differences in Table C on this page, the integrated data. Do you recall that?

A. Yes.

Q. Could you please explain, briefly, the difference between the numeric data and looking at things from the standpoint of statistic significance?

A. Right, which is how the FDA looks at it.

When you're doing any study, even if two things are identical, you use the same exact regimen twice, there's always going to be numeric differences that can be very misleading and meaningless. So the FDA is focused on whether statistically significant differences, which they were not between these, as the FDA concluded.

So these were meaningless differences that one could not make any points about, which is why trying to say there's a difference between 8.7 and 8.4 is just scientifically invalid

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and misleading.

Q. And, Dr. Yancopoulos, if we go back to the first page of this document, which is PTX 311, the Heier 2012 reference, what journal was this published in?

A. *American Association of Ophthalmology*, known in the field as *Ophthalmology*.

Q. Is that a peer-reviewed journal?

A. It's a peer-reviewed journal.

Q. Ms. Mazzochi asked you some questions about individual reviewer opinions from the *New England Journal of Medicine*.

Are all important innovations published in the *New England Journal of Medicine*?

A. No, they are not.

Q. And apart from the reaction of the *New England Journal of Medicine* reviewers that Ms. Mazzochi asked you about, what was the reaction of clinicians at large when Eylea came onto the market with the approved regimen?

MS. MAZZOCHI: Objection, Your Honor. He's not competent to testify to physicians at large. He can talk about his own experience.

MS. OBERWETTER: Your Honor, it's my last question, and she marched us through eight anonymous reviewers. So I think he's allowed to --

THE COURT: Overruled. Ask the question again. I'm

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sorry.

BY MS. OBERWETTER:

Q. Yes. Dr. Yancopoulos, apart from the reaction of those *New England Journal of Medicine* reviewers, what was the reaction of clinicians at large when Eylea came onto the market with the approved regimen?

A. I think the physicians spoke with their actions, just like almost immediately when Lucentis came out, physicians almost completely started switching over to Lucentis from Macugen in the same way, very rapidly with Eylea, Eylea became the preferred drug of choice for the majority of ophthalmologists.

MS. OBERWETTER: Thank you.

At this point I would like to move into evidence the exhibits that we have used with Dr. Yancopoulos, which I am prepared to list if that's the easiest way to do this. I can also reconcile it with your clerk after we go off the record.

THE COURT: In Madam Court Reporter's survival interests, we're going to reconcile those afterwards. But were there any that there's any objections to?

MS. MAZZOCHI: Your Honor, as long as -- let me put it this way: We accept that a lot of these are business records and that sort of thing. I will say, though, again, I just want to ensure that it's not with any prejudice to us to continue to raise this issue that some of these documents

probably shouldn't even be admissible or, at the very least, relied on because they were not part of -- to the extent I think I know where counsel's going to use them for, they were not disclosed, timely disclosed either in the expert report or the discovery responses; so...

THE COURT: That's an issue we'll take up in the posttrial briefing and the rest. Thanks.

It's a bench trial. This Court will receive evidence for the parties' opportunity to create a relatively appropriate record, and then we'll place the appropriate weight, if any, upon the evidence as it comes in and its findings of fact and conclusions of law.

But the transcript will be clear as to what exhibits were referenced. If there are specific objections, we can take those up at another time.

Is there any recross at this point, Counsel?

MS. MAZZOCHI: Two things, Your Honor.

RECROSS-EXAMINATION

BY MS. MAZZOCHI:

Q. First, Dr. Yancopoulos, I'd like to go back to DTX 4070, exhibit page 009. Since your counsel only showed you a portion of the results about optimal timing for injections, let's put the whole thing up.

Did the whole thing -- did the whole set of sentences say, "What is the optimal timing for injections? There

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appeared to be a plateau in the amount of reduction of foveal thickening during the first three months of the study when monthly injections of ranibizumab were given" -- then let's add this in -- "with additional benefit achieved by switching to injections every other month."

Is that what the article said?

A. That's what it said.

Q. Let's call up DTX 916.

Can you confirm that this is an email that you were cc'd on dated January -- Saturday, June 9, 2012? And after you got rejected, did you then use your connections to get your manuscript published in *Ophthalmology*?

A. I did not use any connections since I didn't have them with *Ophthalmology*.

Q. But you'd agree that this is at least an email that you were cc'd on in around Saturday, June 9, 2012?

A. Well, it says here, "In full agreement with you, I want to write back and suggest we" --

THE COURT: Slow down, please, Doctor.

THE WITNESS: Well, I'm reading it. I haven't seen this --

THE COURT: Doctor, here's the issue with your reading. Madam Court Reporter can't listen --

THE WITNESS: Sorry.

THE COURT: Doctor, one second, please. Thank you.

Madam Court Reporter can't read it while you're speed-reading it as well. So if you're going to read, that's perfectly fine. I understand it's your answer to the question. I just need you to slow down while you do that to ensure we have an accurate record. Thank you.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, I just want to confirm that this is an email you were cc'd on.

A. Right. I'm just saying I'm reading this email, and it says, "I am in full agreement with you. I saw this email this morning and wanted to write back and suggest that we submit to *Ophthalmology*. It is a very fine journal."

MS. MAZZOCHI: Your Honor, we request that DTX 916 be moved into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection, Your Honor.

MS. MAZZOCHI: We're done. We're done, Your Honor. Thank you.

THE COURT: Without objection.

Reredirect.

MS. OBERWETTER: None, Your Honor.

THE COURT: Doctor, you may descend the stand, sir. Thank you very much.

I'll leave it to counsel to tidy up the exhibits there.

Is the doctor subject to recall, or is he free to go?

MS. MAZZOCHI: As far as we're concerned, he's done.

THE COURT: All right. We'll proceed then at 9:30 in the morning, subject to counsel squaring up the list of exhibits that were used during the witness's testimony, and we'll see everyone then. Thank you very much.

You can leave whatever you'd like in the courtroom. Nobody will be in here in the interim. But to give everybody advance warning, we do have another criminal matter we need to take up at noon tomorrow or whenever we take a lunch break, just as a planning FYI.

Have a pleasant evening. We'll see you tomorrow.

(Proceedings concluded at 5:46 p.m.)

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CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 12, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 12th day of June 2023.

/s/Cindy L. Knecht
_____
Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 2

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 13, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

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Tuesday Morning Session,

June 13, 2023, 9:30 a.m.

- - -

THE COURT: Convene for day two of trial. Plaintiff may call its next witness.

MS. OBERWETTER: Your Honor, if I may, Ellen Oberwetter for Regeneron. A brief housekeeping matter from yesterday relating to the admission of exhibits used in Dr. Yancopoulos's direct and redirect testimony.

I'm happy to handle this however you would prefer. I can either read the list into the record. We've had an opportunity to make sure our list conforms to what Ms. Kinsey had yesterday so that those are moved into the record as evidence.

THE COURT: Let's go ahead. If you'll read that slowly for Madam Court Reporter's benefit. Go right ahead.

MS. OBERWETTER: I'm happy to do that, Your Honor. PTX 0001, PTX 0003, PTX 3333, DTX 212, PTX 0419.

THE COURT: Is that 19 or 91?

MS. OBERWETTER: My list says 19.

THE COURT: Okay.

MS. OBERWETTER: Your list is correct, Your Honor.

THE COURT: As is Mr. Ruby's.

MS. OBERWETTER: PTX 491, DTX 228, PTX 0311, PTX 0304, PTX 3216, PTX 3187, PTX 3188, PTX 0080, PTX 1028-C,

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PTX 1170, PTX 0932.

THE COURT: I've got two others a little further down my list.

MS. OBERWETTER: Yes.

THE COURT: DTX 4070.

MS. OBERWETTER: That was the Nguyen 2006 reference. That's correct, Your Honor.

THE COURT: And PTX 0311?

MS. OBERWETTER: Yes.

THE COURT: That's the Heier article on wet age-related macular degeneration.

MS. OBERWETTER: Yes, Your Honor. That one was further up in my list. That's correct.

THE COURT: Any objection to any of those, Counsel?

MS. MAZZOCHI: No. But, again, as long we -- I know you instructed we are going to be doing the issue of whether they are allowed to use their conception surveys --

THE COURT: Try it again.

MS. MAZZOCHI: Yesterday the Court indicated -- my understanding is that the Court indicated that, to the extent we had an objection as to whether Regeneron can use any of these exhibits in connection with, for example, its conception or reduction practice theories or other theories not disclosed in their interrogatory responses, we will have the opportunity to raise that in posttrial briefing. Thank you.

THE COURT: Subject thereto, all of those are hereby deemed admitted.

(PTX 0001, 0003, 3333, 0419, 491, 0311, 0304, 3216, 3187, 3188, 0080, 1028-C, 1170, 0932, and DTX 212 were admitted.)

(DTX 228 was admitted.)

MS. OBERWETTER: Thank you, Your Honor.

THE COURT: Anything else we need to do before we hear from our next witness from plaintiff's perspective?

MS. OBERWETTER: No, Your Honor.

THE COURT: Defense perspective?

MS. MAZZOCHI: No.

THE COURT: Plaintiff may call its next witness, then.

MS. KAYALI: Your Honor, plaintiffs call Dr. Karl Csaky.

KARL CSAKY, MD, PhD, PLAINTIFF'S WITNESS, SWORN

MS. KAYALI: With Your Honor's permission, I'll approach to bring a binder to the witness.

THE COURT: Yes, please.

MS. KAYALI: My colleagues have already provided the Court with them.

THE COURT: Understood. Thank you.

MS. KAYALI: I should correct myself. We also have demonstrative slides, which you do not have in front of you.

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THE COURT: I do not appear to.

MS. KAYALI: So I will, if I may, provide these to the witness and to Your Honor.

THE COURT: Thank you.

MS. KAYALI: These contain our slides and a handful of exhibit excerpts that you're going to be seeing a lot of.

THE COURT: Understood. Thank you.

Counsel, go right ahead.

MS. KAYALI: Thank you. Good morning, Your Honor. I'm Kathryn Kayali for Regeneron.

THE COURT: Good morning.

MS. KAYALI: It's my privilege to present the direct testimony of Dr. Karl Csaky. We will offer him as an expert in vitreal retinal diseases and their treatment. We're here to talk today about infringement. He will be back same time, same place next week to talk about validity.

THE COURT: Outstanding.

MS. KAYALI: So today is infringement day. So with no further ado.

DIRECT EXAMINATION

BY MS. KAYALI:

Q. Good morning, Dr. Csaky.

A. Good morning.

Q. Before we go any further, let me ask, have you ever testified in court as an expert witness before?

A. I have not. This is my -- as they say in Texas, my first rodeo.

Q. Well, then let's get back to what you do as your day job. What do you do for a living?

A. So I'm a vitreal retinal surgeon.

Q. What is that?

A. I am somebody that takes care of, studies diseases of the retina.

Q. What's your day-to-day? What do you do as a retinal specialist?

A. As a retinal specialist, we are involved in evaluating patients, offering treatments. There's a host of other activities, but in the clinic our primary responsibilities are seeing, diagnosing, and treating patients with various vitreal macular diseases.

Q. Let's talk about those diseases. Are there any diseases you treat that are particularly relevant to this case?

A. Right. In reviewing this case, the diseases that I take care of are things like age-related macular degeneration, diabetic macular edema, and diabetic retinopathy.

Q. And I have a feeling that you and I are going to lapse into acronyms here shortly; so maybe we can clear some of those up.

Wet age-related macular degeneration, do we often call that wet AMD?

A. Correct.
Q. And diabetic retinopathy is often DR?
A. Correct.
Q. And then, finally, diabetic macular edema, is that DME?
A. Correct. We can call it DME.
Q. Is there an umbrella term for those diseases?
A. So it's not uncommon to term these angiogenic eye diseases.
Q. As a retina specialist, do you use Eylea?
A. Yes.
Q. Where do you currently work?
A. So my present position is at the Retina Foundation of the Southwest in Dallas.
Q. What kind of practice is that?
A. So this is a not-for-profit academic research institution. We see patients. I see difficult-to-treat patients. I get referrals that are more difficult. I interact with the community on challenging cases. We do research, trying to push our understanding of what are the limitations of our present treatments, how we can improve care of these patients.
Q. What's your current title at Retina Foundation of the Southwest?
A. So my current title is a mouthful, unfortunately.

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It's -- I'm the chief executive officer, chief medical officer. I am the T. Boone Pickens director of the molecular laboratory, as well as the director of the Center for Innovation for Age-Related Macular Degeneration.

Q. And where is your practice located?

A. In Dallas, Texas.

Q. How long have you been there? How long have you been at Retina Foundation of the Southwest?

A. I've been there part-time since 2009, and then sometime in 2018 I transitioned to full-time.

Q. I want to come back to your professional experience in a moment, but let's go back in time and start with your education.

Where did you receive your undergraduate degree?

A. I went to Vanderbilt University.

Q. Where did you head next?

A. I went to the University of Louisville for my medical school and graduate school.

Q. What brought you to Kentucky?

A. Well, I'm from Lexington originally, grew up in Kentucky. And, of course, being in state, it's much cheaper to go to an in-state school; and so I continued my training in Louisville.

Q. After you got your medical degree -- let me ask this: What degree did you get at the University of Louisville?

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A. Right. I got a combined what's called an MD-PhD. So I did both a medical degree, and I did some graduate work as well.

Q. Well, then after you received those degrees, your MD-PhD, did you continue your medical education?

A. Correct. I went to Duke University and did an internship in medicine. I then was fortunate to get a Fulbright scholarship and spent a year in Europe in an eye clinic in Germany.

And then I came back, continued some training in retina, and then did my ophthalmology residency at Washington University in St. Louis.

Q. Where in that process did you first start treating patients?

A. So probably -- even as residents, we treat. But probably when I did my fellowship at Hopkins. I went to Johns Hopkins, and I specialized in medical retina. And I started treating patients there more intensely.

Q. Medical retina, is that a distinction you're making between that and other retinal specialties?

A. Right. So in retina, I know somewhat surprising, but, actually, we take retina and we treat it medically, so in the clinic; and we also have surgical approaches for our retinal diseases. So you can get training in both or you can get training primarily in medical retina.

Q. Which one is it of those that you do?
A. I do mostly medical retina.
Q. That's in the clinic?
A. That's in the clinic.
Q. And at some point you found yourself in Washington, DC, right?
A. Correct.
Q. And where were you then?
A. Right. So when I finished my fellowship, I went to the National Institutes of Health and I did some work there. I was also at Georgetown University seeing patients. I also then went from there to the National Eye Institute where I was involved in the clinic, I was involved in clinical research, and also ran a laboratory as well.
Q. Where did you head after DC?
A. I went back to Duke. I was on faculty at Duke University in starting probably sometime around 2005.
Q. At Duke were you treating patients in Durham?
A. I was treating patients in Durham. I was treating patients at the VA hospital in Durham, but I also went to a satellite clinic in Wilson, North Carolina, as well.
Q. What is that? What's a satellite clinic?
A. So satellite clinics are kind of part of a lot of retina practices, and the idea behind satellites are that we go into rural communities; that way the patients don't have to

travel as far. Wilson, for example, is about 80 miles outside of Durham. So we could go to Wilson, and in that way the patients didn't have to travel as far. And so that was a typical clinic that I would go to, let's say, once a week.

Q. So after treating patients in Durham and in Wilson, did you eventually leave Duke?

A. I left Duke in 2009. I then went to Dallas and became a partner at Texas Retina Associates.

Q. What kind of practice is Texas Retina Associates?

A. So Texas Retina Associates is a large private practice retina practice, still one of the largest retina practices in the country. It is a private practice. And we do basically what retina people do. It was very intense clinical kind of work in the clinic.

Q. What were your colleagues like there?

A. So I had a spectrum of colleagues. I had about 16 partners. It's a large practice. And you had a whole variety of individuals. You had people who were a little bit more -- went to meetings; you had other people who just stayed in the clinic and took care of patients, went to the OR. So it's a pretty wide spectrum of individuals that I was exposed to.

Q. And at Texas Retina, again, were you treating patients in Dallas?

A. So I had a clinic -- again, I had a clinic in Dallas, but I also went to a clinic, again, in Paris, Texas. There is

a Paris, Texas, and it's about 120 miles northeast of Dallas. And, again, I went every other week. It's about 120 miles.

And so, again, the idea is a similar idea. Texas is big. And so this was -- we were able to, then, have a big catch basin from patients who lived in that area, and they could drive a shorter period of time to our clinic in Paris rather than having to come all the way to Dallas.

Q. So when you were treating patients at Texas Retina in Dallas, in Paris, about how many patients did you see a day?

A. Right. So during that period of time I was very busy. I mean, clinics in retina practices can vary anywhere from 30, 40, 50 patients a day. In Paris, for example, there could be more because, obviously, we were there only once a week, and so our catch basin was pretty large. So we could be seeing up to 60 or 70 patients in a day at times.

Q. Of those patients you were seeing, up to 60 a day, about how many of them would you say were suffering from diseases like those at issue in this case, AMD, DME, DR?

A. So those are, obviously, the more common diseases we take care of, right? Those are the diseases that people notice vision change, come to our clinics for complaints. And so probably easily over a half to two-thirds of our patients have one of those forms of DM problems.

Q. At some point did you step back from Texas Retina and transition full time to Retina Foundation of the Southwest?

A. Yeah. In 2018 I made the decision that I really wanted to kind of, again, focus on trying to improve some of the aspects of our care that we were providing patients. And so I cut back from the busy clinics and saw patients at the retina foundation in smaller numbers but in a different kind of capacity.

Q. So if you look back on your career, Dr. Csaky, about how long would you say you've been focused on the care of patients with retinal disease?

A. 30 years, 31 years.

Q. Do you attend conferences or give talks relating to AMD, DME, and DR?

A. Yeah. So I've been very fortunate in that I'm part of most of the major what we call societies in retina. There's the Macula Society, the Retina Society, the American Society of Retina Specialists. There's also a more kind of prestigious Society called the American Ophthalmologic Society. So I attend many, many of those meetings.

I'm also involved in lots of committees. So we have very specialized meetings with a small group of individuals that we tend to be -- it's considered the thought leaders. And so we sit around, and we'll have discussions about what our present treatments are for things like diabetic retinopathy, diabetic macular edema. I'm on what's called the classification of AMD committee.

So there's lots of these committees that I end up partaking. And so it's kind of the -- an involvement in the community, and I hear a lot from my fellow colleagues about their thoughts and ideas.

Q. So do you teach other doctors how to treat retinal diseases?

A. Right. I've taught fellows, in fact, two of the fellows still. The Texas Retina Associates are essentially down the hall from me; so we interact a lot. I continue to interact closely with them, and these are fellows that I've trained there. I also train residents.

I also, like I said, go -- I get invited into communities. I was in El Paso three weeks ago or Waco. And I go, and I have discussions with the local docs there, and we -- they get my input or insight, and we talk about how to manage different kinds of cases.

Q. Have you published any papers on retinal diseases?

A. Yes.

Q. Do any of those papers relate to AMD, DME, and DR?

A. Yeah. I would say I published probably over 140. I would say at least a half to more than a half in some capacity related to those diseases.

Q. And then have you participated in the design or evaluation of any clinical trials related to angiogenic eye disorders, retinal diseases?

A. Yes. I've been very fortunate. When I was at the NIH as a government employee, I was able to work closely with the Food and Drug Administration and worked with them on designs and aspects of clinical trials, end points, how to get drugs approved.

I've been involved with lots of clinical trials. I have run clinical trials. I've helped organize clinical trials. And, obviously, right now I'm very much active in clinical trials as well.

Q. Okay. On that note, Dr. Csaky, I'm going to put up what has been marked as DTX 7053.

Dr. Csaky, do you recognize this document?

A. Yes.

Q. What is it?

A. It's my curriculum vitae.

Q. Does your CV provide more detail about your education, your experience, your publications, and your qualifications?

A. Yes.

MS. KAYALI: Your Honor, at this point we offer Dr. Csaky as an expert in ophthalmology with a specialty in angiogenic retinal diseases and their treatment.

THE COURT: Any voir dire or objection to the motion?

MS. LESKO: No objection.

THE COURT: Without objection then, motion granted.

The doctor is so deemed qualified.

MS. KAYALI: Thank you, Your Honor.

BY MS. KAYALI:

Q. Dr. Csaky, we've just taken some time to explain your experience treating AMD, DME, and DR. I want to switch gears and talk about the diseases themselves for a little bit.

Have you assisted in the preparation of a set of demonstratives or slides so that you can illustrate your testimony?

A. Yes, I have.

Q. Let's bring those up.

And do you recognize the slide deck? Is this your slide deck?

A. Yes, I do. Yes.

Q. That's good. So let's take a look at what you're showing here on PDX 4-2.

MS. KAYALI: I recognize this is in two dimensions. So with Your Honor's permission, I'd like to bring up a model of the eye to Dr. Csaky, which, of course, counsel has seen. And this is marked as PDX 4064.

THE COURT: You may. I was wondering what that was.

MS. KAYALI: It does catch the eye. No pun.

THE COURT: I'll note for the record, I know it's only day two, but all this talk about the eyes causing contact lens irritants on the bench. When I start wearing my glasses

later this week and next, you'll know why.

MS. KAYALI: Now I know why. Go right ahead, counsel.

THE WITNESS: Without making too many people nervous, we'll then talk about this is a -- basically a cross-sectional diagram of the eye. Again, the light comes in through the pupil here and then gets focused onto the back of the eye.

The critical structures that I think we need to talk about, of course, obviously, is the retina, and we'll see that better in this kind of three-dimensional model, but it goes all the way to -- almost to the front of the eye here.

And then the critical feature -- it's very interesting in retina that 90 percent of our vision is focused on the macula. So macula is a very dense group of cells, and it translates the light into electricity. But that macula is what gives us the ability to read, drive, see TV, to be able to see people. And so then this electrical signal then gets transmitted to the brain through the optic nerve.

And I'll just -- if I may, Your Honor, just so that you can see, the retina really extends -- so all the way to the front like this.

And the inside of this is the jelly, the vitreous. So this is -- it's a substance, and then, of course, there's this inner limiting membrane that goes all the way and separates the vitreous from the retina.

BY MS. KAYALI:

Q. Well, Dr. Csaky, is this a healthy eye or a diseased eye?

A. So this is a cross section of a healthy eye.

Q. Well, then, let's turn to the next slide, DDX 4-3.

What happens in an eye that has angiogenic eye disorders?

A. So one of the typical aspects of angiogenic eye disorders is -- we heard it yesterday briefly -- there's this protein called vascular endothelial growth factor, called the VEGF for short; and for reasons that we still don't fully understand, these tissues that are affected by these various diseases start to express VEGF in abundance, and so the VEGF levels in the eye go up.

The consequences of VEGF really come down to two major consequences of note. One is the abnormal growth of blood vessels, normal blood vessels in the eye. VEGF actually causes these blood vessels to try to grow abnormally. These are abnormal blood vessels. They can grow on the retina, and we call that diabetic retinopathy in various stages. They can also grow in some cases under the macula as well, so abnormal blood vessel growth.

And then the third kind of aspect of VEGF is the idea that it can cause swelling of the tissue, especially if that swelling occurs in the macula.

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So that's -- those are the three aspects that VEGF can cause.

Q. I just want to pause for one second on what I think is an important point today. Is a lot of VEGF in the retina a good thing or a bad thing?

A. That's a bad thing. So there's, as you heard yesterday, very small normal amounts; but as those levels start to go up, then these bad things start to happen inside the eye.

THE COURT: Counsel, if I could interrupt.

We talked a lot about VEGF. What is VEGF made of? Or is that just the condition?

THE WITNESS: No. VEGF is a protein.

THE COURT: It's a protein.

THE WITNESS: It's a protein, and it's made by various cells in the retina. Okay? And what happens is, when the tissue is affected, let's say in diabetes, it's because it's not getting its abnormal glucose; or in macular degeneration -- we don't know why -- there's some inflammatory, and that causes the tissue to respond and start making too much VEGF. So it's a protein that's made by these cells.

THE COURT: So it's a naturally occurring substance inside the eye, but these various conditions, whether it's folks suffering from diabetes, as you mentioned, whatever causes the age-related condition, it's an overproduction of that protein?

THE WITNESS: Absolutely.

THE COURT: Thank you very much. Understood.

Sorry, Counsel. Go ahead.

MS. KAYALI: No. Please.

BY MS. KAYALI:

Q. So you mentioned, I think you just explained, some of the causes of these disorders, the overproduction of VEGF, and then the kinds of harms that can cause to the eye.

Are the results of too much VEGF in the eye the same or different for all the diseases we're going to talk about?

A. So they're different. And so each disease, they will talk about the consequence of that elevated VEGF level is different in terms of what we see in patients' eyes. So they are disease-specific.

Q. Then let's walk through those and start with wet AMD.

What happens to people's eyes in wet AMD specifically?

A. Right. So just as the term is, wet age-related macular degeneration, all of the activity is in the macula, right? And the macula, again, is this critical part of the eye that allows us to see.

And in this macular degeneration, the VEGF levels cause abnormal blood vessels to grow under the retina, and that also then causes bleeding, swelling, in the overlying tissue.

Q. How does wet AMD -- and we're looking now at

PDX 4.005. How does wet AMD affect patients' vision?

A. Again, when that macula is affected, then it can't work as well. When it can't work as well, then one of the symptoms is you just can't focus. So unlike here where you see a nice focused image, someone who has macular degeneration wet, this now becomes a blurry.

Q. Does it get blurry in the center of the peripheral vision?

A. Mostly in the center. Again, this is involving that center -- what we call center vision.

Q. Dr. Csaky, turning to PDX 4006, are there other facts of AMD on vision?

A. Yes. So especially with wet AMD, as these blood vessels grow under the retina, the retina becomes distorted, right? And so the patient then perceives the vision as distortion. So unlike here where there's -- these are nice and straight pillars, here you can see they're wavy. And that's one of the symptoms of macular degeneration -- wet macular degeneration.

Q. Finally, looking at PDX 4.7, is there a third AMD symptom?

A. Yes. And so what happens is, if those blood vessels are allowed to continue to develop, they will start to cause the tissue itself to stop working. When they stop working, then you're left with areas where the cells don't work and you

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start to see dark spot in your vision.

Q. How does that affect patients' ability to get around in the world?

A. Yeah. So this is the problem. If you have these dark spot right in the center where you need to drive, see vision, read, see TV, in older people, seeing your grandkids, all of a sudden now you see a big black spot. And so essentially that can be very debilitating.

Q. How common is wet AMD?

A. So it's estimated to be somewhere around a million people. There's other forms of macular degeneration, but this form is close to a million. Of course, as we're living longer, and as you see, it's age-related; so the prevalence is going up.

Q. What happens if this doesn't get treated?

A. So if it doesn't get treated, this dark spot gets darker and in some cases a little bit bigger. And so now you've got a permanent dark spot right in the center. And so that results in legal blindness, which means the only letter you can see on the chart is the big E. The peripheral vision is unaffected; so they can still ambulate. But it's a devastating disease because you're retired, you're ready to go play golf, and you can't see right in the center. So it's a truly debilitating disease.

Q. Well, on that happy note, then, let's turn to the

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second of the three diseases we're going to discuss, diabetic retinopathy. Could you explain what happens in the eye with diabetic retinopathy.

A. Correct. So here -- again, we're talking about a different disease. It occurs in a different age population for the most part. These are younger patients who have diabetes.

And what happens here is, again, for reasons unknown, they produce, again, VEGF. And the response is the retina, the normal retinal tissue, the normal retinal blood vessels, become affected. They start forming these little outpouching or microaneurysms. They can bleed. And then eventually, the most devastating, is these little blood vessels again will start to grow on the surface.

They don't do anything, but they're in response to this injury and driven by VEGF. So you now have these blood vessels on the surface of the retina. You can imagine now -- I'll use this model one more time to see it. These will be growing right on the surface all along the surface of the retina like this.

Okay?

Q. So what effect does that have on patients' vision?

A. Well, initially what happens is that these little abnormal blood vessels can bleed. And as they bleed, they bleed into the jelly. Jelly is a jelly. And so these little blood vessels will float around. People will notice kind of

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dark spots in their vision initially as one of the early signs that there's already blood vessels that are starting to bleed.

Q. Can patients also get blurry vision with DR?

A. Correct. So in some cases, they can. But for the most part, the devastating thing about diabetic retinopathy is, in some cases, the central vision is not affected. And so people can be walking around thinking everything's fine. Then they'll notice a couple little dark spots and little floating spots in their vision. And they don't make a big deal about it. So it's a little bit of a tricky issue trying to make sure we get good screening on patients, because their center visions may still be okay.

Q. What happens if this doesn't get treated, if DR goes untreated?

A. So this is by far the most devastating disease we have from a blindness perspective because these abnormal blood vessels, they grow on the surface. They start to form scar tissue. That scar tissue contracts. And eventually that retina becomes detached off the back of the eye. And as that retina becomes detached, there essentially is no function of the retina. And in many cases these are patients who will go totally blind, like, they can't see light. Unlike macular degeneration patients, these are by far the most devastating untreated complications we see in the clinic.

Q. How common is that, Dr. Csaky?

A. So, again, diabetic retinopathy is still roughly around, if you look, about a million people. Again, with the growing prevalence of diabetes, we know that it's a growing epidemic, and so the likelihood, especially in areas that have poor treatment and poor service, these prevalences are going to go up.

Q. Well, then, let's turn to the third and final disease we'll be talking about today. That's diabetic macular edema. Could you explain to the Court what happens to a patient's eye when they have DME.

A. Sure. So here, for whatever reason, again, these are kind of unique features of these diseases. In this case, the VEGF causes the tissue in the back of the eye, the macula, to start swelling. So as you start swelling, the tissue gets thickened. And so in this case the normal little capillaries that are there start to become abnormal, as I said, leak fluid, in some cases, leak a little bit of blood as well.

Q. How does DME affect patient vision?

I should say for the record we're on PDX 411.

A. Right. So it's very similar to macular degeneration albeit a little bit slower. So it doesn't progress quite as quickly as macular degeneration. But, again, the same thing happens. Your macula is the -- I always tell -- it's the Malibu real estate of your retina. You got to keep that intact. And in this case of diabetic macular edema, if that's

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affected, vision gets blurry. And, again, untreated, those cells become dysfunctional.

Q. How common is DME?

A. Again, we think it's somewhere in the order of one to two million people will have some form of diabetic macular edema in this country.

Q. Dr. Csaky, can AMD, DR, and DME all be treated using Eylea?

A. Yes.

Q. How does Eylea work?

A. So Eylea is -- as you heard partially yesterday, the way it works is essentially it's designed to kind of seek out and bind to this VEGF molecule and wrap around it. So it's designed specifically to seek out this protein of VEGF and bind to it.

Q. And when Eylea binds to VEGF, can VEGF still make bad things happen in the eye?

A. Yeah, no. So once you have this bound Eylea VEGF complex, it inactivates that VEGF already.

Q. How is Eylea administered?

A. So we give, you know, Eylea through an intravitreal injection. So there's an area right here in the front part of the eye where you can place a needle. You don't violate the retina. And you can place a needle through this area right into the jelly portion of the eye.

MS. KAYALI: Your Honor, I'm sorry for what's coming next.

THE COURT: I've been bracing. Go ahead.

MS. KAYALI: Let's pull up PTX 963. We're going to look at page 1. It's not going to be too bad yet, but -- you know. Can we blow up the title and author so it's a little easier to see.

BY MS. KAYALI:

Q. What is PTX 0963, Dr. Csaky?

A. Right. So this is a review article that describes an approach for doing these types of injections inside the vitreous.

Q. And now let's blow up the upper right corner of the document and take a look at the images of intravitreal injections.

Apologies to the squeamish among us.

Dr. Csaky, using these images, can you walk us through the process of performing an intravitreal injection.

A. Right. So there are several steps that we routinely do when we're doing an intravitreal injection. The first is we want to clean the eye; so we have some kind of Betadine that we put on the lids.

The second step is we want to remove the eyelids away from the injection site; so we try to keep the injection site as clean as possible.

Then you'll see here in this we place either a pledget -- there's different ways to do the numbing portion, which, of course, is critical for the patient and to try to numb up this area as much as possible.

And then once that area is numbed, in this case, a little caliper is measured. As I said, there's a little area. It's about 3.5 to 4 millimeters from what we call the limbus or this portion of the eye. You make a little mark. And you know that that's a safe area to put your needle through. And then you push your needle through this numbed area into the eye, quickly inject, and remove.

Q. Dr. Csaky, looking at these images I do feel compelled to ask how do patients feel about the prospect of you sticking a needle in their eye?

THE COURT: That's an outstanding question.

THE WITNESS: I can tell you that, of the thousands of injections I've given, I don't think I've had anybody come in saying please, please, please, I want another injection. It's just not a -- this is not something that is on a number one list of things you want to do in your life. So it's not something that is a pleasant experience. No matter -- as much as I try to ensure that they have no discomfort, it is -- you can well imagine it's a problem.

BY MS. KAYALI:

Q. Do you ever have to help patients prepare to receive

these injections?

A. Oh, yeah. I mean, there are people that I've had to give Valium to beforehand. There are a handful of patients who will demand Valium before they come in for their injections. Even though this is their 20th injection, they -- I can't come in unless I have my Valium. So it's -- I can well imagine that it's not -- I don't think anybody would want to go looking forward to this, for sure.

Q. Well, then, let me ask a different question.

Why all these steps to the process?

A. Well, you have to remember that the eye is -- was not meant to be violated. The idea of putting a needle in somebody's eye is not something that the eye really wants us to do. And of course the inside of the eye is sterile, right? So as you're putting a needle into the eye, you want to be really careful that you don't inadvertently introduce bacteria inside the eye. So that's why it's so critical that we try to clean and prevent that from happening.

Q. And I want to turn back to your slide deck now. I'm looking at PDX 4.13. Actually, let's move ahead to 4.14. Excuse me.

Can you use this slide to explain some of the risks or burdens of intravitreal injections.

A. Right. So we can kind of divide it into two kind of buckets, right? The one bucket is the actual risk for the eye,

right? So of course this is what I just talked about, the risk of introducing a bacteria inside the eye. We call that endophthalmitis --

Q. And --

A. Sorry.

Q. I was just going to ask, Dr. Csaky. What happens if patients have infected eyes?

A. So this is infections inside the eye. That's probably the most devastating complication, bacteria inside the eye. In some cases, we can treat it. But in some cases, if it's a really virulent bacteria, you can end up losing the eye itself.

Q. Okay. What about -- what are some other risks?

A. So, again, the eye doesn't like having a needle stuck in it. And so it sometimes will respond with some inflammation. Sometimes just like in the process of binding the tissue, depending on how you inject, so the eye will cause -- have some nonbacterial inflammatory cells that will come into the eye as well.

THE COURT: I'm with the eye on this. I don't think I care for it either, but go ahead.

MS. KAYALI: You and me both, Your Honor.

BY MS. KAYALI:

Q. I see a third risk there, risk of retinal detachment. That also does not sound good. What is that?

A. So as you go in, you're pulling on the jelly. The jelly -- it's a liquid, but -- it's like a Jell-O. And so when you push in, you kind of tug on it. You can sometimes pull on the retina and cause a retinal detachment.

Q. Yikes. Okay. Well, then, let's turn to the second half of the slide here. Patient anxiety, I think the courtroom well understands. What about patient discomfort?

A. We talked about this, right. This is something that none of us want to do in terms of the patient. And so the patients, as you saw, have a lot of anxiety. And, really, it's a point of concern for them. Obviously, every time they come into the clinic and you have to tell them that they're -- you're going to do an injection, it's something that, no matter how many times I've done this, patients are still anxious about it.

Q. Does it hurt?

A. Again, you know, you try to numb it up as best as we can, but you -- you can just well imagine. It's just not something that you can go oh, yeah, it's no big deal. It's a big deal, right? And there's different approaches to kind of numb it up. You try to do it quickly. But there's still -- there's pressure. And just the thought itself, it's something that's not the most pleasant.

Q. Understood.

I see the last item on your slide is burden of travel

and office visit on patient and caregiver. Could you explain that.

A. Right. So this is something that I think we underestimate at some point, but I think it's one of the most critical features, right? And that is that many of these patients who are coming to see us -- again, they're coming to see us because they don't have good vision. They can't drive, right? Or if they're getting the injection, they can't drive home; so they're constantly needing someone to come with them, right, a caregiver, a family member. And imagine you're doing these on a frequent basis.

And so it really becomes an enormous burden on the patients, on the families. It's something that -- it's really in many ways underappreciated, because there are very few things in medicine that require us to constantly see patients. And in many cases it's for an indefinite period of time. I mean, there are patients I've been seeing for ten years.

And so it's a real problem when we talk about, you know, that burden, the patient, and on their caregivers on getting back. And, obviously, this is not something we can do in the home. We can't do it in the pharmacy. They have to come -- and that's one of the reasons that these satellites are so important.

As you can well imagine, if I live in a small town and I can only -- need to go 20 miles, that's easier. If I

have to come all the way to Clarksburg or Wheeling, it's going to be a much more challenging process for me.

Q. And you say you have to give them for an indefinite period of time. By that do you mean these diseases are long in duration?

A. Right. So it depends. There are some cases where we just -- we can control the disease, but we have to continue to give these injections on a continuous basis.

Q. Let's turn to the next slide. And that's 4.015.

What happens when Eylea is injected into the eye? I'll play the animation for you.

A. Right. So what happens is it's really in some ways quite elegant, right, because we know that this VEGF is the bad actor, right? We want to get its levels to come down, right? So we do this injection. And the VEGF is sitting there looking for VEGF molecules. And they bind them, right? So right away there's some degree of inactivity that occurs following an injection.

Q. And then do the Eylea and the bound VEGF depart the eye?

A. Right. So a portion -- during these initial phases, we can start to slowly reduce the VEGFs. And so they get bound. And then the VEGF and bound Eylea then get transported out of the eye. And so there again we've gotten rid of some of it. We've inactivated some of it. Some of the Eylea stays

around a little bit longer. So we're trying to figure out how to control that VEGF level.

THE COURT: Where do the bound VEGF and Eylea go?

THE WITNESS: We had a big argument about this. So it's interesting. They go --

THE COURT: Sounds like a good time, Doctor.

THE WITNESS: We had some good beers on that too. But, you know, the interesting thing is they go out both through the normal retina and also through what's called -- the normal flow -- the eye makes fluid, and it goes out through the trabecular meshwork. And so it kind of gets out through the iris and out around the pupil and then out of the eye. So there's a normal flow. The jelly, I kind of said, it has a static structure. And it is, but there's liquid that's made that's constantly circulating out of the eye. And that's where that complex goes out.

BY MS. KAYALI:

Q. So when the VEGF gets bound and when it exits the eye -- I'm going to ask this as simply as I can -- does the bad stuff go away?

A. Well, it begins to go away, right? So, again, as we're trying to control the disease, we're trying to control the VEGF levels, right? And so this relationship with reducing the VEGF levels and then getting the tissue to start to kind of quasinormalize is what we're attempting to do with our

treatments.

Q. And so the macular edema, the leaking blood and fluid, the abnormal blood vessel growth, when the bound VEGF departs, some of that resolves. Is that what you're saying?

A. Right. So it will take some time and it depends on the disease. It's not an immediate effect in some cases. As you start to lower the VEGF levels, the tissue will start to try to repair itself to some degree.

Q. Well, then, Doctor, let's talk about the dosing regimen for Eylea. And I'm looking at PDX 4.17. I think we may have covered this, but does one injection of Eylea solve the whole problem here?

A. No. So, again, we're dealing with VEGF in different locations inside the retina. In some cases, in the jelly, we've got a certain amount. And so it's not a one and done kind of process. We know extreme -- lots of experience that you have to again start to think about injecting the Eylea and then repeating it and repeating it, again, first slowly bring those levels of VEGF down, and allow the tissue to repair itself.

Q. Are you familiar, Doctor, with the concept of loading doses?

A. Yes. Yes.

Q. What is a loading dose? And you may want to use the slide to explain.

A. So in the clinic, we think -- a new patient comes into the clinic, right? New patient comes in. I make the diagnosis of whatever these angiogenic disorders. I then think, okay, so I'm going to have to give an initial injection. So that's what we see. And the loading means that we're trying to load up the eye with some Eylea and try to start to change the concentrations of VEGF.

So the idea is that I'm beginning to do the injections. That's my kind of initial loading dose. And then it will have some effect. And that'll be a process of, again, going from what's typically high levels of VEGF. These are patients coming in off the street. They've been walking around for weeks or months, and so I'm trying to now slowly reduce their VEGF levels.

Q. So how frequently do ophthalmologists administer Eylea during the loading dose phase?

A. So it's disease-dependent, right? Each disease has its own level of VEGF and its own ability to repair its tissue. So the amount of loading doses that you would give is disease-specific.

Q. So it sounds like you're saying the number of loading doses is disease-specific. How often do you give loading doses?

A. So we all -- I mean, it's very standard that we give loading doses every four weeks.

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Q. And is that what's being shown on PDX 4.19?

A. Correct. So we see at the bottom here that this was -- you know, the first time I saw a patient, I see them, make the diagnosis. I inject, let's say, in this case, Eylea, with a loading dose. And then I tell the patient, okay, let's see what happens. I'm going to have you come back in four weeks.

And at four weeks I'm going to administer another loading dose because I know from experience and from clinical trials that, again, depending on the disease, we're going to need multiple loading doses to bring those levels down and let the tissue start to repair itself.

Q. So is there an initial loading dose and then some secondary loading doses after that?

A. Correct. So the initial is always the first. And then you've got these secondary loading doses that occur afterwards.

Q. And then let's talk about the number of loading doses now. I think you mentioned this.

For age-related macular degeneration, how many loading doses of Eylea do ophthalmologists administer?

A. So we typically give -- we have usually the initial and two secondaries. So we have three loading doses. And part of that is because, as I said, in macular degeneration it's only the macula that's involved. And so the levels of VEGF

tend to be a little bit lower. So we can typically get away with using a fewer number of loading doses to kind of bring down that VEGF level and try the tissue to start to repair itself.

Q. And what about for DME?

A. For DME, it's different. So DME, we know from multiple studies that the levels of VEGF are higher. So you can imagine, if it's higher, I've got to give more to first reduce it, keep it reduced, and let that tissue repair itself.

Q. And that description, that's a 2023 perspective, right?

A. Correct.

Q. So are you familiar -- well, let me ask a better question.

What happens after secondary -- let me try that again.

What happens after the loading dose phase is complete?

A. So the -- after these loading doses, we know from research and also just from observation that these are in general -- and, again, we have to always remember that every patient is different, right? So these are all -- no patient is the same. But, in general, you know, you would say in the average macular degeneration patient, I give three of these doses. I can be pretty comfortable that I'm going to get as

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good a response that I can to the tissue repairing itself, right?

However, the Eylea -- and this is critical -- doesn't cure the disease; it's just curing what we would call a symptom, which is VEGF levels. So the patient still has macular degeneration. I tell patients I ain't curing anything; I'm just trying to control the disease. And so the patient is continuing to make VEGF, albeit now at a slower rate because I've controlled it at the beginning.

And so now I can wait eight weeks in some cases and say, okay, let's make sure that that repair that I -- I've achieved kind of can be maintained so that I can keep -- not only get your vision a little bit better in some cases but keep you at that stable level.

Q. And I think I heard you say you're going to maintain their vision. Do you call these maintenance doses?

A. Correct. You try to maintain the anatomy and the vision.

Q. And we're going to talk about this in some more detail in a moment, but how frequently does Eylea's label recommend that doctors administer maintenance doses?

A. Right. So the label recommends in both conditions that maintenance doses be given every eight weeks.

Q. Let me ask a different question, then. Why do you switch? Why do you transition from four weeks to eight weeks

instead of just going on administering every month?

A. Well, there's two reasons. Initially, when we were -- at the very beginning of anti-VEGF therapies, right, the thinking was that maybe we just give it every week -- I mean, every month forever, right? And, in fact, that was the original trials and those were the original recommendations of ranibizumab was to give every-four-week injections almost indefinitely.

And, of course, that is unattainable. Patients just can't come into the clinic. And so the thinking was that is there an alternative to try to reduce the number of injections and still be able to keep the tissue as healthy as possible, not let the VEGF levels get to a critical point where we have to start over from square zero? So that's really the key here is to find that interval. And it turned out that eight-week interval was kind of a sweet spot where we could keep the vision stable, the tissue relatively under good control, in these eight-week blocks.

Q. Let's take a look at Eylea's label.

Can we pull up PTX 917.

And, Dr. Csaky, do you recognize this document?

A. Yes.

Q. Is this the -- what is it?

A. This is the prescribing information and label for Eylea.

Q. And do you see in the bottom right-hand corner, what's the date on this label?

A. The date is August 2022.

Q. So in the August 2022 version -- let me withdraw that.

Let's take a look at what Eylea's label recommends for the treatment of AMD, DME, and DR, please. And I'm going to pull up -- this is still on page 1 of Exhibit 917.

Let's take AMD first, just to do one at a time. How does Eylea's label recommend that doctors administer Eylea for the treatment of AMD?

A. Right. So under "Dosage and Administration" it states that for neovascular AMD, the recommended dose for Eylea is 2 milligrams to be administered by these intravitreal injections every four weeks, or approximately 28 days, for the first three months; so three loading doses. And then we can switch to 2 milligrams with this intravitreal injection once every eight weeks. So that's for neovascular wet AMD.

Q. And then what about for DME and DR? How does Eylea's label recommend that doctors administer Eylea?

A. Right. So the label here is a little different. Again, we're still administering 2 milligrams or administering those 2 milligrams every four weeks, but in this case we're doing five injections, not three; and then it's recommended that you can then switch to an every-eight-week dosing

interval.

Q. So what's the difference between how Eylea's label recommends doctors administer Eylea for AMD versus for DME and DR?

A. Right. So the big difference, as we showed in the little cartoons up there, is the idea that you need more loading doses to reduce that VEGF level in diabetic retinopathy and diabetic macular edema. So you need to give five monthly injections at the beginning, again, to get that tissue resolved, try to get some repair. And that's the big difference -- three with macular degeneration; five with DR and diabetic macular edema.

Q. We're going to talk about this in a little more detail in very short order, but let me just ask at a high level. Do some doctors follow the instructions in Eylea's label for the treatment of AMD, DME, and DR?

A. Yes.

Q. How do you know?

A. Well, I mean, for one, I've done this, and this is not -- this is evidence-based approach and it's a recommended approach so we know that it works. I've also, again, in talking with my colleagues and discussing various approaches, this is an approach that clearly people use in some patients, in some conditions, both in diabetic macular edema, diabetic retinopathy, and for wet AMD.

Q. Let me ask a different question.

Do some doctors ever change the frequency of the maintenance doses in a way other than the label suggests?

A. Absolutely.

Q. And in what way?

A. So, again, over time we have still -- we're still kind of struggling with figuring out this idea of when you're getting to these maintenance phases, right, how best to control the tissue, control the VEGF, and trying to prevent or trying to keep -- having to keep doing injections.

And so there's been various approaches that people have used and especially in the maintenance phases to try to alter those intervals and see what is the best interval, meaning how far can you go or what can you change to keep the tissue as healthy as possible before it kind of regresses and yet, as you saw, not having to have the patients come back as frequently.

Q. We heard yesterday about prn, or pro re nata, dosing. Is that one option for maintenance phase?

A. Correct, that's one option.

Q. What does that mean?

A. So prn was really one of the first approaches that my good friend Phil Rosenfeld worked on, and the thinking was that we had a machine called OCT, optimal coherence tomography, and you could see if the tissue was swelling.

So this was especially true for wet AMD initially. And the idea was that, as these blood vessels would start to become active, you could start to see swelling of the tissue. And so you could use this OCT in the vision to say this patient needs an injection. Right?

So prn would mean having patients come back, you look at them, and then decide do I need to do an injection? I don't see any of these signs of activities. No. Come back.

So we would have patients come back, not every time you would inject, but you would see them frequently because you would have to see them frequently because that was the time when you would make the determination if they needed treatment or not.

Q. Let me make sure I understand. For prn a patient comes into the office, but you don't know yet whether you're going to inject them?

A. Correct.

Q. And then you make an assessment, and you, on the basis of that assessment, decide whether to inject them?

A. Correct. That's the typical beginning stages of a prn approach.

Q. Do people use that approach anymore?

A. You know, that fell out of favor for several reasons. One, is it really -- well, in some cases cut down the number of injections. People still had to come into the clinic. So

while the injections are terrible, no doubt, coming into the clinic is also equally as challenging. And so it became challenging to figure out do I want to let Ms. Smith have to come in every four weeks or every five weeks? And so that was a problem.

The other problem was it was -- the treatment paradigm was driven by reactivation of the disease. So unlike a normal maintenance that we just talked about where we try to keep everything at bay, here we're allowing the tissue to kind of -- the disease to kind of come back, then we inject, and then we go forward.

So it kind of fell out of favor. You know, there's some people who do use it in some circumstances, but for the most part, at least in wet AMD, the majority of my colleagues don't use this type of approach.

Q. And so notwithstanding the fact that some doctors use prn, and it sound likes some doctors extend the maintenance dose phasing beyond eight weeks, why do some doctors use Eylea on the fixed-dosing regimen the label prescribes?

A. Well, I think -- there are certain advantages to having a fixed dosing. Again, it's -- it depends. It's very -- one of the things that I think is important to understand is that all of our approaches are very disease-specific, patient-specific, location-specific. You know, it's a negotiation in many cases between the patient,

their families, and the disease, right?

A good example is you have to remember that wet AMD typically will affect both eyes, right? So if a patient comes in, the first eye is affected and -- but the second eye still sees well, my approach for the first eye may be one that I want to give that patient a little bit more kind of regularity. I don't want them to come back and forth and come back and forth. So I might tell that patient, Look, let's just plan out, here's the strategy for this eye. We're going to give you this fixed-dosing schedule; we're going to give you these three -- in the case of wet AMD three loading doses; and then I'm going to see you every two months going forward.

So it's really kind of -- there's scenarios in which that kind of fixed-dosing approach has some benefits, again, very location-specific, patient-specific, disease-specific, eye-specific.

So there is -- and, of course, the other option, the other idea is that there's some of my colleagues who really want to be evidence-driven, and clearly they are -- the evidence around can you get the best vision for patients using this type of approach? There is evidence to suggest that's the case.

Q. When you say there's evidence to suggest that this type of approach gives the best vision, are you talking about the fixed-dosing regimen of the label?

A. Correct.

Q. Are there other drugs, drugs other than Eylea that can be used to treat AMD, DME, and DR?

A. Absolutely.

Q. Then why do doctors choose to use Eylea?

A. Well, I mean, again, these are all patient-specific, disease-specific, situation-specific. By far the most common drug we use now is Avastin. And the real reason we use Avastin is cost, right? Avastin is roughly about $150; injection fees, depending on the carrier, $75. So it's clearly a very cheap alternative for treating patients. And in most cases it's effective.

Now, the reason, for example, personally I choose in some cases Eylea is because there has been evidence, for example, diabetes, where in certain types of patients the outcomes with Eylea are better. A little bit better vision, a little bit better response. And there is a sense within the community -- and I've sat on many committees where, when we think about it from a community perspective, we all kind of believe that Eylea still is the best anti-VEGF agent out there.

Q. Dr. Csaky, let's shift gears slightly. What is Yesafili?

A. So my understanding is Yesafili is a biosimilar for Eylea.

Q. Do you know whether Yesafili has been approved yet by

the FDA?

A. I've been informed that it has not been approved.

Q. So thinking back to the time you wrote your opening report in this case, what company was seeking approval for Yesafili?

A. That was Mylan.

Q. Are you aware that Mylan has now sold its biosimilar business to an India company called Biocon and that they have now joined the case?

A. Yes. I was informed that you-all -- you-all informed me that Mylan has sold and now Biocon will be marketing Yesafili.

Q. So do you understand that, if anyone sells Yesafili, it will be Mylan's successor in interest, Biocon?

A. Yes, that's what I've been told.

Q. In the course of forming your opinions regarding infringement in this case, did you review proposed labeling for Yesafili?

A. I did.

Q. Let's put up PTX 3097.

Dr. Csaky, is this the version of label you relied on in forming your opinions as set forth in your reports?

A. It is.

Q. How can you tell?

A. Well, the date, the date, again, is August 2022.

Q. And if we flip to the last page of the label -- that's page 26 -- is this a Mylan label or a Biocon one?

A. Clearly it says Mylan.

Q. In the last few days have you had an opportunity to review a new label from Biocon?

A. I have.

Q. Let's put that up. That's PTX 3338.

Is this the Biocon label you reviewed?

A. Yes. This appears to be, based off the word Biocon and the date, that this is the Biocon label.

Q. And so if we turn to the last page, can you see for sure whose label this is?

A. Yes. It says Biocon Biologics.

Q. Let's put the label you analyzed in your report on the left side of the screen. That's PTX 3097. And let's put the label that we just looked at, PTX 3338, Biocon label on the right side. And now can we pull out the dosing instructions for AMD, DME, and DR.

Dr. Csaky, based on your review, is there any difference between how the Mylan label you relied on in your report recommends that doctors use AMD, DME -- excuse me. Is there any difference between the dosing recommendations in the Mylan label you relied on as to how doctors should use Yesafili to treat AMD, DME, and DR versus how the new Biocon label recommends that doctors should use Yesafili to treat AMD, DME,

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and DR?

A. No, I didn't see any difference.

Q. Okay. Because you used the Mylan label when you formed your opinions for purposes of the report, we're going to proceed with that copy during your testimony, but I just want to be clear. Is there any difference between the Mylan label in your report and the new Biocon label that's at all relevant to your infringement analysis?

A. Not that I could find.

Q. Let's bring back up the demonstratives and take a look at PDX 425. Sorry. If we could go -- I apologize. Let's go back two slides to PDX 23.

Dr. Csaky, do you understand that Regeneron is asserting Claims 6 and 25 of the '572 patent and Claims 11 and 19 of the '601 patent at this trial?

A. Yes, that's what I've been told.

Q. Okay. And will you understand if I call those the asserted treatment claims?

A. Yes.

Q. In the course of performing your analysis in this case, were you asked to determine whether Mylan, or now Biocon, will induce infringement of each of the asserted treatment claims if Mylan or Biocon markets Yesafili?

A. Yes.

Q. We're about to walk through the bases for your

opinions in some rather painstaking detail, but let's start with the bottom line first.

In your opinion, if Mylan or its successor Biocon markets Yesafili, will Mylan or Biocon induce infringement of the asserted treatment claims?

A. Yes. My opinion was yes.

Q. Let's dig in. We're about to spend a lot of time talking about the proposed labeling for Yesafili. We've already looked at the Eylea label in some detail. I'd like to bring up Mylan's label for Yesafili and compare it to Eylea's label from Regeneron.

Can we bring up PTX 917 on the left and PTX 3097 on the right.

Dr. Csaky, on the left you've got the Eylea label, and on the right you've got the Mylan/Biocon label.

Do you understand that?

A. Yes.

Q. Is there any difference between how Regeneron recommends that doctors use Eylea to treat AMD, DME, and DR as compared with how the proposed labeling for Yesafili recommends that doctors use Yesafili to treat AMD, DME, and DR?

A. I did not see any difference.

Q. So we're going to come back to various portions of this slide once or twice throughout this examination, but I wanted to set the stage first.

So let's just dig in. Let's jump to Claim 6 of the '572 patent. If we could put PTX 3 up on the screen.

Dr. Csaky, do you recognize this document?

A. Yes.

Q. What is it?

A. It is a U.S. patent, for abbreviation, '572.

Q. And have you reviewed the '572 patent in total, in full, over the course of your work on this case?

A. I have.

Q. You've read the whole thing?

A. Yes.

Q. I want to focus on just one part of it for today. Let's turn to Claim 6. And this is on page 25 of the -- of Exhibit PTX 3.

What does Claim 6 require?

A. So Claim 6 basically, my understanding, requires two things. It requires that aflibercept be formulated as an isotonic solution and that it is -- it's, what I was taught, is a dependent claim, and it depends on Claim Number 3.

Q. And so because it's a dependent claim, do you understand that that means it incorporates all the limitations of some claims that come before it?

A. Yes.

Q. Let's pull those claims up on the screen. That's the first two claims of the '572 patent.

We're still looking at page 25 of PTX 3, and you see on the screen Claims 1, 2, 3, and 6. And I understand you said Claim 6, shown in purple at the bottom, references Claim 3.

Do you see that Claim 3 itself references Claim 2 which references Claim 1?

A. Yes.

Q. And do you understand that to mean that Claim 6, in fact, incorporates all the limitations of Claims 1, 2, 3, and 6?

A. Yes.

Q. Let's add your slide deck back up to the screen, and I think we're looking at PDX 424.

On PDX 424 have you tried to compile all the limitations of those claims into one list?

A. Right. I tried to redo it so it's rewritten in an independent form.

Q. Is it okay if I refer to language on PDX 24 as Claim 6 or Claim 6 independent form? Will you understand that this is what I'm talking about?

A. Yes.

Q. Let's take down the patent and just look at the claim for a second. And then I want to take a moment to explain to the Court the questions you're going to try and answer today in your testimony with respect to infringement. So if we progress to Slide 25. Let's turn to the first question.

What's the first question your testimony will answer today?

A. So in my process I was asked to -- I asked myself the first question, which is does Mylan, in this case Biocon's label encourage, recommend, or promote doctors to perform methods that infringe?

Q. And we're going to talk about that question now in the context of Claim 6 of the '572 patent.

So let's turn to PDX 426.

Is this the same language you had on the colorful slide before but now just in a checklist?

A. Yes.

Q. Before we get going, I noticed that one of the items in the checklist is crossed out. Could you explain why that is?

A. Well, I was informed that the Court had decided that that claim was nonlimiting and so could not be included in my analysis.

Q. So are you going to present any testimony about infringement of that particular limitation today?

A. No.

Q. Well, then, let's go back to the top. What is the first limitation you analyzed in order to attempt to determine whether Mylan or Biocon's label encourages, recommends, or promotes infringement?

A. The first limitation was the method of treating angiogenic eye disorder in a patient in need thereof.

Q. Let's add the Mylan Biocon label to the screen. That's PTX 3097. We're looking at the first page.

Dr. Csaky, does Mylan or Biocon's label recommend that doctors use Yesafili to perform a method of treating an angiogenic eye disorder in a patient in need thereof?

A. Yes.

Q. Where does it do that?

A. So it says specifically that Yesafili, the VEGF inhibitor, is indicated for the treatment of patients with these diseases. I'm not going to name them all, but all of these diseases are angiogenic eye disorders.

Q. And you say "all of these diseases." Are you referring to neovascular wet AMD, macular edema following retinal vein occlusion, diabetic macular edema, and diabetic retinopathy? Are each of those angiogenic eye disorders?

A. Yes.

Q. And does Yesafili's proposed labeling recommend doctors use Yesafili to treat each of those diseases?

A. Yes.

Q. Which of those four diseases are you going to be focusing your testimony on today?

A. So three of these is where I'll be really focusing: neovascular wet AMD, macular edema -- I mean, diabetic

macular edema, and diabetic retinopathy.

Q. For the next bit of your testimony, I want to ask you just to focus on the AMD indication. Okay?

A. Uh-huh.

Q. So let's take down PTX 3097 and go back -- actually, before we do that let me ask this.

Can we check off the box in Claim 6 for the first limitation that Mylan or Biocon recommends the first step of Claim 6?

A. Yes, that would be correct.

Q. Let's take down PTX 3097, and then let's keep moving.

What's the next limitation of Claim 6 that you analyzed to determine whether Mylan's label or Biocon's label recommends infringement?

A. So the next limitation is that the treatment, the method, comprises sequentially administering to the patient by intravitreal injection a single initial dose of 2 milligrams of aflibercept.

Q. Dr. Csaky, does the proposed Yesafili labeling encourage, recommend, or promote doctors to sequentially administer to the patient by intravitreal injection a single initial dose of 2 milligrams of aflibercept?

A. Yes.

Q. Let's bring back up the label. That's PTX 3097, and we're looking at page 1 and the "Dosage and Administration"

section for AMD. Excuse me. We're looking at page 2, and that's the "Dosage and Administration" section for AMD.

Where does Mylan or Biocon's label recommend that doctors sequentially administer to the patient by intravitreal injection a single initial dose of 2 milligrams of aflibercept?

A. Right. So under the, again, "Dosage and Administration," it says the recommended dose for Yesafili, 2 milligrams, to be administered intravitreal injection every four weeks, monthly.

Q. Okay. And you said every four weeks, monthly. Are any of those monthly doses a single initial dose?

A. Yes.

Q. Which one?

A. Well, it's the first -- first one would be the initial dose.

Q. Fair enough.

We're going to move to the next requirement of Claim 6 here in just a second, but before we do I want to talk about a few issues that I think we're going to see over and over again, and I want to see if we can clear the air on those first to streamline things.

The patent claims on the right, they refer to administering aflibercept. Do you see that?

A. Yes.

Q. Yesafili's label on the left -- that's PTX 3097 --

refers to administering Yesafili. Do you see that?

A. Yes.

Q. What is the active ingredient in Yesafili?

A. Aflibercept.

Q. So whenever PTX 3097 recommends administration of Yesafili, is it recommending the use of aflibercept?

A. Yes.

Q. The patent claims also all require that the doses of aflibercept be 2 milligram doses.

Do you see that?

A. Yes.

Q. And that will appear in the other claims we look at, right?

A. Yes.

Q. Turning back to the "Dosage and Administration" section we looked at earlier -- that's again PTX 3097, page 2 -- what dose of aflibercept does Yesafili's label recommend that doctors administer?

A. 2 milligrams.

Q. I know we're only looking at AMD on the screen right now, but have you reviewed PTX 3097 -- that's the proposed labeling -- in full?

A. Yes.

Q. Is there any dose referred to in PTX 3097 that is not a 2-milligram dose?

A. Not that I could find.

Q. Okay. So whenever PTX 3097 recommends administration of Yesafili, is it recommending the use of 2 milligrams of aflibercept?

A. Yes.

Q. All right. Last but not least, the claims are all going to require intravitreal administration, I think an image that is now burned into our brains.

How does Mylan or Biocon recommend administering aflibercept in PTX 3097?

A. Through intravitreal injection.

Q. Again, any kind of administration other than intravitreal administration that's described at all in this label?

A. Not that I could find.

Q. For shorthand, whenever PTX 3097 recommends administering Yesafili, is it, in fact, recommending that doctors administer a 2-milligram intravitreal dose of aflibercept?

A. Yes.

Q. All right. Then let's keep cruising here. You can take down PTX 3097 for a moment and turn back to your slides.

Can we check off this box that Yesafili's label recommends sequentially administering to the patient by intravitreal injection a single initial dose of 2 milligrams of

aflibercept?

A. Yes.

Q. All right. Then let's turn to the next set of limitations, and I see you've highlighted two.

What are the next limitations of Claim 6 that you'll address?

A. So the next limitations are these idea of secondary doses. And the claims are that there should be one or more secondary doses of 2 milligrams of aflibercept and that each of these secondary doses be administered approximately four weeks following the immediate preceding dose.

Q. Let's bring back up PTX 3097, still looking at page 2.

Does Mylan or Biocon's labels recommend that doctors administer -- excuse me -- does Mylan or Biocon's label recommend that doctors follow the initial dose with one or more secondary doses of 2 milligrams of aflibercept wherein each secondary dose is administered approximately four weeks following the immediately preceding dose?

A. Yes.

Q. Where?

A. So, again, it says under "Dosage and Administration," the recommended dose of Yesafili is 2 milligrams to be administered every four weeks for the first 12 weeks or three months.

Q. And of those first three injections, which, if any, of those correspond to the secondary doses of the claim language?

A. So the secondary doses in this case would be the second and third injections.

Q. Those are the ones after the initial one?

A. Correct.

Q. Does PTX 3097 recommend that doctors administer those secondary doses approximately four weeks following the immediately preceding dose?

A. Yes.

Q. Where does it do that?

A. It says right here that these injections should be administered every four weeks, approximately every 28 days or monthly.

Q. So then let's turn back to your slides. We're looking at PDX 4028.

Dr. Csaky, can we check off these boxes? Does the label recommend -- excuse me -- does PTX 3097 recommend both of these steps of the method of Claim 6?

A. Yes.

Q. All right. What's next? What's the next limitation of Claim 6 you analyzed?

A. So the next are the "followed by one or more tertiary doses of 2 milligrams of aflibercept," and this too has another

limitation in that each tertiary dose be administered approximately eight weeks following the immediate preceding dose.

Q. Okay. After recommending the initial and secondary doses we just looked at, does PTX 3097 encourage, recommend, or promote that doctors administer one or more tertiary doses of 2 milligrams aflibercept wherein each tertiary dose is administered approximately eight weeks following the immediately preceding dose?

A. Yes.

Q. Let's pull back up the label. That's PTX 3097.

Dr. Csaky, where is that recommendation?

A. So, again, it states here under "Dosage and Administration" that, after the initial doses, they should be followed by 2 milligrams of the intravitreal injection once every eight weeks or two months.

Q. And just in the language of the claims, which of those 2-milligram intravitreal injections once every eight weeks or two months are the tertiary doses of the claim?

A. All of them.

Q. Any of them that are administered?

A. Any of them that are administered would be considered tertiary doses.

Q. And, again, does the label explicitly recommend administering tertiary doses once every eight weeks?

A. Yes.
Q. Where is that?
A. Again, it says to be -- injection once every eight weeks under the dosage and administration label.
Q. All right. So turning to Slide 29, that's PDX 429, can we check off these boxes? Does Mylan/Biocon's label recommend that doctors perform the tertiary dose steps of Claim 6?
A. Yes.
Q. All right. Looking at PDX 430, we've now made it to the crossed-out limitation. Can we skip this one for purposes of your analysis?
A. Yes, I did.
Q. Then let's turn to Slide PDX 431. What's the last limitation of Claim 6, Dr. Csaky?
A. It says, "wherein the aflibercept is formulated as an isotonic solution."
Q. Dr. Csaky, did you evaluate whether the Yesafili aflibercept that Mylan's label recommends doctors administer is formulated as an isotonic solution?
A. I did not.
Q. Why not?
A. I'm not a formulation expert.
Q. Do you know if anyone did address that limitation?
A. I've been informed that Dr. Trout performed that

analysis.

Q. And just to set expectations, Dr. Trout will testify as to infringement shortly. I expect him to address that limitation. And so with that in mind, Dr. Csaky, let's turn to the next slide, PDX 432. And I just want to ask you, for the rest of your testimony about Claim 6, I need you to assume that Dr. Trout will testify that the aflibercept recommended by Mylan Biocon's label to be administered is formulated in an isotonic solution.

Do you understand that?

A. Yes.

THE COURT: While those boxes are checked, Counsel, would it be a good time to take our morning break?

MS. KAYALI: Absolutely, Your Honor.

THE COURT: We'll do that, then. We'll take 15 minutes. If everybody could be ready to resume at ten after 11:00, we'll resume the doctor's testimony.

Sir, you can take a break if you'd like, and you can step down. I'll give you the same speech. I recognize you're an expert; but for purity of our circumstances, yes, the same speech you heard me give Dr. Yancopoulos yesterday applies to you. You're a man without a country. No one's being rude or discourteous, but they're not allowed to talk you midstream. So we'll go with that.

Otherwise, we'll see everyone here in 15 minutes.

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Thank you all.

(A recess was taken from 10:59 a.m. to 11:15 a.m.)

THE COURT: Counsel, you may proceed.

MS. KAYALI: Thank you, Your Honor.

BY MS. KAYALI:

Q. Dr. Csaky, we're going to hop right back to Slide 32 where we left off. But before I ask the next question there, earlier in your testimony, I believe you testified that about 1 million patients suffer from AMD. Is that about 1 million in the United States?

A. Correct.

Q. And DME and DR, you also explained that those diseases are common. Are they common in the United States?

A. Correct.

Q. So then let's turn back to where we left off. We had just checked off all the boxes. Let me just ask this: Is there anything else in Claim 6 we need to look for in Mylan's label?

A. No.

Q. We got them all. That's all the limitations?

A. Correct.

Q. All right. So then let's go to the next slide. And I want to turn back to the question we started with. That's PDX 433.

In view of your testimony, in your opinion, does the Mylan Biocon label, PTX 3097, recommend that doctors perform every step of the method of Claim 6 to treat AMD using Yesafili?

A. Yes.

Q. Okay. In view of that, does the Mylan Biocon label recommend that doctors perform a method that infringes Claim 6?

A. Yes.

Q. Let's turn to the next slide, then, and ask -- let's focus now on Question Number 2. Okay?

And, actually, I should back myself up.

Before we focus on Question Number 2, I want to see if we can do something to help us move just a little faster through the rest of this examination. We've been looking at page 2 of PTX 3097.

If we could bring that back up, please. And if we could call out the -- there you go, Section 2.2, the dosing instructions for AMD.

Is there anywhere else other than this section on page 2, "Dosage and Administration," that communicates the same information about Mylan or Biocon's label recommends that doctors use Yesafili to treat AMD?

A. Not that I can see.

Q. Let's take a look at page 1 of the label. And page 1, are they what's called the "Highlights of the

Prescribing Information"?

A. Yes.

Q. Okay. Do the highlights of the prescribing information say the same thing about how doctors should administer Yesafili to treat AMD as the more -- the longer section on page 2 of the exhibit?

A. When I read these, they are identical.

Q. Okay. So, really, what I'm asking is, to avoid flipping back and forth, can we stick with the highlights of the prescribing information as we move forward?

A. That would be fine.

Q. It says the same thing as the more detailed stuff later?

A. Yes.

Q. All right. Now, let me ask while we have this up, I see three bullet points under -- on the left. This is PTX 3097, page 1, the dosage and administration section and the highlights of the prescribing information. I see three bullet points that look like they correspond to the three sentences in the full Section 2.2 dosage and administration on page 2.

Do you see that?

A. Yes.

Q. Which of those bullet points have you focused your testimony on today?

A. The first bullet point.

Q. Why did you do that?

A. I did that because that's the only place in reviewing this document that I could see that the term "recommended" was used.

Q. So how many recommended dosing regimens are there in Mylan or Biocon's label as to how doctors should administer Yesafili in order to treat AMD?

A. There's only one recommended way.

Q. Is that the one you've offered testimony on today?

A. That's the one I've offered testimony on.

Q. Now, let's look at this briefly, because we're going to get there, for diabetic macular edema and diabetic retinopathy too.

Are there also highlights of the prescribing information for diabetic macular edema and diabetic retinopathy?

A. On here all I'm seeing is neovascular wet AMD.

Q. Okay. If we go back to page 1 of PTX 3097, could we pull up the highlights of the prescribing information at the bottom for diabetic macular edema and diabetic retinopathy?

Will we also be referring to the highlights of prescribing information -- let me ask a better question.

Do the highlights of the prescribing information also instruct doctors about how to use Yesafili to treat DME and DR?

A. Yes.

Q. And we're going to come back to that in a minute. I just wanted to sort of establish where we're headed next.

Let's go back. Let's go back to PDX 4/34 and turn back to Question Number 2. We're in a world where you just answered yes to Question Number 1, and now we're asking ourselves -- you're asking yourself -- will any doctor perform infringing methods as a result of Mylan or Biocon marketing Yesafili using the proposed labeling we've just looked at?

And so I want to get into the nitty-gritty of your answer in just a second, but let's answer that at a high level first.

In your opinion, if Mylan or Biocon sell Yesafili with the proposed labeling we've just looked at, will doctors perform the method of Claim 6 and infringe Claim 6 as a result?

A. Yes.

Q. Okay. I want to talk a lot more about how and why you know that. Let's ask some prefatory questions first.

Do ophthalmologists like yourself read labels?

A. Yes.

Q. Why?

A. Well, there's several reasons. Especially when a drug comes onto the market, it gives us a good synopsis of the important information of that drug, right? It tends to be a synopsis of the data that supported its approval. So there typically is a recommended usage that we now can be understood

should be an approach that we should consider. It outlines again some of the issues, contraindications, reasons why you would not want to use it, what to look for.

Other reasons -- for example, we have continuing medical education lectures, right? And those typically require that, if you're going to give a lecture on a drug, that you give it on-label, which means that, as you're talking about the aspects of the drug, that you're talking about it per the label. So that's typically either a requirement or that you have to notify the audience that you're going to be going off-label.

And then of course in many cases sometimes insurance carriers, they utilize the label for reimbursement purposes, and so it's something you have to be aware of. So it's something that all of us from time to time will be either exposed to, read, or understand what's in the label.

Q. Well, does what the label say influence the way that ophthalmologists use ophthalmic drugs?

A. Of course.

Q. Why?

A. Well, because, again, I mean, we have to understand that there's several reasons that we'd want to look -- you know, as we look at a label, these are the guideposts, right? These are the instructions. And for many people, these are kind of a good way to start. They're going to say, okay,

here's how the agencies like the Food and Drug Administration, who has approved the drug, is -- has recommended that it be used. So, again, it gives us a starting point for how do we utilize the drug.

So, again, there's lots of reasons to begin to review that, especially with a new drug as it comes out, that's something that we'll be exposed to and read.

Q. So in view of that, Mylan or Biocon sells Yesafili with a label that recommends that doctors infringe Claim 6. Will some doctors actually do what that label says and use Yesafili according to the method of Claim 6?

A. Some doctors will in some patients.

Q. So I want to break things down a little bit because you're offering testimony about Yesafili, and I think we've established that drug's not on the market yet, right?

A. Yes.

Q. So how is it that you can form an opinion about how ophthalmologists will use Yesafili even though it hasn't been sold yet?

A. Well, in forming my opinion I looked at how people use Eylea. And I reviewed the Eylea label and I asked myself is there any doctor with any patient that follows the label of Eylea in order to make my decision.

Q. And if we bring back up PTX 917 on the left and PTX 3097 on the right, is there any difference between how

Regeneron recommends that doctors use Eylea and how Mylan or Biocon recommends that doctors use Yesafili?

A. Not that I can see.

Q. All right. In view of the fact that these labels make the same recommendations and in view of the fact that we just walked through your opinion that Mylan or Biocon's label encourages, recommends that doctors perform every method of claim -- excuse me -- every step of the method of Claim 6, does Eylea's label also recommend that doctors perform every step of the method of Claim 6?

A. Yes.

Q. Now, we touched on this at a high level before, but let's be a little more granular now. Do some doctors use Eylea in the way that Regeneron's label recommends?

A. Yes.

Q. How do you know?

A. Well, in doing my assessment, I kind of reviewed several aspects. One, of course, is thinking back on how I have used Eylea. And, again, as I said, there are certain circumstances with certain patients, certain situations, where I have followed the label for lots of reasons.

I've also -- when we sit on these committees and talk about various approaches, clearly there are lots of alternatives that people use, but there's still people who feel as if these label indications still in many cases they have

that comfort in knowing that this will give them good visual acuity in the patients that they want to treat.

So I used several kind of indicators of trying to determine our -- again, are there some doctors in some patients who will utilize this approach? And the conclusion I came to was yes.

Q. I want to take each of those reasons that you just offered in turn and dive in in a little more detail.

You said you have used Eylea in the way the label recommends in accordance with the method of Claim 6. When and why?

A. So, again, sometimes -- again, if you look -- I mean, the label basically suggests that, you know, I need to be giving three injections, which is again a very common approach for neovascular AMD. And then it instructs me to say, okay, wait eight weeks after that initial injection and do eight-weeks injections.

And, again, there's certain circumstances, especially when there is -- I think back specifically to times when, for example, patients had challenges with scheduling, right? They want to know exactly kind of what to expect. They want to be able to figure out, Dr. Csaky, tell me exactly when I'm going to be coming in. I can give them some guideposts and metrics using this kind of approach.

So there again, it's lots of reasons to have this

wider range of treatment options for patients as you talk with them and you ask them questions about what specifically -- remember, this is a burdensome approach. And if somebody, especially in areas where they have trouble getting back and forth and they have to arrange certain trips, you know, having kind of a known schedule in certain circumstances can be really helpful for the patient. So, again, there have been some cases where I tried to and I have reviewed with the patient and I've used this approach.

Q. Are there particular circumstances that stand out?

A. Again, I think, you know, when I look back -- again, and this is typically in areas where getting to and from certain regions are challenging -- like, again, sometimes in these rural communities, it can be very challenging. If I'm there once a week and I don't have the luxury of being there often, it's nice to have that comfort to know the patients are coming back and forth.

Also sometimes when I'm sharing a clinic with -- in this case in one of my satellite clinics, we can easily share patients because we kind of know what the schedules are going to be like. So, again, there's certain circumstances in which this type of approach can have some benefits.

Q. And this type of approach, that's the fixed-dosing approach that's recommended by Eylea's label and covered by Claim 6?

A. Correct. So this is a -- an approach where, again, if you look at this label, it suggests that you want to have that patient come in once every month for three months and then start extending it to eight weeks.

Q. Well, I understand that's your experience, Dr. Csaky. Is the retinal community such that you're familiar with how other doctors use Eylea?

A. Yeah. I mean, I have -- like I said, I'm involved in lots of committees, discussions. Even with some of my fellow colleagues at Texas Retina, we talk about various approaches that people use. So, again, this is -- it's part of our armamentarium. What we want is we want to have different approaches in our armamentarium that we can offer patients and try to meet some of their needs and what they can have in terms of their scheduling and things like that.

So that's really kind of a critical aspect to work with patients and fully appreciate what's the best for them in trying to get the best treatments.

Q. And just to be very clear, in your conversations that you mentioned with other doctors, have you become aware as to whether other doctors used the fixed-dosage regimen recommended by Eylea's label and covered by Claim 6?

A. Yeah, I've had certain -- like I said, discussions. And also I've seen certain documents where people have talked about using these kinds of approaches.

Q. Okay. During the course of preparing your opinion, did you come across a document reflecting how any particular doctor used the fixed-dosing approach?

A. Yes.

THE COURT: One second, Doctor.

Yes, Counsel?

MS. LESKO: Objection, Your Honor. I believe what -- the document that counsel's about to refer to is the declaration of Dr. Do, who was an expert on behalf of Regeneron in a separate proceeding. That is hearsay. It should not be admissible. If they wanted to introduce Dr. Do as an expert in this case, they could have done it.

THE COURT: Agreed, but, Counsel, go ahead.

MS. KAYALI: Your Honor, we don't intend to seek admission of this document. Under Rule 703, Dr. Csaky is permitted to rely on such things. And he only intends to testify as to what that declaration said and how he relied on it.

THE COURT: Understood. Assuming that foundation is laid, objection overruled; but we'll keep an eye on it.

MS. KAYALI: Thank you. So let's bring up -- well, I'm not sure if we got an answer to the last question; so let me just ask it again.

THE COURT: Yeah, let's repeat that question.

BY MS. KAYALI:

Q. In the course of your work on this case, did you come across a document reflecting how any particular doctor -- or whether any particular doctor uses a fixed-dosing regimen recommended by Eylea's label and covered by Claim 6?

A. Yes.

Q. And what document is that?

A. So this was a document that was -- there was some testimony by a good friend of mine, Dr. Diana Do, and I reviewed part of that in coming to my opinion about -- in this case.

Q. Okay. Well, let's bring up PTX 1527.

And, Dr. Csaky, is this the declaration of Diana Do you are referring to?

A. It is.

Q. And do you see highlighted above her name, "Inter Partes Review Number 202100881"? Do you see that, Dr. Csaky?

A. I do.

Q. Do you understand that this is a declaration Dr. Do submitted in a different litigation before the patent office about a different Regeneron patent?

A. Yes.

Q. And if we flip to the last page of the document, that's page 67, do you see that she signed this declaration under penalty of perjury?

A. Yes.

Q. Let's take a look at what she said. If we could go to paragraph 137. I believe that's on page 54.

What does Dr. Do say in her signed declaration about how doctors use Eylea to treat wet AMD?

A. Right. And, again, I want to make it clear that I know Diana very well, and I value -- I think she's a phenomenal doctor; so I really respect her opinion and her approach. And so that's why it was important for me when I used this document to come to my opinion.

And what she says here is that physicians, including herself, typically and frequently treat wet AMD in particular by administering one or more monthly doses subsequent to the initial dose. And she calls these out, secondary doses, approximately four weeks after the immediate preceding dose.

And then she goes on to say -- and, again, in the second paragraph, she talks about patients following these loading doses, she talks about physicians, including herself, and that typically and frequently follow the monthly loading doses by transitioning, like I have, from monthly or four-week visits to bimonthly or eight-week visits and injections.

Q. If -- we just walked through the steps of Claim 6. If a doctor uses Eylea in the way Dr. Do describes here, will that doctor perform the method of Claim 6 for the treatment of AMD?

A. Yes. That is my opinion.

Q. And just to be clear, this is what Dr. Do does and what she says other physicians do. Is this also something you do?

A. Yes.

Q. And I know that this document is going to surface again in our later discussions, but I want to again see if we can save a little time. And so I'm just going to ask does Dr. Do also describe using the method of Claim 6 for indications like DME and DR?

A. Yes. So she includes these other diseases. And when I formed my opinion on these other diseases like diabetic macular edema, DME, or diabetic retinopathy, she points out in both cases that she too uses this approach of these initial dose and secondary dosing and then transitions to these bimonthly or eight-week visits and injections.

MS. KAYALI: I think we can take that down.

BY MS. KAYALI:

Q. Dr. Csaky, in the course of forming your opinions, did you come across any other documents reflecting how physicians use Eylea according to the method of Claim 6?

A. I did.

Q. Let's pull up PTX 586.

What is this document, Dr. Csaky?

A. So this is a manuscript in the public domain

published in 2023 by Mark Gallivan. And what Mark did here was to review this database called the IRIS Registry.

Q. Well, if we turn to page 2 of Exhibit 586, Plaintiff's Exhibit 586, can you explain to the Court what the IRIS Registry is.

A. Yes. So the IRIS Registry is a database, very -- you know, a kind of interesting database that the American Academy of Ophthalmology started many years ago with the intent of collecting real-world data -- anonymized real-world data. Many of us have EHR, or electronic health records. And so the idea was an anonymized way you could upload some of that data to a central server and then have availability of that data to be studied and reviewed.

Q. The records in the IRIS Registry, are those records of patients that were treated in a clinical trial or records of patients that were treated in just normal clinical practice?

A. These are primarily just in normal clinical practice. So these are -- it's a voluntary registry and -- but it's been very successful, and people want to be able to upload so we can analyze what's happening in the real world.

Q. When the authors in Dr. Gallivan's papers -- so Dr. Gallivan and his colleagues -- reviewed the IRIS Registry for patients treated during their normal clinical practice, did they find any patients who received an initial dose of aflibercept, one or more secondary doses of aflibercept four

weeks after the preceding dose, and one or more tertiary doses of aflibercept eight weeks after the preceding dose?

A. Yes. And so the purpose of this study was really interesting. They wanted to -- we knew what the VIEW 1-VIEW 2 data -- clinical data showed. And so what the intent was to say, okay, those are clinical trial patients. Can we find patients in the real world that emulate those trial -- those approaches that we took?

And of course one of the approaches in the VIEW 1 and VIEW 2 was exactly what we're talking now, this approach where we give monthly dosing and then switch to every-eight-week dosing. So, indeed, they went through and they found a group of patients that fulfilled that criteria.

Q. And if we skip ahead in the document to page 6, let's pull up Table 5.

Dr. Csaky, how many patients in the IRIS Registry did Dr. Gallivan and his colleagues find that received, essentially, the method of Claim 6?

A. Right. So they went through -- and, of course, these registries, you have to remember, when you're trying to emulate a VIEW 1 or VIEW 2 trial data, there's lots of data that wasn't available, but what was available was in some cases the dosing schedule that these patients underwent. And in this case they were able to identify 154 patients who were following exactly the approach that was -- that we're discussing now, this

approach of giving, as it says right there, three initial monthly doses and then converting 2 milligrams every two months after that.

So these were a group of patients that they identified in the real world who were being treated this way.

Q. Just to be very clear, if doctors administered aflibercept 2 milligrams intravitreally every two months after three initial monthly doses, did those patients receive the method of Claim 6?

A. Yes.

Q. One last question, Dr. Csaky. Does the IRIS Registry contain data about every patient who's ever received Eylea?

A. No.

Q. So this is a sampling?

A. Yeah. So the IRIS Registry, again, it's a voluntary approach. It's a significant portion, but it clearly does not capture everybody who's being treated with Eylea in the real world.

Q. So let's turn back to your slides. Let's look at PDX 434.

Dr. Csaky, let's focus on the second question here on the slide. In view of everything we've just discussed -- in view of your own experience, your discussion with colleagues, Dr. Do's declaration, the Gallivan article -- can we answer Question 2?

A. Yes. I did answer Question 2.

Q. Well, then, what's the answer? What is your opinion as to whether, if Mylan or Biocon market Yesafili in accordance with the proposed labeling in PTX 3097, will some doctors follow the label's instructions and use Yesafili to treat AMD in a way that infringes Claim 6?

A. Yes.

Q. Any doubt in your mind about that?

A. No, no doubt.

Q. All right. Then let's turn to PDX 4.35. And I want to take a step back.

Having answered both these questions, that is in view of your opinion that Mylan or Biocon's label recommends that doctors perform a method that infringes Claim 6 and in view of your opinion that some doctors will, in fact, perform the method of Claim 6 as a result of the recommendations in the label, have you formed an opinion as to whether or not Mylan or Biocon will induce infringement of Claim 6 if they sell Yesafili?

A. Yes.

Q. And what is your opinion?

A. My opinion was that Mylan or Biocon will infringe Claim 6 by promoting Yesafili.

Q. At this point I have some good news, which is that we are done with Claim 6 for wet AMD.

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I also have some really good news, which is that we get to do it again.

We are going to now discuss Claim 6 in the context of DME and DR. And I promise we're going to do those far more quickly and that we're going to take them together, but I just want to set the stage.

So let's go back to the beginning of Claim 6. Can we please put up the Mylan -- excuse me. That would be Slide PDX 4.26. Thank you. Can we please bring back up the Mylan/Biocon label on the right. Let's focus on the "Indications and Usage" section for DME, and that's -- we're looking now at page 1 of PTX 3097.

Dr. Csaky, we're taking it from the top here. If Mylan or Biocon market Yesafili with the labeling that's PTX 3097, will Mylan or -- will that label recommend that doctors perform a method of treating an angiogenic eye disorder in a patient in need thereof in the context of DME and DR?

A. Yes. The answer is yes.

Q. How do you know?

A. So, again, under the "Indications and Usage," we see that Yesafili will be indicated for the treatment of patients with diabetic macular edema and diabetic retinopathy.

Q. And are both of those angiogenic eye disorders?

A. Yes.

Q. So excuse me. Looking back to PDX 4.26, can we check

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off the first limitation of Claim 6, understanding that Mylan and Biocon's label recommends doctors perform this step?

A. Yes.

Q. Right. We're going to be talking about both DME and DR at the same time for the next few questions. So I want to, again going back to the difference between the highlighting and the full label, see if we can move this along more quickly.

Let's pull up the full dosage and administration instructions for DME. That's on page 2 of 3097.

Dr. Csaky, how does Mylan or Biocon recommend that doctors use Yesafili for the treatment of DME?

A. Yes. Under "Dosage and Administration," it recommends that Yesafili be given 2 milligrams by intravitreal injection every four weeks, or approximately 28 days monthly, for the first five injections.

Q. And just like I asked for AMD, can we find this information in the highlights of the prescribing information as well?

A. Yes.

Q. Let's take a look at that on page 1.

Dr. Csaky, is there any difference in how the full dosage and administration section recommends that doctors use Yesafili to treat DME and how the highlights of the prescribing information recommend that doctors use Yesafili to treat DME?

A. No.

Q. Sorry. Let's turn to DR. Can we bring up the full dosage and administration instructions for DR on page 3 of PTX 3097.

Dr. Csaky, on the right we now have the highlights of the prescribing information under "Dosage and Administration" for DR. That's page 1 of 3097.

So do you see we have page 3 on the left and page 1 on the right?

A. Yes.

Q. Same question. First, how does Mylan/Biocon's label instruct doctors to administer Yesafili for the treatment of DR?

A. Again, it recommends that the treatment for DR be 2 milligrams intravitreal injection every four weeks for the first five injections.

Q. And comparing that to the highlights of the prescribing information on the right, is there any difference at all between recommended dose on page 3 and the recommended dose on page 1?

A. No.

Q. So we're going to use the highlights of the prescribing information moving forward since it's going to be a little faster, but do you have any problem with that?

A. No.

Q. One more question about the highlights of the

prescribing information here.

For both DME and DR -- and we're look at PTX 3097, page 1 -- how many bullet points are there under the highlights of prescribing information for DME and DR?

A. There's two bullet points.

Q. Which one of those are you going to focus your testimony on today?

A. My testimony is on the first one.

Q. Why?

A. Well, again, it's before this was -- this -- it states the recommended dose for Yesafili in this bullet point.

Q. How many recommended dosing regimens are there for the treatment of DME and DR using Yesafili and Yesafili's label?

A. Only one.

Q. And that's the first bullet point here, right?

A. Yes.

Q. Okay. With that background out of the way, let's go back to your slides and look at the next limitation of Claim 6 in the context of DME and DR.

Can we pull up PDX 427. Thank you.

Dr. Csaky, we just checked off the first box a minute ago. What's the next limitation of Claim 6?

A. So the next limitation is that it be administered by intravitreal injection with a single initial dose of

2 milligrams of aflibercept.

Q. Does the Mylan or Biocon label recommend that doctors administer an intravitreal injection of a single initial dose of 2 milligrams of aflibercept for the treatment of DME and the treatment of DR?

A. Yes.

Q. Let's bring back up page 1 of PTX 3097.

And, Dr. Csaky, can you show us where that recommendation is.

A. Yes. Right there it says under the dosage and administration, the recommended dose of Yesafili is 2 milligrams administered by intravitreal injection every four weeks for the first five injections.

Q. Same question as the last time around. Which of those intravitreal injections every four weeks for the first five injections -- try that again. Which of those first five injections is the single initial dose?

A. The first one.

Q. Fair enough.

Can we check off the box, then, that Mylan or Biocon recommends doctors perform the second step of Claim 6 in the context of DME and DR?

A. Yes.

Q. Let's turn to PDX 28, which we have up on the screen.

Dr. Csaky, what are the next two limitations you'll

address in the context of DME and DR?

A. Right. The next two limitations are that there be one or more secondary doses of 2 milligrams and that the secondary doses be administered every four weeks following the immediate preceding dose.

Q. Does PTX 3097, the proposed labeling for Yesafili, recommend doctors perform these steps when treating DME and DR using Yesafili?

A. Yes.

Q. Let's bring back up the label.

Looking at page 1, Dr. Csaky, familiar question, where do you see that recommendation?

A. Right. It says here again that the dose is 2 milligrams by intravitreal injections every four weeks for the first five injections.

Q. Which of those first five injections, Dr. Csaky, correspond to the one or more secondary doses of 2 milligrams aflibercept in the claims?

A. The last four injections.

Q. Does Mylan's label recommend that those four secondary doses be administered approximately four weeks following the immediately preceding dose?

A. Yes.

Q. Where does it recommend that?

A. It says specifically that they should be administered

every four weeks.

Q. Is that a recommendation both for the treatment of DME and DR?

A. Yes, for both.

Q. So turning back to Slide 28, can we check off the boxes that Mylan or Biocon's label recommends the secondary doses limitations of Claim 6 in the context of DME and DR?

A. Yes.

Q. Let's turn to Slide 429.

What's the next limitation of Claim 6, Dr. Csaky?

A. So the next limitation is two-part. It says that it should be followed by one or more tertiary doses of 2 milligrams and that these tertiary doses be administered every eight weeks.

Q. Let's bring back up the label. That's PTX 3097 at page 1.

Dr. Csaky, this proposed labeling for Yesafili recommends that doctors administer, after that initial dose and the secondary doses, one or more tertiary doses of 2 milligrams aflibercept wherein each tertiary dose is administered approximately eight weeks following the immediately preceding dose.

A. Yes. It says exactly that these injections should be -- after five injections should be followed by 2 milligrams every eight weeks.

Q. And, Dr. Csaky, I noticed when you turned to face your screen, sometimes your microphone slips away from your face. It might be helpful to Madam Court Reporter if we try to keep that in front of you.

So sorry. Let me just -- I want to make sure I heard the answer to that last question.

Does the label recommend one or more tertiary doses of 2 milligrams aflibercept wherein each tertiary dose is administered approximately eight weeks following the preceding one?

A. Yes.

Q. Can you point that out to us, please.

A. Yes. It says, again, right under the dosage and administration, it's 2 milligrams via intravitreal injection once every eight weeks.

Q. Is that for both the treatment of DME and DR?

A. Yes.

Q. Can we check off those boxes, then? Does the label recommend doctors perform both of the tertiary dose steps?

A. Yes.

Q. Turning to the next slide then, that's PTX 430, are we -- will you perform any analysis of this limitation in the new DME, DR context?

A. No.

Q. And why is that?

A. So again if -- again, I've been told that this is a nonlimiting claim, and so it was not included in my analysis.

Q. Just to be clear, when you say a "nonlimiting claim," do you mean a nonlimiting portion of Claim 6 -- limitation of Claim 6?

A. Right.

Q. Let's move on to PDX 4.31.

Is it the same story, Dr. Csaky, for aflibercept formulated in isotonic solution as we talked about in AMD?

A. Correct. I did not include that as I am not a formulation expert.

Q. Okay. So I'm going to ask you to make the same assumption I did last time, which is for the remainder of your testimony about Claim 6, please assume that Dr. Trout will testify that the aflibercept recommended to be used by Mylan/Biocon's label is formulated as an isotonic solution.

Can you make that assumption?

A. Yes.

Q. Let's turn to PDX 4.32.

What's left, Dr. Csaky? Anything else in Claim 6 we need to cover?

A. Nothing.

Q. Have you hit all the limitations?

A. Yes.

Q. Turning back to your questions, PDX 433.

In view of what we just reviewed in PTX 3097, does the proposed labeling for Yesafili recommend that doctors perform the method of Claim 6 for the treatment of DR and DME?

A. Yes. My opinion was yes.

Q. Let's turn to Question Number 2. We talked about it in the context of AMD already, about whether doctors will actually follow the recommendations in Yesafili's label in the event Yesafili is marketed.

Is your opinion the same for DME and DR?

A. Yes.

Q. And what was the answer to Question Number 2? Sorry.

A. The answer was yes, that there will be some doctors who will perform these methods.

Q. Does your opinion, again, relate to the way that doctors currently use Eylea?

A. Correct.

Q. Let's bring back up PTX 917 on the left and PTX 3097 on the right.

Dr. Csaky, does Regeneron recommend that doctors use Eylea to treat DME and DR in the same way that Mylan or Biocon recommends that doctors use Yesafili to treat DME and DR?

A. Yes. I see no difference.

Q. In view of that and in view of your testimony reviewing Mylan's label regarding -- excuse me. Let me try that again.

In view of your testimony that the Mylan or Biocon label recommends that doctors perform every method of Claim 6 for the treatment of DME and DR, is it also the case that Regeneron's label recommends doctors perform every step of the method of Claim 6 for DME and DR?

A. Yes.

Q. Let me ask again. Do doctors follow this label recommendation for treatment of DME and treatment of DR when they use Eylea?

A. Yes. As I said, you know, in certain circumstances, in certain patients, there are reasons that some doctors will use this approach for the treatment of diabetic macular edema and diabetic retinopathy.

Q. Have you personally used this method for the treatment of DME and DR?

A. Yes.

Q. Have you personally used the method of Claim 6 for the treatment of DME and DR?

A. Yes. I have tried -- I have treated patients with diabetic macular edema and diabetic retinopathy using an approach like this in some patients.

Q. And what are the circumstances that lead you to do that?

A. Well, you know, again, as we talked about at the very beginning, what's critical in diabetic macular edema is that

there's more VEGF that's usually present. And so, again, this idea that we want to give multiple injections more than we do for the neovascular AMD has been well-supported.

And so again, in certain cases where you really want to be able to communicate here's going to be our approach, it's very common to say we're going to try five injections at the very beginning, especially for someone with diabetic macular edema; and then, of course, if they respond well, then you want to start extending them to a longer period, like eight weeks.

In terms of diabetic retinopathy -- so again these are patients sometimes with both, and we know that, again, the alternative for diabetic retinopathy can be laser photocoagulation. It's a destructive procedure. And so for certain patients, they would prefer and my colleagues now are extending -- they're going more and more to using this type of approach for treating diabetic retinopathy in particular.

Q. So you said the alternative can be laser. How does that work?

A. So laser is a destructive procedure. It's basically a light, and you shine it into the eyes with patients with more advanced diabetic retinopathy. And it was shown 50 years ago that, if you destroy the retina -- surprising, but if you destroy the retina in the periphery, that causes some of that retinopathy to regress.

And while it's still in many ways a very effective

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treatment for a lot of patients, again, you want to be able to offer patients alternatives. And so this approach of using a proven way to regress the retinopathy by using this approach is becoming an attractive option for patients.

Q. And just to be very clear, Dr. Csaky, you have used the method of Claim 6 to treat patients with DME and DR?

A. Yes. So in the past I have treated patients who have DME and DR, and in using this approach, it's been very effective.

Q. And just referencing back to Dr. Do's declaration, did she also explain that she and others have used the method of Claim 6 to treat patients with DME and DR?

A. Yes. And so that was -- again, I know Dr. Do very well, and I respect her thoughts and opinions. And so I used that as well to kind of confirm in addition to, you know, other discussions with other doctors and hearing about what their approaches have been, it was just another step that I used to help confirm and form my opinion that, again, some doctors in certain patients under certain conditions will use this approach.

Q. And you mentioned conversations with other doctors.

Have you had a chance to understand how the retinal community uses Eylea to treat DME and DR?

A. Yeah. In certain situations I've been on, you know, committees where we actually had some very intense discussions

about the utility of Eylea, especially -- again, in the community, Eylea -- especially for diabetic macular edema and its adjoining entity, diabetic retinopathy, there's been some actual evidence that in certain severe cases, Eylea seems to have a better efficacy. And so there's a fair amount of, I think, thought in the community that Eylea, for these types of conditions, again, is the best anti-VEGF drug out there.

MS. LESKO: Objection, Your Honor. I've been trying to give some leeway, but these opinions are going very far afield of the opinions that are in his report. I think he has one sentence in his report about how the community or doctors would prescribe Eylea.

THE COURT: Understood. It's overruled. That opinion's been disclosed, and as we discussed earlier, Dr. Do's declaration and other information is information upon which this witness has relied in forming an expert opinion. Overruled.

MS. KAYALI: Thank you, Your Honor.

BY MS. KAYALI:

Q. So, Dr. Csaky, I think we've now covered your experience and we've covered your conversations with other doctors about their experience. We talked about Dr. Do's declaration.

I want to just briefly mention, we talked earlier about the Gallivan article, right? Is the Gallivan article

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limited to AMD?

A. Yes.

Q. Let's set that aside, then, and turn back to Question Number 2 on PDX 4034.

In view of your own personal experience, your conversations with colleagues, Dr. Do's declaration, what is your opinion as to whether some doctors will use Eylea in accordance -- excuse me. Try that again.

In view of your own personal experience, your own conversations with colleagues, and Dr. Do's declaration and the recommendations in the proposed Yesafili labeling, what is your conclusion as to whether some doctors will use Yesafili in accordance with its label to treat DME and DR and perform the method of Claim 6 if Yesafili is on the market?

A. Yeah. My conclusion that some doctors under certain circumstances will use these infringing methods was yes.

Q. Then let's turn to PDX 4.35. And, again, let's take a step back.

In view of your opinion that Mylan or Biocon's label recommends that doctors perform the method of Claim 6 to treat DME, DR and in view of your opinion that some doctors will, in fact, perform the method of Claim 6 in order to treat DME or DR as a result of those recommendations in the label, what is your opinion as to whether or not Mylan or Biocon will induce infringement of Claim 6 if they sell Yesafili?

A. My conclusion was that they will infringe on Claim 6.

Q. And I just want to be clear for the record. When you say "they will infringe on Claim 6," do you know that Mylan or Biocon will induce the infringement of Claim 6?

A. Yes. Yes, Mylan and Biocon will induce the infringement of Claim 6.

Q. Okay. We're really done with Claim 6 now.

We're going to move on to Claim 25 of the '572 patent. We're one down, three to go, but it gets faster from here.

Let's turn to page 25 of PTX 3.

Dr. Csaky, what does Claim 25 of the '572 patent require?

A. Yes. The 25 method is a method of Claim 15 -- so it's dependent on 15 -- wherein four secondary doses are administered to the patient.

Q. And let's bring back up PDX 4.36. Bring back up your slides and look at Slide 36.

Just like you did for Claim 6, have you assisted in preparing a slide that shows how every limitation of Claim 5 feeds into Claim 25 when it's rewritten in independent form?

A. Yes.

Q. So do you understand that we need to review each of these limitations in order to assess infringement of Claim 25?

A. Yes.

Q. Let's focus on the language of the rewritten independent form of Claim 25. And that's on PDX 4.36. And let's turn to the checklist form on PDX 4.37 -- excuse me -- PDX 4.38.

Dr. Csaky, we're going to -- again, I'm going to ask you to address the first of your two questions regarding infringement, which is whether Mylan or Biocon's label encourages, recommends, or promotes infringement of Claim 25. Okay?

A. Yes.

Q. What is the first requirement of Claim 25?

A. The first requirement is that it be method for treating diabetic macular edema.

Q. Let's bring back up PTX 3097.

Let me ask a familiar question, Dr. Csaky. Does Mylan or Biocon's label recommend that doctors use Yesafili to treat diabetic macular edema?

A. Yes. It specifically indicates -- says that it's indicated for the treatment of patients with diabetic macular edema.

Q. Can we check off the first box in Claim 25 suggesting that Mylan or Biocon's label recommends that doctors perform the first limitation of Claim 25?

A. Yes.

Q. Dr. Csaky, let's turn, then, to PDX 4039. What is

the next limitation of Claim 25 you'll analyze?

A. The next limitation is that there are a single initial dose of 2-milligram aflibercept be given.

Q. Let's bring back up PTX 3097.

Does the Mylan Biocon label instruct sequentially administering to the patient a single initial dose of 2 milligrams of aflibercept?

A. Yes.

Q. Where is that recommendation?

A. It says the recommended dose for Yesafili is 2 milligrams administered by intravitreal injection every four weeks for the first five injections.

Q. Okay. Same question as before. Which of those first five injections is the single initial dose?

A. The first one.

Q. So can we check off the box that Mylan -- the proposed labeling for Yesafili recommends that doctors perform the method of sequentially administering to the patient a single initial dose of 2 milligrams of aflibercept?

A. Yes.

Q. Let's turn to the next set of limitations. It's on PDX 4.40.

What is the next set of limitations you'll analyze for infringement?

A. The next set of limitations are the secondary doses,

2 milligrams to be administered every four weeks, and these are four secondary doses.

Q. You mentioned four secondary doses. Is that the last limitation of Claim 25 there?

A. Yes.

Q. That's a difference from Claim 6, right?

A. Yes.

Q. So let's bring back up the label, PTX 3097. After that first initial dose proposed -- does the proposed labeling for Yesafili recommend that doctors administer to patients, after the first single initial dose, one or more secondary doses of 2 milligrams of aflibercept wherein each secondary dose is administered to the patient by intravitreal injection approximately four weeks following the immediately preceding dose and wherein four secondary doses are administered to the patient?

A. Yeah. It explicitly says that, again, every four weeks for the -- every four weeks for the first five injections.

Q. And you said every four weeks for the first five injections. Which of those five injections correspond to the secondary doses of the claims?

A. The last four.

Q. So then how many secondary doses does the proposed labeling for Yesafili recommend?

A. Four.

Q. How frequently -- how often does Yesafili's label recommend that doctors administer those four secondary doses?

A. Every four weeks.

Q. So can we check off the box that Mylan's label recommends the secondary dose requirements of Claim 25?

A. Yes.

Q. Let's do that, then, and turn to the tertiary dose limitations.

What does Claim 25 require in terms of tertiary doses?

A. Yes. There are two requirements: 2 milligrams be provided, one or more, and that those be administered every eight weeks.

Q. Let's bring back up the label, PTX 3097, at page 1.

After the single initial dose and after the four secondary doses, does the proposed labeling for Yesafili recommend that doctors administer one or more tertiary doses of 2 milligrams of aflibercept wherein each tertiary dose is administered to the patient by intravitreal injection approximately eight weeks following the immediately preceding dose?

A. Yes. It says again under the dosage and administration, "followed by 2 milligrams via intravitreal injection once every eight weeks."

Q. Which of those injections once every eight weeks corresponds to the tertiary doses of the claims?

A. All of them.

Q. Any of them that are given?

A. Yes.

Q. So then can we check off the box that Claim 25 recommends the tertiary dose steps of Claim 25?

A. Yes.

Q. Let me try that again.

Can we check off the box that Mylan or Biocon's label recommends the tertiary dose steps of Claim 25?

A. Yes.

Q. Thank you.

What else is missing -- are we missing anything from Claim 25? What else does it require?

A. We don't miss -- everything's there.

Q. So then turning back to your question on PDX 4.43, what's the answer to Question Number 1? Does Mylan or Biocon's label recommend that doctors perform every step of the method of Claim 25 of the '572 patent and thereby infringe Claim 25 of the '572 patent?

A. In my opinion, the Mylan and Biocon label does encourage, recommend, or promote doctors to perform a method that infringes.

Q. And that's Claim 25, right?

A. That's Claim 25.

Q. So can we check off that box?

A. Yes.

Q. All right. Let's turn, then, to Question Number 2. Thinking back to your earlier testimony, Dr. Csaky, if Yesafili is marketed, will some doctors actually use Yesafili as its label tells them to and thereby perform the method of Claim 25?

A. In my opinion, yes.

Q. How do you know?

A. Again, similar to the evidence or the basis for my opinions in the previous discussions, you know, these are an approach that I have used in a patient or some patients. And, again, in discussion with my colleagues, we've also had discussions about these types of approaches.

And, again, very similar to the discussion we had last time about diabetic macular edema and the need for a series of injections, five injections, and knowing that that has the evidence base to give the best outcomes in some patients, some doctors will use this approach.

Q. And you mentioned the first five injections monthly. Do you also use the method where you switch to eight-week dosing after that?

A. Yes. That's very common. If a patient does well after those injections, as we talked about, you want to start to extend that interval. And what -- this label, based off the

trial data, suggests that you can do that safely.

Q. And so I just want to be very clear, Dr. Csaky. Have you used Eylea in a -- according to the method of Claim 25 to treat DME and DR?

A. Yes. In the past I have definitely used this method.

Q. And are you -- through your conversations with colleagues, are you aware that other doctors also use the method of Claim 25 in order to treat DME and DR?

A. Yeah. In fact, like I said, we've been on various committees about approaches to DME and how best to treat, especially more severe, DME. And this is an approach that I've had doctors talk to me about as a method, again, in some cases with some patients they've used.

Q. And that's with Eylea, right?

A. Yes.

Q. And let's take a look at -- again, at how Regeneron recommends doctors use Eylea and how Mylan or Biocon recommends doctors use Yesafili in order to treat DME. Actually, let me try that again.

Have we already looked at how Regeneron recommends that doctors use Eylea and compared it to how Mylan or Biocon recommends doctors use Yesafili in the context of DME?

A. We haven't done the comparison, no. You haven't showed me that.

Q. Oh. Well, then, let's take a step back because I

thought we did that in Claim 6, but we can certainly do it.

A. We did that in Claim 6, yes.

Q. Let's just take a look. Give me one moment.

Can we pull up PTX 917 on the left. And can we call out the highlights of prescribing information for DME and DR. And then put up PTX 3097 on the right and call out the same information.

So, Dr. Csaky, just to be very short, is there any difference in how Regeneron recommends that doctors use Eylea to treat DME and DR shown in PTX 917 on the left when compared with how Mylan or Biocon would recommend doctors use Yesafili to treat DME and DR on the right?

A. No.

Q. No difference?

A. No difference.

Q. Okay. So in view of the fact that we've just walked through your opinion that Mylan or Biocon's label recommends doctors perform the method of Claim 25, if doctors used Eylea according to the label, have they also performed the method of Claim 25?

A. Yes.

Q. So in your opinion, if doctors use Eylea according to the method of Claim 25 and if doctors will use Yesafili in the same way, does that inform your opinion as to whether some doctors will perform the method of Claim 25 using Yesafili?

A. Yes.

Q. And in the context of Claim 25, we mentioned that that last limitation, the four secondary doses, is different than Claim 6. I just want to be clear.

When you say you have used Eylea to treat patients with DME and DR according to the method of Claim 25, have you also done that four secondary doses step?

A. Yes. In certain cases where there is severe DME, you need five injections, multiple injections. And, again, having, as I said before, that confidence that five injections gets us to a good place both anatomically and visually is a nice approach to take in some patients.

Q. So you've performed the method of Claim 25 using Eylea in patients with DME and DR?

A. Correct.

Q. And when you say your colleagues have used the method of Claim 25 to treat DME and DR, that's also including that four secondary doses step, right?

A. Right. Right. That's again a very common challenge we have in diabetic macular edema, that in certain cases you need these multiple injections to get the retina to really respond.

Q. So your colleagues have -- you're aware that your colleagues have performed the method in DME and DR, the method of Claim 25?

A. Correct. As I said, when we talk about this -- the connection and how we approach these diseases, we want to be able to get -- especially in diabetic disease, we want to get it as responsive as possible. And so we really want to be able to ensure that we get good regression of the diabetic retinopathy and good resolution of the diabetic macular edema.

Q. Let's head back to your slide PDX 4.45.

THE COURT: Counsel, before we do that, are we at a good spot to break or do you have a couple more on this particular issue?

MS. KAYALI: I think we could close out this claim, Your Honor. That might be advisable, and then we can break.

THE COURT: I would concur. Go right ahead.

BY MS. KAYALI:

Q. Let's head back to PDX 4.45. Am I right, then, that your answer is -- or what is your answer to Question Number 2?

A. Yeah. The answer -- the opinion that I formed after reviewing all of the evidence that I was able to take in my own approach to patients with diabetic macular edema in particular and also my colleagues and their now approaches to diabetic macular edema and diabetic retinopathy, the answer to this was yes.

Q. So taking a step back, then, in view of claim -- excuse me -- Claim 25, in view of your opinion that Mylan or Biocon's label recommends that doctors perform the method of

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Claim 25 and in view of your opinion that some doctors will, in fact, perform the method of Claim 25 as a result, have you formed an opinion as to whether or not, if Mylan or Biocon markets Yesafili, they will induce infringement of Claim 25?

A. Yes.

Q. And what did you conclude?

A. My conclusion was that Mylan/Biocon will induce infringement on Claim 25.

MS. KAYALI: With that, Your Honor, we've reached the end of the claim.

THE COURT: Understood. I jumped the gun a little bit. My apologies, Counsel.

We'll go ahead and take our midday break at this point. Let's be ready to pick back up at 1:00. That will give everybody here 40 minutes or so. We can resume then.

As I mentioned, I think yesterday, we do have a proceeding that we need to take up during our break. So if I could ask lead counsel at the trial tables just to stack some things up out of the way. That shouldn't take all but a minute or two, but we do need the courtroom for that.

Doctor, you remain on your own. They're permitted to feed you, and I hope that they do. But, otherwise, you're still without a country. Thank you, sir.

We'll stand at ease until 1:00. Thank you all very much.

(A recess was taken from 12:22 p.m. to 1:08 p.m.)

THE COURT: Doctor, are you ready to resume, sir?

THE WITNESS: Yes.

THE COURT: Could I ask you to pull that mic back down. There you go. Perfect.

All right. Counsel?

MS. KAYALI: Thank you.

BY MS. KAYALI:

Q. Dr. Csaky, let's pick up where we left off. I think we ended with Claim 25. So I've got Slide 45 up here.

And am I right that you had answered yes to Question Number 2? In your opinions, at least some doctors will perform the method of Claim 25 in administering Yesafili to treat DME in accordance with Claim 25 as a result of Mylan's label?

A. Yes.

Q. As a result of that opinion, did you conclude that Mylan will, in fact, induce infringement of Claim 25?

A. Yes. My opinion was that Mylan will induce infringement on Claim 25.

Q. Okay. Let's turn to Claim 11. We're two down, two to go. And we're turning to the '601 patent.

Dr. Csaky, this is PTX 1. Do you recognize this document?

A. I do.

Q. And what is it?

A. This is the U.S. patent -- and we're going to call this the '601 patent -- for the use of VEGF antagonists to treat angiogenic eye disorders.

Q. In the course of your work on this case, have you reviewed the '601 patent in full?

A. I did.

Q. Let's go take a look at the first of the asserted claims in the '601 patent. That's Claim 11. This is page 21 of PTX 1.

What does Claim 11 of the '601 patent require?

A. Claim 11 again is a dependent claim. And it is dependent on the method of Claim 10, but in and of itself it has a limitation with an approximately every four weeks, comprising approximately every 28 days or approximately monthly.

Q. Let's bring up your slides again and compare this to PDX 4.46. Dr. Csaky, just like for the last two claims, do you understand that Claim 11, because it depends from Claim 10, therefore incorporates all the limitations of Claim 10?

A. Yes.

Q. And just like before, have you made a slide that attempts to rewrite Claim 11 in independent form?

A. Yes. Correct.

Q. So we're going to focus on the independent form of

Claim 11 in assessing infringement.

Let's turn to some familiar questions on PDX 4.47.

Dr. Csaky, in the context of Claim 11 we're going to march through the same two questions we have all day. And the first one of those is does Mylan or Biocon's label encourage, recommend, or promote doctors to perform methods that infringe Claim 11 of the '601 patent?

So let's jump in, PDX 4.48. Dr. Csaky, what is the first limitation of Claim 11 of the '601 patent that you analyzed?

A. The first limitation is a method for treating diabetic macular edema.

Q. Let's pull up PTX 3097.

Dr. Csaky, does Mylan's or Biocon's proposed labeling for Yesafili, PTX 3097, recommend that doctors use Yesafili in a method for treating diabetic macular edema in a patient in need thereof?

A. Yes.

Q. Where does it do that?

A. Yes. It says under indications and dosage you can clearly see that Yesafili is indicated for the treatment of patients with diabetic macular edema.

Q. We're looking at page 1 of PTX 3097. And, Dr. Csaky, I think I heard you say indications and dosage. Is that the title of this section?

A. Yes.
Q. Do you see the words "indication and usage"?
A. I'm sorry. Indications and usage, right.
Q. So the recommendation that Mylan -- or excuse me. The recommendation in PTX 3097 that doctors use Yesafili to treat a patient in need of treatment for diabetic macular edema, that's in the indications and uses section on PTX 3097, page 1, right?
A. Yes.
Q. Can we check off that box, then? Can we check off that Mylan's label or Biocon's label recommends that doctors perform the first step of the method of Claim 11?
A. Yes.
Q. Let's go to the second one. What are we looking at here?
A. Right. So there are now two limitations here. One is that there's an effective amount of aflibercept, which is 2 milligrams. And it's approximately every four weeks for the first five injections. And then there's a further stipulation that this approximately every four weeks comprises approximately every 28 days or approximately monthly.
Q. Let's pull PTX 3097 back up.
Dr. Csaky, does PTX 3097, proposed labeling for Yesafili, recommend that doctors administer Yesafili intravitreally in an effective amount of aflibercept, which is

2 milligrams approximately every four weeks, for the first five injections?

A. Yes.

Q. Where does it make that recommendation?

A. In the very first bullet point, the recommended dose is 2 milligrams administered by intravitreal injection every four weeks for the first five injections.

Q. The claim states an effective amount of aflibercept which is 2 milligrams. Do you see that?

A. Yes.

Q. Is that an effective amount -- is 2 milligrams an effective amount of aflibercept?

A. Yes.

Q. How do you know?

A. We know that from both multiple clinical trials as well as our own clinical experience.

Q. And the first five injections that are recommended in the proposed labeling for Yesafili, how frequently does Yesafili's label recommend that those be given?

A. Those -- on the label it's approximately every 28 days, or monthly, four weeks.

Q. So when Yesafili's label recommends that doctors administer Yesafili every four weeks (approximately every 28 days, monthly) for the first five injections, does Yesafili's proposed label recommend that doctors meet that final

limitation of Claim 11 wherein approximately every four weeks comprises approximately every 28 days or approximately monthly?

A. Yes.

Q. Let's turn back to PDX 450.

Excuse me, Dr. Csaky. I should have asked you.

Can we check off those boxes --

A. Yes.

Q. -- for the first five injections being administered approximately every four weeks, approximately every 28 days, or monthly?

A. Yes, we can check those off.

Q. All right. What's the next limitation you addressed?

A. The last limitation is that it be followed by 2 milligrams approximately once every eight weeks, or once every two months.

Q. Let's bring back up the label. That's PTX 3097.

Dr. Csaky, does the proposed labeling for Yesafili recommend that doctors, after those first five injections, administer Yesafili in 2-milligram doses approximately once every eight weeks, or once every two months?

A. Yes, it says that specifically under dosage and administration, followed by 2 milligrams via intravitreal injection once every eight weeks, or two months.

Q. So can we check off the method -- excuse me -- that the limitation requiring 2 milligrams approximately once every

eight weeks, or once every two months, is satisfied?

A. Yes.

Q. Looking at PDX 4051, Dr. Csaky, what else does Claim 11 require?

A. Nothing else.

Q. Have we caught all the limitations?

A. Yes.

Q. Does Mylan or Biocon's label recommend that doctors perform them all?

A. Yes.

Q. So turning back to your questions, let's look at PDX 4.52. What's the answer to Question Number 1? Does Mylan or Biocon's label encourage, recommend, or promote doctors to infringe Claim 11 of the '601 patent?

A. Again, in my opinion, the answer to that first question is yes.

Q. Let's talk about Question Number 2.

Dr. Csaky, you've spent quite a bit of time, I think, explaining in your opinion how -- how doctors use Eylea and how doctors will use Yesafili.

In your opinion, if Mylan or Biocon markets Yesafili with the label that's reflected in PTX 3097, will some doctors actually do what that label says and use Yesafili to perform the method of Claim 11?

A. Yes. In my opinion, there will be some doctors in

some situations who will perform that method.

Q. And is that substantially for the reasons which you've already explained?

A. Correct.

Q. Now, the final limitation of Claim 11 requires that the first -- wherein approximately every four weeks comprises approximately every 28 days or approximately monthly. When you were describing your practice and the practice of other physicians with whom you've spoken and explaining that they use methods of treating patients with DME using Eylea with five monthly injections followed by every-eight-week dosing, do you or do those doctors administer those five monthly doses approximately every 28 days, or approximately monthly?

A. Yes. I would say that we often do this approximately every 28 days.

Q. Or approximately monthly?

A. Or approximately monthly, correct.

Q. Let's take a look quickly at the Eylea label compared to the Yesafili label. And we're going to put PTX 3097 on the right here and PTX 917 on the left.

Does the Eylea label contain language regarding administering the first five injections approximately every 28 days, or approximately monthly?

A. Yes.

Q. And so if physicians follow the Eylea label, do they

administer the first five injections approximately every 28 days, or approximately monthly?

A. Yes. In some cases, they do.

Q. So when they follow the label, they do that. And in your opinion, do some people do that?

A. Yes.

Q. So does the Eylea label also recommend that doctors use Eylea to treat DME according to the method of Claim 11?

A. Yes.

Q. Well, then, let's see if we can turn to Question Number 2. That's Slide 54 -- let's back up one -- excuse me -- slide 53.

Dr. Csaky, you have your own experience with Eylea that you've described. In view of your conversations with colleagues about how they use Eylea, what is your opinion as to whether, if Yesafili is marketed, some doctors will administer Yesafili according to the recommendations in its label and thereby infringe Claim 11?

A. Yes, my opinion is that there will be, again, some doctors who will perform this method as described.

Q. Let's take a step back on Claim 11, then.

In view of your opinion that Mylan or Biocon's label recommends that doctors perform the method of Claim 11 and in view of your opinion that some doctors will, in fact, perform the method of Claim 11 as a result, have you formed an opinion

as to whether or not Mylan or Biocon will induce infringement of Claim 11 if they sell Yesafili?

A. Yes.

Q. What did you conclude?

A. Yes, in my opinion, Mylan/Biocon will infringe on Claim 11 by marketing Yesafili.

Q. And just so the record is clear, when you say infringe, do you mean induce infringement?

A. Induce infringement.

Q. Okay. Dr. Csaky, we are three claims down and one to go.

Let's turn to the final asserted claim. And that's Claim 19 of the '601 patent. What does Claim 19 of the '601 patent require?

A. So, again, we have this dependency on Claim 18. And in and of itself Claim 19 requires that these injections be given approximately every four weeks, comprising approximately every 28 days or approximately monthly.

Q. And just like the last three times, have you compiled all the limitations of Claim 19, including the incorporated limitations of Claim 18, into a single slide?

A. Yes.

Q. Let's take a look at that. That's PDX 455. Let's go straight to your questions now, PDX 4056.

Dr. Csaky, this is probably going to sound familiar,

but our first question is does Mylan or Biocon's label encourage, recommend, or promote that doctors perform methods that infringe Claim 19 of the '601 patent?

A. Yes. In my opinions, it does.

Q. Let's take a look at that. It's PDX 4057.

Dr. Csaky, what is the first limitation of Claim 19?

A. The first limitation is treating diabetic retinopathy.

Q. Is that an indication we've discussed already today?

A. Yes.

Q. So in your opinion, Dr. Csaky, does the proposed labeling for Yesafili, PTX 3097, recommend that doctors use Yesafili in a method for treating diabetic retinopathy in a patient in need thereof?

A. Yes.

Q. Let's take a look. PTX 3097, where is that recommendation?

A. It says specifically that Yesafili is indicated for the treatment of patients with diabetic retinopathy.

Q. And that's on page 1 under the indications and usage section?

A. That's on indications and usage section.

Q. So can we check off the box, then, that the proposed labeling for Yesafili recommends this first step of Claim 19?

A. Yes.

Q. What's the next step of Claim 19?

A. The next step is a two-part step, again where it says intravitreally administering aflibercept to patients every four weeks for the first five injections and that this four weeks comprise approximately every 28 days or approximately monthly.

Q. Let's pull back up PTX 3097.

Dr. Csaky, does the proposed labeling for Yesafili recommend doctors intravitreally administer to a patient an effective amount of aflibercept, which is 2 milligrams, approximately every four weeks for the first five injections to treat DR?

A. Yes. It explicitly states that Yesafili is to be administered intravitreally every four weeks, approximately between 28 days, monthly for the first five injections.

Q. That's on page 1 of PTX 3097 under "Dosage and Administration"?

A. That's under the "Dosage and Administration."

Q. And I just want to make sure we hit every point of that.

Does the recommendation recommend 2 milligrams?

A. 2 milligrams.

Q. And for the first five injections, are those recommended to be given every four weeks?

A. Yes, every four weeks, approximately every 28 days, monthly.

Q. Let's turn then -- pardon me. May we check off those boxes, then? Have you concluded that Mylan or Biocon's label recommends both of these steps of the steps shown on PDX 4058?

A. Yes.

Q. What's the last limitation you'll address today, Dr. Csaky, of Claim 19?

A. The last limitation is that the 2-milligram dose be given approximately once every eight weeks, or two months, following the first five injections.

Q. Well, let's pull back up PTX 3097.

Does the proposed labeling for Yesafili recommend that doctors treat patients with diabetic retinopathy using 2-milligram doses approximately once every eight weeks or two months after the first five injections?

A. Yes.

Q. Where does it make that recommendation?

A. Under "Dosage and Administration," it says followed by 2 milligrams via intravitreal injection once every eight weeks, two months.

Q. That's on PTX 3097, page 1, right?

A. Yes.

Q. So, Dr. Csaky, can we check off that last limitation shown on PDX 4059?

A. Yes.

Q. Dr. Csaky, what else does Claim 19 require?

A. Nothing. It does not require anything else.

Q. So let's head to PDX 461.

Turning back to your questions, can we answer Number 1? In your opinion, does Mylan or Biocon's label encourage, recommend, or promote doctors to infringe Claim 19 of the '601 patent?

A. Yes. In my opinion, Mylan/Biocon label does encourage, recommend, or promote these methods that will infringe.

Q. Now, let's turn to Question Number 2.

Dr. Csaky, this is about diabetic retinopathy, right? This claim?

A. Yes.

Q. And you testified earlier that you have personally and others have performed the method of Claim 19 in the context of treating diabetic retinopathy?

A. Yes. In the context, I've treated patients with diabetic macular edema and diabetic retinopathy.

Q. You've treated them in a method of Claim 19 where you administer intravitreal 2-milligram doses approximately every four weeks for the first five injections followed by 2 milligrams approximately once every eight weeks or two months wherein approximately every four weeks comprises every 28 days or approximately monthly?

A. Yes.

Q. Okay. And in conversations with other doctors, as you've testified earlier, do they also perform that method?

A. Yes. As I said, there's been more and more interest in using anti-VEGF in particular for diabetic retinopathy, especially if it's more severe, in certain cases where the alternative is laser photocoagulation. So there's more and more interest in using this approach, and so I've had physicians -- we've talked about the utility of this approach in treating these types of patients, and they claim that they are using this approach.

Q. And I know we spent a lot of time talking about those first five injections being administered monthly. I just want to make sure, when you're thinking back on that testimony when you spoke about those first five injections being administered monthly -- excuse me -- every four weeks, were those doses administered approximately every four weeks where that comprises approximately every 28 days or approximately monthly?

A. Yes.

Q. Let's pull up the comparison of the labels one more time here. That's PTX 917 on the left, PTX 3097 on the right.

Dr. Csaky, does Eylea's label also recommend that, when doctors administer intravitreal injections every four weeks for the first five injections, they do so approximately every 28 days or approximately monthly?

A. Yes.

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Q. So when doctors administer Eylea according to the label for the treatment of diabetic retinopathy, do doctors perform the method of Claim 19?

A. Yes.

Q. And does that inform your opinion as to whether, if doctors -- if Yesafili is marketed with the label that we see at PTX 3097, some doctors will use Yesafili in exactly the same way?

A. Yes.

Q. So let's turn back to Question Number 2. That's on PDX 464 -- excuse me -- PDX 462.

Dr. Csaky, can we answer Question Number 2 at this point?

A. Yes.

Q. In your opinion, if Mylan or Biocon markets Yesafili with the label containing the recommendations in PTX 3097, will some doctors actually follow those recommendations and perform the method of Claim 19?

A. Yes, some doctors will follow that label and infringe on the methods.

Q. So then let's switch to PDX 463, and let's take a step back one last time.

In view of your opinion that Mylan or Biocon's label recommends that doctors perform the method of Claim 19 and in view of your opinion that some doctors will, in fact, perform

the method of Claim 19 if Yesafili is marketed, have you formed an opinion as to whether or not Mylan or Biocon will induce infringement of Claim 19 if they sell Yesafili?

A. Yes. My opinion is that Mylan or Biocon will induce infringement on Claim 19 if they market Yesafili.

Q. Okay. Dr. Csaky, we've made it through the claims, and we're nearly done. I want to touch on just two things briefly.

Thus far, your testimony about how Mylan or Biocon intends doctors to use Yesafili has been based on the proposed Yesafili labeling, right?

A. Yes.

Q. And was that proposed labeling enough for you to draw your conclusions about infringement?

A. Yes.

Q. Nevertheless, in the course of your work on this case, did you come across additional evidence of how Mylan or Biocon intends for doctors to use Yesafili?

A. Yes.

Q. Let's bring up PTX 331.

Dr. Csaky, what is this document?

A. So this is the first slide of a presentation that Dr. Susan Bressler at the American Academy of Ophthalmology where she is summarizing the INSIGHT study with Mylan 1701P, which we can now call Yesafili. And as you can see the title,

this is a proposed biosimilar to aflibercept, and she is outlining the outcomes from the Phase III study.

Q. Is this the document that also -- excuse me. Strike that.

I think you may have said this, but where did Dr. Bressler present this presentation?

A. At the very bottom it says AAO. The AAO is the American Academy of Ophthalmology.

Q. Who attends AAO?

A. It's the largest ophthalmology meeting in this country at least, and all general ophthalmologists, retina specialists will attend the American Academy of Ophthalmology meeting.

Q. So if a company wants to inform ophthalmologists about how to use a prospective drug, is this a place to do it?

A. This is the one place where you can disseminate information and share the results of data with the community.

Q. This is a Phase III study, right?

A. Correct.

Q. Did Mylan do any additional Phase III studies?

A. Not that I'm aware of.

Q. What indication is this about?

A. This indication is for diabetic macular edema.

Q. Let's take a look at page 5 of the slide deck.

What regimen did Mylan test and did Dr. Bressler

present in this study?

A. I think what you have to look under, you see at the very bottom -- I'm not trying to do this -- so here is the regimen that they're recommending -- not recommended -- they did for the trial. And you can see that, essentially, there was an injection -- all these needles being injections -- there's an injection at baseline, and then the injections are done every four weeks. So five injections monthly to begin with, and then there's a transition, you can see, from there to the 20 four-month injection going forward.

So the -- it's essentially a five loading doses and then transitioning to every eight weeks.

Q. So does this regimen reflect the regimen of at least Claims 6 and 25 of the '572 patent and Claim 11 of the '601 patent?

A. Yes.

Q. I see a note there at the end it says "with Q4w optional doses."

Do you see that yellow text?

A. Yes.

Q. What does that mean?

A. So this is not uncommon in a clinical trial. When you are assessing a drug and you want to make sure that there's safety, these patients are seen every month, and there's typically what's termed "rescue criteria," which means if they

are not doing well, they'll receive either an additional injection or some other modality.

So that's not a required injection. It's simply to indicate that these were times when patients were evaluated and, if they did not meet -- say the vision did not get better, they didn't get more swelling, they were not treated.

Q. So just to be clear, were those q4 optional doses given to every patient in the study?

A. No. So this was only those patients who met these criteria and needed, for example, another injection based on prespecified reasons.

Q. Did many patients in this study, in fact, receive the methods of Claim 6, 25, and 11 where they got five monthly loading doses followed by q8 dosing?

A. Yes. My understanding is that the vast majority of patients who went through that regimen.

Q. Let's turn to the last slide in Dr. Bressler's presentation. That's PTX 331, page 12.

Looking at the top of the slide, Dr. Csaky, what, if anything, is Dr. Bressler, on behalf of Mylan, telling doctors about how to use Yesafili?

A. Well, what Dr. Bressler is communicating -- there's the conclusions, and what she's demonstrating here is that the INSIGHT study demonstrated therapeutic equivalence. Again this is now -- we're going to call this Yesafili and aflibercept in

the treatment of diabetic macular edema. And then she goes on to say why, and she goes on to talk also about the bottom safety of the drug as well, and that was very similar to Eylea.

Q. And so just to make the record clear, MYL-1701P, I think you said that was Yesafili, right?

A. My understanding is that's Yesafili.

Q. And the reference to aflibercept there, is that a reference to Eylea?

A. That's my understanding.

Q. So if we look at the very bottom green box there, "Following regulatory approval, MYL-1701P is expected to be a new treatment option for patients with DME."

What, if anything, is Mylan telling doctors about what to do with Yesafili if and when it gets approved?

A. Well, I think here what's being communicated is that following approval, essentially, as we review her conclusions, the fact that there was therapeutic equivalence and safety equivalence, I think the ophthalmologists, in seeing this presentation, that their interpretation would be that I can use Yesafili essentially in an identical way that I'm using Eylea in the treatment of DME.

Q. And the regimen that Dr. Bressler recommended in this study -- or described in this study, that's the method of Claim 6, 25, and 11, right?

A. That's correct.

Q. Let's turn back one last time to PTX 3097.

I want to talk briefly, Dr. Csaky, about a portion of the Mylan or Biocon label we haven't looked at yet today. In the upper left-hand corner, I see some highlighted language right under the prospective approval date. It reads, "Yesafili (aflibercept-jbvf) is interchangeable with Eylea (aflibercept)."

Do you see that?

A. Yes.

Q. What does that mean to an ophthalmologist?

A. Again, for an ophthalmologist who's reading this, it's essentially telling us that the two drugs are the same.

Q. How is it telling doctors they can use Yesafili?

A. Well, it's essentially indicating that we would then, like you said, look at the label, and the label would then instruct us on how to use it. But even with this statement alone, the thinking of the ophthalmologist would be that I can essentially exchange and use Yesafili in the exact same fashion that I'm using Eylea in the clinic.

Q. And then finally, if we turn to some language in the bottom right of the highlights of the prescribing information -- so we're still on page 1 -- do you see the highlighted language stating that "There are no clinically meaningful differences between the products and it" -- Yesafili -- "can be expected to produce the same clinical

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result as the referenced product" -- Eylea --

A. Yes.

Q. -- "in any given patient"?

A. Yes.

Q. What does that language alone tell you about how Mylan or Biocon intends for doctors to use Eylea?

A. Yeah. Again, this is communicating to ophthalmologists that the two drugs are the same.

Q. And how does it communicating to doctors that you can use those two drugs?

A. Because it's indicating it is expected to produce the same clinical result as the reference product. In this case the reference product was Eylea. So it's explicitly telling the ophthalmologist that, when you use it, you can expect the exact same clinical result.

Q. So is that an instruction that you can use Yesafili in the exact same way you can use Eylea?

A. Yes.

Q. Do you need to look at anything else in the label to know whether Mylan is -- Mylan or Biocon is telling you to use Yesafili in the exact same way as you use Eylea?

A. For the ophthalmologist who sees only this, I think the average ophthalmologist would read this and interpret it as saying these two drugs are essentially the same.

Q. And you can use them the same way?

A. And you can use them the same way.

Q. And just to close things off, does that new Biocon label we reviewed, PTX 3338, have you had an opportunity to confirm whether it contains the same language here?

A. Yes.

Q. And does it?

A. It does.

MS. KAYALI: One moment, please.

With that, Your Honor, we pass the witness.

THE COURT: Counsel, cross.

MS. LESKO: Your Honor, we have a couple of binders for cross. May we pass them up?

THE COURT: Permission granted. I'd be disappointed if there weren't binders.

MS. LESKO: May I proceed, Your Honor?

THE COURT: You may. Go right ahead, Counsel.

CROSS-EXAMINATION

BY MS. LESKO:

Q. Good afternoon, Dr. Csaky.

A. Good afternoon.

Q. I'm Ms. Lesko.

Dr. Csaky, you just offered a lot of opinions about my clients. But let's be clear, you do not contend that Mylan or Biocon directly infringed the asserted '572 or '601 patents, right?

A. Correct.

Q. Dr. Csaky, do you recall participating in a roundtable discussion at a Retina Society meeting in Washington, DC, on October 5th, 2012?

A. I do not recall that.

Q. Let me try to help refresh your recollection.

If you can please open your binder, there should be a document in the front pocket that is without a tab.

A. Uh-huh.

Q. It should be an article titled "Treating the Patient," dated January 1st, 2013. We'll put that up on the screen as well.

This article is described as highlighting a roundtable discussion during the Retina Society meeting.

Do you see your name there on the first page?

A. I do see my name.

Q. It indicates you were one of the participants?

A. Correct.

Q. Does this help you confirm that you were a participant in the roundtable discussion?

A. Yes, it does confirm that I was part of the roundtable discussion.

Q. Let's go to page 2 of this document. I'd like to direct your attention to the second full paragraph from the bottom.

Do you see the statement attributed to you that says, "Dr. Csaky: There is no set guideline that is applicable to a majority of patients with wet AMD. When is persistent fluid bad? I may tolerate a little subretinal fluid that remains despite several reinjections more than intraretinal fluid which has been shown in the CATT study to be associated with more severe vision loss. It is those variations that necessitate individualized decisions. I am finding there is no one-size-fits-all treatment."

Did you make that statement before your peers?

A. I did make that statement before my peers.

Q. Is it true for you today that, when it comes to treating your patients, there is no one-size-fits-all when treating patients with VEGF inhibitors?

A. That's correct. I mean, every patient requires -- as I mentioned earlier, that there is a whole range of decisions that you have to make in deciding what's the best treatment for that individual.

Q. Let's move to another statement attributed to you at the Retina Society roundtable, which appears at the top of this document, page 6. We'll put that up on the screen.

Do you have that?

A. Yes.

Q. Did you make the statement "That is what has surprised me the most, the number of patients who need

injections every six weeks or even every five weeks instead of every two months. We have seen very inconsistent results with that two-month window in our practice."

A. Yes, I made that statement.

Q. Okay. Let's talk about another time when you discussed the topic of settling on an anti-VEGF dosing regimen.

In around 2013 did you participate in a discussion about settling on an anti-VEGF discussion dosing regimen?

A. I'm sure you're going to tell me I did.

Q. If you want to flip to the back of your binder, there should be an article in the back pocket.

THE COURT: Feels like a safe assumption, Doctor. Go ahead. Feels like a safe assumption. Go ahead.

THE WITNESS: I'm starting to remember all these things. Yes. Go ahead.

BY MS. LESKO:

Q. So does that help refresh your recollection?

A. It does help refresh my recollection.

Q. And this is a review of *Ophthalmology* article titled "Settling on an Anti-VEGF Dosing Regimen" dated August 5th, 2013?

A. That's correct.

Q. It's directed to "Current options for anti-VEGF treatment, including continuous treatment at a fixed interval, prn treatment, and a treat-and-extend strategy."

Do you see that?

A. That's correct.

Q. Let's go to the third page of this exhibit.

A. Third page.

Q. Towards the middle of the page, do you see some quotes attributed to you?

A. Correct. The third paragraph is where I say some comments.

Q. I'd like to direct your attention to the first sentence, which states that "Karl Csaky, MD, PhD, of the Retina Foundation of the Southwest in Dallas, says, 'The challenge is that the three agents typically used all have very similar pharmacokinetics and durability, plus or minus a week or so.'"

Is that right?

A. Correct.

Q. You were also quoted in the second sentence of that paragraph as saying, "One confounding problem is that there appears to be an individualized durability interval that each patient demonstrates."

Correct?

A. Correct.

Q. In the third sentence, did you then explain, "It becomes a question of what strategy you use to dial in that sweet spot between injections and find out whether they are, for example, a five-weeker or a six-weeker."

Is that what you said?

A. Correct.

Q. Is it still true for you today that, when it comes to your patients, that you have to dial in that sweet spot between injections to find the correct dosing interval?

A. Yes. For a significant number of patients, it's important to try to figure out what's best for them. That's correct in the majority of patients.

Q. Let's move along in this third page of the article "Settling on an Anti-VEGF Dosing Regimen." We'll pull that up -- it up on the screen for you as well.

It's the one that starts with "he also notes that choosing a treatment strategy."

Do you see it in your paper exhibit?

A. Yes. "One confounding problem." Is that what we're talking about?

Q. There it is.

A. "He also notes." Perfect. "He also notes," yes.

Q. Were you quoted as saying that "So if it is the only good seeing eye, then you might want to be a little bit more aggressive with the interval. At the interval after which such an eye demonstrates recurrent fluid, we might want to have the patient come back even every four weeks just to be absolutely sure that we don't put them at risk for a bleed. That is the major catastrophic event that we want to avoid."

That's what you said, right?

A. Correct.

Q. And even today, do you believe that choosing a treatment strategy also depends somewhat on the status of the eye?

A. Yes, absolutely. So as we talked about, what we want in our armamentarium, right, is a host of approaches. There's some that we go to for sure and, depending on if it's the first eye or the second eye, what the vision in the first eye is versus the second eye, these are all various kind of considerations in making these treatment decisions.

Q. Let's turn back to the second page, if you will.

A. Sure.

Q. Towards the middle of the page it says, "Treat and extend is a more customized approach to treatment."

A. Yes.

Q. Do you agree with that?

A. It is a more customized approach to -- than other approaches, yes.

Q. Okay. We can pull that down.

Dr. Csaky, we can agree that you understand the Yesafili label instructs four alternative wet AMD regimens, one RVO regimen, and two alternative DME and DR regimens, right?

A. So we have one neovascular -- let me make sure. One neovascular AMD, one RVO, and one diabetic retinopathy and

diabetic macular edema protocol. That's what they recommend, correct.

Q. No, my question was slightly different.

Do you understand that the Yesafili label instructs four alternative wet AMD regimens?

A. My understanding is it doesn't recommend four alternatives; it recommends one.

Q. Right. But my question was asking about whether the label instructs for alternative regimens.

A. I think you said "recommend," and if it instructs, that's different.

Q. If I did, I apologize. So I'll ask it again just so it's clear.

We can agree that you understand the Yesafili label instructs four alternative wet AMD regimens, one RVO regimen, and two alternative DME and DR regimens, right?

A. Right. I guess I would use the term "describes," right? Instructs -- yeah, I mean, we can call it -- it tells how to do it.

Q. Okay. Just to make it easier, why don't we take a look at DTX 2028, exhibit page 24, in your binder?

A. 2028. Sure.

Q. Which is your March 30th, 2023, reply report.

A. Yes.

Q. I'd like to direct your attention to the top of this

page, and we're on page 24. It's also up on your screen, if that's easier.

A. Is it DTX 24? Are you using the bottom, not the actual page of the document?

Q. That's correct. DTX 24.

A. Okay. Yes, please.

Q. Looking at the top of this page, which is a part of your reply report, paragraph 43 -- and we have it up on the screen for you.

A. Yes.

Q. In your report did you give the opinion, "Far from offering 11 alternative dosage regimens for one indication, as Dr. Russell's language suggests, the labels instruct four alternative wet AMD regimens, one RVO regimen, and two alternative DME DR regimens"?

A. Right.

Q. Next let's pull up DTX 3311, the Eylea labeling.

A. DTX -- I'm sorry. Say that again.

Q. 3311.

A. 3311. Okay.

Q. Page 1. I'd like to take a look at a new indication that was recently put into the Eylea labeling under the dosage and administration section at the top in the right column that is titled "Retinopathy of prematurity, ROP."

A. Correct.

Q. Do you have that?

I would like to direct your attention to the recommended dose for retinopathy of prematurity which is 0.4 milligrams, 0.01 milliliters, or 10 microliters, administered by intravitreal injection.

Do you see that?

A. I do see that.

Q. Can you confirm that, for retinopathy of prematurity, the dosing regimen on the label calls for treatment that may be given bilaterally on the same day, injections may be repeated in each eye, that treatment interval between doses injected into the same eye should be at least ten days?

A. Yes.

Q. Next let's pull up PTX 3338. This is the proposed Yesafili labeling, 3338.

A. Have to get to the back of the binder here. Just a second.

Okay. All right. Very good.

Q. Do you have it?

A. I have it now.

Q. And, again, I would like to direct your attention to the dosage and administration section on the first page.

A. Yes.

Q. We also have it up on your screen.

A. Uh-huh.

Q. We can agree that the phrase "isotonic solution" is not in the dosage and administration section, right?

A. I didn't -- again, I did not opine on anything to do with isotonic solution; so I didn't review the label for that term.

Q. And on your direct examination, you did not opine that the phrase "isotonic solution" appears anywhere in the Yesafili label, correct?

A. I can't recall. But if I did, then I did not see it.

Q. Well, let's take a look at the text in the Yesafili label under the heading "Macular Edema Following Retinal Vein Occlusion, RVO."

A. Yes.

Q. For RVO it states that the recommended dose for Yesafili is 2 milligrams, 0.05 milliliters, administered by intravitreal injection once every four weeks, approximately every 25 days, monthly. Agree?

A. Yes.

Q. Can we agree that an only monthly dosing regimen here in the label is not any kind of eight-week dosing regimen?

A. Correct. For macular edema following retinal vein occlusion, there's no recommendation for extending the dose.

Q. Right. And a monthly dosing regimen is different from an eight-week dosing regimen, right?

A. Correct.

Q. Looking at the DME and DR heading that is titled "Diabetic Macular Edema, DME, and Diabetic Retinopathy, DR," do you have that?

A. I see that, yes.

Q. Let's look at the second bullet under DME/DR, last full sentence. We have it up on the screen as well. It says, "Some patients may need every-four-week, monthly, dosing after the first 20 weeks, five months," correct?

A. That's what it states, yes.

Q. Let's look at the AMD section. Are you there?

A. Yes. I see it right above it, yeah.

Q. And this is under the heading titled "Neovascular (wet) age-related macular degeneration, AMD." I would like to first direct your attention to the second bullet, last sentence. We can agree that it says, "Some patients may need every-four-week, monthly, dosing after the first 12 weeks, three months," yes?

A. Yes, we can agree.

Q. If we move to the third bullet under the AMD dosing and administration instructions in the Yesafili labeling, can you confirm it states, "Although not as effective, patients may be treated with one dose every 12 weeks"?

Correct?

A. Correct. After one year of -- after one year -- every 12 weeks after one year of effective therapy.

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Q. And when we were talking about that 12-week dosing interval, we can agree that it is not the approximately eight-week dosing interval that is called for by Claim 6 of the '572 patent, right?

A. That's correct. That's not in the '572 patent.

Q. And we can agree that a four-week (monthly) dosing regimen is not an eight-week dosing regimen, right?

A. I'm sorry. Repeat that again. The four-week dosing schedule --

Q. The four-week (monthly) dosing regimen is not an eight-week dosing regimen?

A. That's true, yes.

Q. And we can also agree that an every-12-week regimen is not an eight-week regimen?

A. Yes.

Q. Dr. Csaky, can we agree that the various dosing regimens discussed in the Yesafili labeling that relates to dosing for CRVO, DME, DR, or AMD that is just monthly will not satisfy any of the asserted claims of the '601 and '572 patents?

A. So the monthly loading doses are within the claims, correct. And your question is if you go beyond the loading doses, correct?

Q. Correct.

A. So yes, if they go beyond the loading doses as

outlined -- now, it does say -- I'm not sure because it does say -- can you just refresh my memory on the -- you said the '572 patent?

Q. Yes. The asserted patent in this case.

A. Right. So can I just look at that real quickly?

Q. Can you answer this question first, and then we'll go back to that later.

A. Well, because I think you're asking does monthly dosing not apply to the '572. Is that what you asked?

Q. I'm just asking about the asserted claims of the '601 and '572 patents.

A. And I'm just trying to remember off the top of my head. And we can get to that. But I just want to make sure I understand because -- I may be wrong. I thought in the loading -- I thought in the -- it says one or more -- I just have to look at the '572 to be absolutely sure.

Q. Sure. Can we pull up the '572 patent, please.

A. I may be misremembering. I'm sorry. There's so many claims and such.

THE COURT: Agreed, Doctor.

THE WITNESS: Yeah, if you're confused, I'm confused. Okay.

BY MS. LESKO:

Q. And let's look at Claims 1 through 6 if we can pull that up. It should be in your binder as well, Dr. Csaky. It's

PTX 3, if you want to --

A. PTX? I'm sorry.

Q. 3.

A. 3. I'm sorry. I just want to make sure, if you don't mind. I apologize. I just want to make sure I don't misspeak.

So my understanding would be that in the '572, right, it has a method of treating an angiogenic eye disorder, correct, in a patient in need thereof, comprising sequentially administering to the patient by intravitreal injection a single initial dose followed by one or more secondary doses, which would imply that you can give more down the road, and then at some point down the road you follow that by one or more tertiary doses.

So there could be -- I guess you could interpret this that, for a period of time, you would be giving monthly doses, correct?

Q. So I just want to make sure we're understanding each other. For Claim 1, would a straight monthly regimen be within the scope of Claim 1?

A. Well, again, it would depend on -- you know, if I'm giving one or more loading doses and I am looking at that monthly regimen, it's kind of I'm having to just keep giving monthly injections. You know, as kind of an ophthalmologist reading this, I could interpret this as saying, well, I'm just

having to give monthly secondary doses, right? So for a while, depending on how long that went, I might have to give a series of secondary doses for a while and this claim would be still valid. Would that be a fair assessment?

Q. Well, the question is for you.

A. I'll ask myself. If I would ask myself, I guess that would be yes.

Q. You know what? Let's move on.

THE COURT: That's the beauty of being qualified as an expert, Doctor.

THE WITNESS: I'm sorry.

THE COURT: Ask yourself a question.

Go ahead, Counsel.

BY MS. LESKO:

Q. Let's talk about clinical judgment. Now, Dr. Csaky, a physician must exercise their clinical judgment to decide whether their patient needs dosing for the first three months followed by intravitreal injections once every eight weeks versus once every four weeks versus once every 12 weeks, yes?

A. Yes, absolutely.

Q. And, again, a physician must be the one who decides if their patient has had enough monthly doses or needs more monthly doses beyond five for DME or DR, right?

A. We make -- you know, yes, we make assessments. As we are treating patients, you know, we'll make assessments from

time to time to alter regimens depending on their response.

Q. And that comes down to the clinical judgment of the physician?

A. Yes. I mean, the -- as we see a patient, then yes, I can determine -- I'll give you an example. That if I'm treating a patient and I know that that patient, like I mentioned in my direct, that they have bad macular edema and I want to go ahead and say I'm going to go ahead and give five, I give five. And then I use my clinical judgment at that point to determine the next step.

Q. Could we also agree that the decision to use aflibercept in a fixed dosing regimen versus a prn regimen versus a treat-and-extend regimen is an issue left to the clinical judgment of physicians?

A. Yes. It's up to the clinician to determine what regimen is best for that patient. And that's -- like I told you, there's a whole series of decisions that we make deciding what our regimen is going to be for that patient.

Q. Okay. And you were aware that there are clinicians who exercise their clinical judgment to use Eylea in a treat-and-extend method, yes?

A. Oh, yes.

Q. And we can agree that there are some clinicians who exercise their clinical judgment to use Eylea in a prn dosing regimen?

A. Yeah, some. Most of my colleagues probably don't do that for macular degeneration. We tend to do it a little bit more for diabetic macular edema. But some people do.

Q. Right. My question was we can agree that there are some clinicians?

A. Clearly, yeah, there are some.

Q. And Claim 1 of the '572 patent does not cover treat-and-extend dosing regimens, correct?

A. So the -- I think in my deposition you asked me this question. And the term itself -- so we just want to make sure how we define treat and extend, right? So there are various terms for how we define treat and extend, correct. So at least among my colleagues, you can get variations on what the term "treat and extend" means, right? How -- and the term itself, from my perspective, is really that step when you are treating and extending, right? So that's a specific step of treatments, protocols, that I make as I go forward, right?

So that portion of treat and extend is very specific. And, again, each doctor, I can tell you, has -- we all have our own individual algorithms and paradigms and what eye and which patient, what our algorithm is for treat and extend.

So I'm not sure -- I'll give you an example. If I take a patient and I start with, let's say, three monthly dosing, right, and I switch to eight weeks, and I go for eight weeks, let's say, two or three injections, and then I start

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extending, right. So that portion of the extension is definitely treat and extend, but the treat and extends can be very much about -- there can be variations.

So I think we have to understand that the term "treat and extend" is -- there's some variations in how we approach it. Every patient is different. That's really the bottom line.

Q. Well, Dr. Csaky, you were correct. You were asked this question at your deposition. So let's turn to your deposition transcript, which is at DTX 7224 --

A. Uh-huh.

Q. -- in your binder, Exhibit page 59.

A. Say that again.

Q. We'll put it up on the screen as well for you, but it's DTX 7224. Transcript page 232, lines 2 to 6. Do you see it up on the screen?

A. Sure do.

Q. Were you asked Claim 1 of the '572 patent also does not cover treat-and-extend dosing regimens, correct?

A. Yes.

Q. And the answer you gave was it does not appear to extend to incorporate the various aspects of treat-and-extend protocols?

A. That's correct.

Q. So I just asked you -- I just asked you about the

'572 patent. So now let's go to the '601 patent. Does the '601 patent cover treat-and-extend dosing regimens?

A. So, again, that portion of the treat and extend, it does not.

Q. And let me ask this just to be clear for the record.

Does Claim 1 of the '601 patent cover treat-and-extend dosing regimens?

A. So that portion that we talk about when we say treat and extend does not, right? It depends on the context in which you define -- so if we're talking about a true treat and extend when -- let's say right from the beginning I'm treating and extending, then it does not.

But if there's other regimens when I'm, let's say, doing a certain portion and then I start to treat and extend down the road at some point, then you might say that, well, at the beginning, I did something of the -- you know, in this case, '572. So the term "treat and extend" didn't apply. So as I said, it doesn't apply directly in that context because it's not that concept of treat and extend, right?

So it's important to understand what treat and extend is. It's truly what it means, right? It's -- you're treating and extending, treating and extending the interval, right?

Q. So, Dr. Csaky, I'm sure you're not surprised you were asked this question as well at your deposition.

A. Yeah.

Q. And the answer you gave then was a little bit with less commentary. So let's just look back at your deposition transcript and see what exactly you answered.

Were you asked the question, "Does Claim 1 of the '601 patent cover treat-and-extend dosing regimens?"

And the answer you gave was, "Of the -- Claim 1 of the '601 patent does not appear to extend to treat and extend."

Were you asked that question and you gave that answer?

A. Absolutely.

Q. So we just went through treat and extend. Let's now talk about prn dosing.

Is it your opinion that prn dosing regimens are not covered by the asserted claims here?

A. So that phase of the prn dosing regimen is not covered. By the '601 or the -- whatever the -- repeat -- the claims. That portion of what we would term prn is not covered.

Q. And you would agree that prn is significantly different than a dosing schedule that happens at fixed intervals?

A. Yes.

Q. Let's switch gears for a moment. Do you know Dr. Carl Regillo.

A. I know Carl.

Q. He's well-known and highly regarded in the

ophthalmology field?

A. Carl's a good friend and highly regarded.

Q. According to your CV, you have even published articles together?

A. Yes.

Q. So let's go to the "Settling on an Anti-VEGF Dosing Regimen" article that we previously looked at. It was one of the standalone documents.

A. Yes.

Q. Do you have that? We'll put it up on the screen as well.

A. Can you give me the -- do I need the PTX thing?

Q. This is one of the ones that was in the pocket.

A. Oh, okay.

Q. It's titled "Settling on an Anti-VEGF Dosing Regimen."

A. Okay. So there were two pocket articles. Right? They were these two, correct?

Q. Yes. And it's up on the screen.

A. Perfect. Okay. Thank you so much.

Q. Okay. So directing your attention to page 1 and specifically on the first page of that article, third paragraph, do you see Dr. Regillo's statement here that "You can do a continuous treatment at a fixed interval where you treat every month or every two months. That's the least

popular approach."

Do you see that?

A. Yes.

Q. Do you agree with Dr. Regillo that, even as early as 2013, fixed-interval dosing was the least popular anti-VEGF dosing regimen?

A. Yeah. I mean, it's hard to know back then, but I think it's fair to say that the term "popular" assumes that people didn't -- I think that it was -- there was only some indications in which people would use it. It clearly was in the minority. I would agree with that statement.

Q. Okay. We can take that down, please.

And do you see that the next sentence says, "Very few people do that because it may represent overtreatment in some people"? Do you see that?

A. Correct.

Q. The next is "Prn treatment, which is an approach to individualized therapy and minimize overtreatment."

A. Yes.

Q. Would you agree with that statement?

A. It definitely -- I just want to make sure we're clear because you heard you say about prn.

It's important -- and Carl said it correctly here. It definitely minimizes overtreatment, but it can minimize -- you can maximize undertreatment.

Q. And then the final line is "You treat monthly until the macula is dry, and then you monitor closely and treat recurrences."

A. Yes.

Q. And you agree with that?

A. That's Carl's approach to his description of what he's doing.

Q. And that's a prn approach?

A. Well, if you looked -- I mean, again, I think it's important to recognize that we all have our own -- you know, there's no set -- you know, these definitions -- prn, treat and extend -- are very much individually -- we all use our own kind of vocabulary, if you want to call it, right?

So our vocabularies that we use can be somewhat individual, right? You call it tomahto; I call it tomato. What you call prn, I call it something else. But this is Carl's -- his definition of prn.

Q. And let's look at Carl's -- Dr. Regillo's third statement here. "The third approach is the treat-and-extend strategy, which some believe may represent the best of both worlds in disease control and treatment burden."

Do you see that Dr. Regillo stated that?

A. Yes.

Q. And do you agree with Dr. Regillo's statement there?

A. You know, so again, I think -- I mean, we all use it.

We all do treat and extend. You know, the interesting thing about treat and extend is, you know, in many cases we end up with more injections, depending on the level of willingness to accept some degree of fluid, right?

So again, you know, some believe it's the best. Some believe it's the best; some don't believe it's the best.

Q. Let's put up on the screen DTX 2042.

And, Dr. Csaky, during your direct examination you testified that you are part of the American Society of Retina Specialists, correct?

A. Yes, I am.

Q. Can you confirm that DTX 2042 is the association of retinal specialists, 2017 PAT Survey?

A. I can.

Q. You've seen this before?

A. I have seen that.

Q. You have reviewed the PAT Surveys before?

A. I have reviewed the PAT Surveys.

Q. Do you typically review PAT Surveys?

A. I do -- again, I would say, you know, it just depends on kind of what mood I'm in, but yes.

MS. LESKO: And, Your Honor, we move to admit DTX 2042 into evidence.

THE COURT: Any objection?

MS. KAYALI: No objection, Your Honor.

THE COURT: Without objection, so admitted, DTX 2042.

(DTX 2042 was admitted.)

BY MS. LESKO:

Q. So let's look at DTX 2042 at exhibit page 17, which is Slide 7 of the 2017 PAT Survey.

A. Yes.

Q. It has the heading "In general, how do you treat wet AMD patients with active CNV"?

A. Yes.

Q. I'd like to direct your attention to Option 8, which reads, "Treat until dry on OCT, then as needed, prn."

A. Yes.

Q. Can we agree that Option A is a prn dosing regimen that was the preference of 9.8 percent of the physicians surveyed?

A. Yes. Again, I just want to make sure we're clear because I think it's these terminologies. When you say a prn, this is -- when doctors fill this out, there's choices --

Q. Sir, I'm just asking you to say what's on the screen, actually.

A. Oh, you want me to just repeat what's on the screen?

Q. I'm sorry. Go ahead. I didn't mean to cut you off. Do you want to finish your answer?

A. No. All I was saying was, when you asked does this represent prn, it represents to these individuals the choice of

whatever they chose as prn, correct.

Q. Okay. And that's 9.8 percent?

A. That's 9.8 percent.

Q. And Option B is described as a regimen of treat until dry on OCT, then extend -- treat and extend, correct?

A. Correct.

Q. That was the overwhelming preference of over 70.9 percent of physicians surveyed?

A. That is, again, this definition of "treat and extend until dry" and then how the physicians determined in their -- whatever regimen they're using for treat and extend, they would have chosen, you know, this category of -- on the survey.

Q. Let's look at Option C, which reads, "Treat until dry on OCT; then follow up every three or four months."

Do you see that?

A. Yes.

Q. Does the Option C regimen fall within the scope of the asserted claims here?

A. As written, this would not fall under the regimen as far as I can tell. So --

Q. Let's pull up Option D, which reads, "Inject monthly regardless of fluid or exam," yes?

A. Yes.

Q. Does the Option D regimen fall within the scope of the asserted claims here?

A. So again, as we talked about, could someone in the '572 be injecting monthly as a way to say I can inject on a -- with my secondary doses for a while, but I would say in general this would not fall under the '572 patent.

Q. We then have Option E, which encompasses Options A or B, and that was the stated practice of 60.3 percent of physicians responding to the survey, right?

A. Yes.

Q. That leaves Option F, other, at 1.2 percent in the PAT Survey, right?

A. Correct.

Q. We can pull that exhibit down.

In your opinions in this case, did you offer any data comparable to what we saw in the PAT Survey for physicians specific to treatment practices for diabetic retinopathy or diabetic macular edema?

A. I did not.

Q. In fact, you have not endeavored and did not attempt in your direct examination to quantify the number of ophthalmologists who currently employ the claimed methods with Eylea or the number who actually would follow the instructions to employ those methods with Yesafili, true?

A. I did not.

Q. Dr. Csaky, let's go back to PTX 586, which your counsel showed you in your direct exam. Let's start with

exhibit page 1. We'll put it up on the screen as well.

A. Yes.

Q. If we look at the background and objective section, this analysis of the IRIS Registry tried to see if they could emulate the VIEW randomized clinical trials, eligibility criteria, treatment protocol regimen, and primary end point, right?

A. That's what it states, correct.

Q. Let's take a look at the results section on the first page of PTX 586, bottom left-hand corner. It says that there were 90,900 patients who met the VIEW randomized clinical trial eligibility criteria, right?

A. Correct. I'm sorry. Say that again. I lost my train of thought. Say that last statement before. What did you say?

Q. In the results section, bottom left-hand corner, first sentence, it says that there were 90,900 patients who met VIEW RCT eligibility criteria?

A. That's correct.

Q. And that's the randomized clinical trial eligibility criteria?

A. That's correct.

Q. Let's go to the top paragraph in the upper right-hand column of exhibit page 1 of PTX 586, the conclusion section.

A. Yes.

Q. We can agree that in the conclusion section, they reported that a small percentage of real-world patients met the view randomized clinical trial study eligibility criteria and treatment protocol regimen, right?

A. Correct.

Q. Now let's go to the fourth page of this exhibit, Table 3, what is titled "Inclusion Criteria for Treatment Arms."

Do you have that on your screen?

A. Yes, I've got it. Thank you.

Q. If we look at the right-hand column, that is the one that is titled "IAI 2q8," right?

A. Yes. "IAI 2q8." Gotcha.

Q. That is the one you identified as the one covered by the claims here?

A. Correct.

Q. Let's look at the inclusion criteria of patient needed to meet that entry description of IAI 2q8.

Do you see that on the screen?

A. Yes. That's true. Yes, I see that.

Q. The first entry says, "Three consecutive monthly injections every 28 days plus or minus seven days," right?

A. Gotcha. Sorry. I was one page behind.

Yes. Go ahead. Yes, three monthly injections. Yes.

Q. So the first three loading doses could be spaced

anywhere from 21 days, three weeks, to 35 days, five weeks apart?

A. Correct. They can be plus or minus seven days.

Q. Now let's look at the last entry in this right-hand column titled "IAI 2q8." It states, "After the third monthly injection, injections needed to occur every 56 days, plus or minus seven days," right?

A. Correct.

Q. Every eight weeks would be every 56 days, true?

A. Correct.

Q. So their criteria included patients who were dosed every seven weeks as well as every nine weeks?

A. They could have been, plus or minus seven days, right. So it could have been eight weeks or nine weeks or seven weeks, correct.

Q. Let's sum this up, then. For a patient's medical record in the study to be put into the IAI 2q8 bucket, the term "monthly" was used to mean every three to five weeks and the extended interval afterwards was allowed to be seven to nine weeks. Is that correct?

A. Correct.

Q. Let's go to exhibit page 5 in PTX 586, right-hand column, near the bottom of the page, last full paragraph, please.

A. You're going a little faster than I can process. Say

that again.

Q. Exhibit page 5.

A. Exhibit page 5.

Q. Right-hand column.

A. Gotcha, gotcha, gotcha. Just a little faster than I am. Okay.

Q. I apologize. Last full paragraph.

A. Yes. I gotcha. The word "total." Yes, I gotcha.

Q. The one that starts off "there was a total of 606,971"?

A. Correct.

Q. It says in the first sentence that "For this publication, there was a total of 606,971 patients who had an anti-VEGF injection during our study period," right?

A. Correct.

Q. So that means in the patient records screened, the patient got at least one injection of aflibercept, bevacizumab, or ranibizumab or another VEGF inhibitor?

A. Those would be -- for this period of time, we don't have -- those are the three anti-VEGF agents we have right now.

Q. Let's go to the Table 5 you pointed to, which is at exhibit page 6 --

A. Yes.

Q. -- in PTX 586.

A. Yes.

Q. There were only 154 patients out of the over 90,000 screened that met the IAI 2q8 criteria, right?

A. So, again, you have to remember here that there was a restriction, right? I think you pointed out that restriction yourself, I think. And that is that there had to be -- maybe you didn't, but I will. So if you look on Table 2 -- and that's PTX 0003. Do you see that?

Q. Yep.

A. Okay. So the important thing here is to recognize that what they were trying to do is not identify everybody who was receiving this regimen, right? They were trying to identify the regimen that -- in people who met the VIEW 1-VIEW 2 inclusion criteria, right?

So there could have been people who didn't meet that inclusion criteria, right? They would not have been counted. They could be on this regimen.

So this is not a full survey. What they were trying to really do is emulate VIEW 1 and VIEW 2. So they didn't necessarily go -- say, hey, let's take everybody who received that regimen regardless of what -- how they fit into the VIEW 1-VIEW 2 eligibility criteria, right? So we have to understand that the purpose of this study was to really not just understand that we already excluded patients who didn't meet those inclusion --

Q. Dr. Csaky?

A. I'm sorry. Am I talking too much?

Q. No, I'm sorry. Go ahead. My question was slightly different, but I don't want to cut you off.

A. No, no. You were asking me -- because I think the question is this represents some number, and I wanted to make sure we're clear that there could have been other patients in the IRIS Registry who received this treatment protocol but would not have been included in this study.

Q. Okay. 20 times more patients in this chart were given monthly aflibercept injections as compared to patients in the IAI 2q8 group, right?

A. So 20 times more patients were given -- you're saying every four months -- four weeks. I'm sorry. I'm a little bit slow.

Q. 20 times more -- 15 times more patients in this chart were -- I apologize.

A. I miss --

THE COURT: It's math. That's all you, Counsel.

THE WITNESS: Okay. Yes.

MS. LESKO: Someone else drafted this particular question.

THE COURT: Noted.

THE WITNESS: Okay. Yes.

BY MS. LESKO:

Q. I believe it's 15 --

A. It's approximately 15.

Q. -- times more patients in this chart were given monthly aflibercept injections as compared to patients in the IAI 2q8 group; is that right?

A. On the patients -- again, you have to remember -- I just want to make sure we're clear for the record -- that this is in the groups of patients who met the eligibility criteria and then were allowed to be examined for when they got their treatment. So in this subset of patients, yes, your math is correct.

Q. And there were over ten times as many patients being treated with ranibizumab monthly as compared to patients in the IAI 2q8 group, right?

A. Yes. Again -- I'm not going to keep repeating the caveats, but yes.

Q. And, Dr. Csaky, let's take one more look at PTX 1527, which is Dr. Do's declaration.

A. Okay.

Q. In the front page do you see the title "Inter Partes Review Number 2021-0081"?

A. Yes.

Q. It says U.S. Patent Number 9,254,338 B2?

A. Yes.

Q. Are you aware that the '338 patent is in the same patent family as the '572 and the '601 patents here?

A. I'm not aware of any of those patents -- those patent issues.

Q. Are you aware that inter partes review proceedings are contested proceedings between Regeneron and Mylan in the PTO?

A. I'm not -- again, I hate to say this, but I'm -- when I can play down "I'm not a lawyer" card; and so I don't know all the details. I'm sorry.

Q. That's okay. Let's go to PTX 1527, the third page of Dr. Do's declaration.

A. Is it in my --

Q. We can pull it up on the screen.

A. So I don't have to find it through this -- go ahead.

Q. Can you confirm that Dr. Do stated in her declaration that she was retained by counsel for Regeneron when she made these statements?

A. Yes. She said, "I've been retained by counsel for Regeneron," correct.

Q. If we look at the bottom of exhibit page 3 in paragraph 2, did Dr. Do confirm that she was acting as a paid expert for Regeneron when she made the statements you relied on here?

A. Yes. She is being paid at an hourly rate, correct.

Q. Can you identify for me any of your published papers where you have relied on a paid litigation statement by an

expert witness as the basis for your scientific opinions?

A. No, I don't think I've ever relied on a -- I'm trying to remember because we do sit on scientific advisory boards, right? We all get paid to be on a scientific advisory board. And so in some of those cases, people are paid.

And so when people give opinions -- not to digress, but it is an important question because, as I think about it, right, in today's world, there's an interplay between industry and academics. And so, many times ideas are exchanged in the context of a scientific advisory board by a company, right?

And so I'd have -- I think -- I'd probably say I have used opinions in the context of somebody being paid from an advisory perspective from a company and used that in my thinking and how I write a paper or think about things for sure.

Q. So just to be clear, I wasn't just asking about any paid consulting relationship. I'm asking can you identify for me any of your published papers where you have relied on a paid litigation statement by an expert witness as the basis for your scientific opinion?

A. No, that's true. I don't think I've ever used a litigation document -- I mean statement for my scientific advisory.

Q. These conversations with doctors that you talked about in your direct examination, can you identify for me any

time when you talked about treatment guidelines and how to dose patients based on what was said in a statement they were paid to make in a litigation-type proceeding?

A. No. As I said, I don't think I've ever relied on a paid litigation context. But am I allowed to just say one other thing just because I know Dr. Do? Is that --

THE COURT: Is it in response to the question, sir?

THE WITNESS: Yeah. No, I just want to make sure because Diana Do is a good friend. She's an incredibly ethical person. And so I guess when I read this, for me it reflected Diana's opinions, right? And so from my perspective, because I know Diana -- I think you have seen my CV; Diana and I have published together -- I used -- my reliance was really on knowing Diana and knowing how ethical she is and what she's going to say reflects what she truly believes.

BY MS. LESKO:

Q. Can you identify for me any of your published scientific work before your peers where you have relied on assertions made in a declaration from legal proceedings?

A. I have not.

MS. LESKO: Your Honor, in view of this testimony, we renew our motion to exclude for noncompliance with Rule 703. We are happy to address it in posttrial submissions if you prefer.

THE COURT: The Court will hold that motion in

abeyance until the parties have a chance to brief in posttrial motions.

Any other questions on cross-examination, Counsel?

MS. LESKO: Nothing further at this time, Your Honor. Thank you.

Thank you, Dr. Csaky.

THE COURT: Redirect, Counsel?

MS. KAYALI: I do, Your Honor. If I could ask the Court's indulgence for a brief personal comfort break, I'd really appreciate it.

THE COURT: Certainly. Motion granted. We'll take ten minutes.

Doctor, you remain countryless, sir.

So we'll take ten primarily for counsel's benefit. I'll ask everyone else to let her head to the front of the line.

(A recess was taken from 2:36 p.m. to 2:52 p.m.)

THE COURT: Counsel, assuming an appropriate level of personal comfort has been restored, you may proceed.

MS. KAYALI: It has been, with sincere gratitude, Your Honor.

THE COURT: Outstanding. Go right ahead.

REDIRECT EXAMINATION

BY MS. KAYALI:

Q. Let's pull up PTX 3, if we could, and I want to look at Claim 6, please.

And, Dr. Csaky, I want to see if I can clarify the kinds of regimens that are in the scope of Claim 6. So I want you to imagine for me a regimen in which you gave three monthly loading doses followed by a switch to dosing once every eight weeks for at least one or two doses, and then you chose to extend the regimen from there in duration.

Have you performed the method of Claim 6?

A. If I did that, then I would have performed the method of Claim 6. Claim 1, actually.

Q. Claim 1 and then by virtue of assuming Dr. Trout testifies that Yesafili is isotonic, then you would have performed the method of Claim 6; is that right?

A. Correct.

Q. Let's turn, then, to DTX 2042, and I want to look at Slide Number 7. And so that's DTX 2042, page 17.

Do you see this?

A. Correct.

Q. And do you recall being asked about this slide and this document during cross-examination?

A. Yes.

Q. So I want you to imagine the very same regimen. A physician gives three monthly doses, followed by dosing once

every eight weeks for one or two doses, and then chose to extend the treatment interval from there.

Which of the options would the physician have selected in this survey?

A. So, again, this is what I was trying to explain was that the -- when I opined previously the treat-and-extend is a very specific regimen, right? It's -- and so it could very well be, and many times what we really are using treat and extend is for the extended maintenance period.

You have to remember that we don't cure a lot of these patients. We cure very few patients. And so we're trying to -- we struggle to get to that interval that's right for them.

The beginning stages are somewhat different, right? The beginning stages, as we've talked about, we want to control the disease, we want to give those almost three loading doses. Very common approach to give three loading doses. And then what this has taught us is we can go to eight weeks, right? And there's some people who would then go eight weeks for one or two just to make sure the disease is nice and quiet, and then they will start to extend.

So if I'm treating someone like that and I've been out a year or two, then I'm going to have picked B because they're on treat-and-extend regimen, right? But it could very well have been that at the beginning of my treatment regimen I

would have used a method that we just talked about where I'm giving three monthly loadings; I'm extending to eight weeks; I may give one or two eight-week injections, maybe even three; and transition to a treat-and-extend.

So that's what I was trying to explain, is that these treat-and-extend regimens are highly variable and there is no such thing as this is what treat and extend is because it all depends on the interval when you decide to choose, how aggressively you want to go to that treat-and-extend interval.

And so the beginning stages can be in some cases more like the claim; other cases you can go right into a treat-and-extend. So, for example, if I take -- see a patient, I inject, have them come back in four weeks, they're dry, I go right to six weeks, right to eight weeks, I'm treat-and-extending right from the beginning, then I'm not following the claim.

So there is -- you know, there's some complexity and tremendous amount of heterogeneity in this choice that physicians would have chosen in this PAT Survey.

Q. And, Dr. Csaky, I just have really one more set of questions. I believe you were asked on cross-examination about various ways doctors use Eylea that don't necessarily conform precisely to the label.

Does it remain your opinion that, if Yesafili is marketed, at least some doctors will do exactly what that label

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says and perform the method of the claims?

A. Yeah. I mean, as we said, there would still be some doctors who will do, as we talked about, the methods of the claim.

MS. KAYALI: No further questions, Your Honor.

THE COURT: Recross, Counsel?

MS. LESKO: No, Your Honor. Thank you.

THE COURT: All right. Doctor, thank you very much, sir. You can step down. Yes, you're allowed to speak to other humans.

THE WITNESS: Thank you, Your Honor.

THE COURT: I don't know if that's good or bad.

THE WITNESS: They're all lawyers.

THE COURT: Trust me, I know.

That wasn't a personal comment on anyone here.

Counsel, I suspect I know what you're doing.

MS. KAYALI: Yes. Your Honor, I had wrote it on a sticky note and it went nowhere.

I would like to move the admission of the exhibits that we used in Dr. Csaky's direct examination.

I'm sorry, Ms. Lesko, to have you return.

THE COURT: All right, Counsel. Thank you. Do you have a list of those?

MS. KAYALI: I do.

THE COURT: If I could ask you to do that slowly,

please.

MS. KAYALI: Yes, Your Honor. Just for counsel's comfort, I do not intend to move the admission of Dr. Do's declaration; so I suspect we are otherwise in agreement.

The first was DTX 7053. The next is PTX 001, which I believe is already in evidence. The next is, again, PTX 003. I believe that's also already in evidence. The next is PTX 331. After that, PTX 586. And I have PTX 917, PTX 963, PTX 3097, and PTX 3338.

THE COURT: Any objection to any of those, Counsel?

MS. LESKO: No objection, Your Honor.

THE COURT: Without objection, those are hereby deemed admitted.

(PTX 331, 586, 917, 963, 3097, 3338 were admitted.)

MS. KAYALI: Thank you, Your Honor.

THE COURT: Thank you.

Musical chairs may resume. Thank you all.

Yes, Mr. Berl.

MR. BERL: Yes, Your Honor. Plaintiffs want to call Dr. Eric Furfine. I think opposing counsel has stated a request to note some objection before he takes the stand; so I'll yield so he can do that.

THE COURT: Counsel.

MR. SALMEN: Thank you, Your Honor. Heinz Salmen on

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behalf of the defendant. I'll be very quick, Your Honor, but there was one issue that we wanted to bring to Your Honor's attention before Dr. Furfine took the stand.

Regeneron identified several dozen documents that Dr. Furfine is going to be testifying about today, and our objection to these documents -- to those exhibits is that the vast majority of them were not disclosed in response to our interrogatories regarding a prior invention and conception and reduction to practice.

Now, we anticipated this issue in our Motion in Limine Number 5. That's at Docket Number 449. And we are happy to defer argument on this to our posttrial briefing, but we wanted to make it clear that, in our view, plaintiff had an obligation to disclose these documents in response to our interrogatories. They did not, and they had an obligation to disclose them with particularity. They also did not do that.

THE COURT: Do you have these documents now, Counsel? Were they disclosed in discovery at some point?

MR. SALMEN: They were. They were produced, Your Honor. They were never disclosed in response to our interrogatories.

So we're not taking a position that Dr. Furfine cannot state his knowledge with respect to them, but in our view they should not be -- Regeneron should not be permitted to rely on these documents to establish that prior invention date.

THE COURT: Understood. The Court will continue to hold that issue in abeyance until posttrial briefing. For purposes of our trial record, the Court will presumably receive them as we go. They were produced in discovery, as counsel indicated. I realize there's a looming issue with respect to how specific those discovery responses may be. And we'll take that up I'm sure in posttrial briefing in the Court's ultimate order.

MR. BERL: In case it wasn't clear to Your Honor, we disagree with virtually everything that Mr. Salmen just said.

THE COURT: I assumed as much, Mr. Berl. I know what happens when you assume, but I feel safe doing that here.

With the -- I came to change of shift in a coal mine, but with that, Mr. Berl, plaintiff may now call its next witness.

MR. BERL: Thank you, Your Honor. Plaintiffs call Dr. Eric Furfine.

ERIC FURFINE, PhD, PLAINTIFF'S WITNESS, SWORN

MR. BERL: Your Honor, may I approach with exhibits and demonstratives?

THE COURT: You may.

Thank you, Counsel. You may proceed.

MR. BERL: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. BERL:

Q. Good afternoon, Dr. Furfine. And try to speak into the microphone and rather slowly. I'll try to do the same. I have a fear that Ms. Knecht is going to oppose my next pro hac vice application if we don't.

THE COURT: I'll take the fifth. Go ahead.

BY MR. BERL:

Q. Good afternoon, Dr. Furfine.

A. Good afternoon.

Q. Would you please introduce yourself to the Court.

A. My name is Eric Furfine.

Q. What do you do for a living, Dr. Furfine?

A. I'm a drug discovery and development scientist.

Q. How did you become interested in science?

A. My interest in science started many years ago when I was a child, and I guess I'm an example of the apple doesn't fall very far from the tree. My dad was a biochemist. And I remember when young, he would take my brother and I into the lab with him and, you know, we would help his graduate students and postdocs -- what we called washing the dishes, but was mostly really cleaning their glassware. And I just remember becoming fascinated with science and the work in the lab at a very early age.

Q. And what did you want to do when you grew up when you were a kid?

A. I was always headed towards some scientific endeavor. As I progressed through my schooling, college, and graduate school, it became clearer and clearer to me that I really wanted to work in making medicines, that that would be something I could get excited about on a regular basis and draw me into work.

Q. What do you do now?

A. I am the chief scientific and executive officer of a company called Mosaic Biosciences. We do drug discovery for other companies.

Q. Who are your clients for whom you help drug discovery?

A. Most of our clients are very small biotech companies that are looking to be able to build their company without actually hiring a lot of people and finding labs. We actually provide the service for them and a lot of strategic guidance.

Q. Can you briefly describe your education, Dr. Furfine.

A. I got an undergraduate degree from Washington University in St. Louis in chemistry. I got a graduate PhD degree at Brandeis University in biochemistry. And I did postdoctoral work at the University of California, San Francisco, in molecular parasitology. That's the study of the gory details of how parasites work.

Q. What did you do after that?

A. I went pretty much straight into industry at that

point, in fact, to pursue trying to learn how to be a drug hunter, which I've become. And that's why I went to Burroughs Wellcome to start. It was a fairly medium- to large-sized pharmaceutical company.

Q. How long did you stay there?

A. I was there about 13 years. And from there I went to Regeneron.

Q. And while you were at Burroughs Wellcome did you do any work on formulation research?

A. Yes, I did.

Q. Why did you decide to go to Regeneron at that point?

A. There were three big reasons for me. One is an opportunity to work with a graduate student colleague of mine who I had a lot of respect for, Neil Stahl, and to have an opportunity to work with him again was an exciting thing for me.

It was exciting that Regeneron was a smaller company and was a biotechnology company working in protein therapeutics and an opportunity to expand my understanding of new types of drugs, proteins instead of small molecules that I was doing earlier. So that was a good opportunity.

And there was also a major opportunity to expand my understanding of the later stages of drug development and discovery and to really work in more of the development end. So that was also enticing to me.

Q. What year did you join Regeneron?

A. 2002.

Q. How long did you stay?

A. I was there till summer of 2006.

Q. And you said it was a relatively small company. Can you describe what Regeneron was like during the years that you worked there?

A. Yes. You know, there was several hundred people there, probably 5 or 600 people, I would guess, but -- which is much smaller than Burroughs Wellcome which is a major pharmaceutical company. And I just was always interested in the fact that there was just so much discussion of science at Regeneron and how strong a force it was in driving decision-making there. It was a great place in that regard.

Q. Since 2006, have you had any professional relationship or association with Regeneron?

A. Nothing professional. I maintained friendships and collegial interactions with people I know there, but nothing other than that.

Q. Dr. Furfine, I'd like to discuss with you today your role on the project with the aflibercept molecule.

What was your role at Regeneron during that time?

A. I was the head of preclinical development, it was called. Preclinical development involves -- a big part of what it involves is to do formulation development for the proteins

that we were working on.

A second, similar sized part was to really understand what happens in animals, in humans, and to be able to measure those things and prepare drugs to get ready to move into the clinic.

Q. When did you begin working on the VEGF Trap or a VEGF Trap?

A. I would say approximately a year after I was there, maybe 2003.

Q. And what was the result of that project?

A. The biggest thing that came out of it was Eylea.

Q. Now, I'm going to place on the screen what's been marked as PTX 2 in this case.

Dr. Furfine, is this the patent that describes and claims your inventions working on the project on aflibercept?

A. Yes, it is.

Q. We've highlighted various people who are listed as inventors. The first one, Eric Furfine, we know.

Who is Daniel Dix?

A. Daniel Dix was the head of the formulation group that reported to me.

Q. How about Kenneth Graham? Who is he?

A. Kenneth was a scientist in the formulation group, and he reported to Dan.

Q. And Kelly Frye, who is that?

A. Kelly Frye was also a formulation scientist that reported to Dan.

Q. Dr. Yancopoulos, from whom the Court heard yesterday, is not listed as an inventor on the patent.

What was his role vis-a-vis the project that you were working on with aflibercept?

A. Yeah. I mean, as a senior leader in the company, George was very intimately involved in all the things that were required to move a drug into the clinic and follow it throughout the clinic. And he stayed abreast of the work that we were doing to prepare drugs to be ready to go into clinical trials and to be able to maintain them in clinical trials.

Q. Did you meet with Dr. Yancopoulos during this period?

A. Absolutely. Yes, on a regular basis.

Q. Now, we've highlighted under Number 73 there "Assignee: Regeneron Pharmaceuticals."

What is your understanding about how Regeneron Pharmaceuticals is the assignee of the patent that you helped invent?

A. All employees of Regeneron were required to assign their inventions to the company. That was a condition of your employment.

Q. Was that true throughout the time that you were at Regeneron?

A. Yes, it was, absolutely.

Q. Now, we've been talking in this case about aflibercept. What is aflibercept?

A. Aflibercept is a man-made, humanly devised protein where you take two receptors that are normally on the surface of the cell and you genetically engineer them to be on an antibody part. We call that the FC domain.

So you make this construct of receptor domains fused to an antibody part, and that creates a drug.

Q. And when you say they're fused, does that make them what we've heard of called as a fusion protein?

A. Correct. It's referred to commonly as a fusion protein.

Q. And was aflibercept the only VEGF blocker known at the time that you were working on the project?

A. No, it was not.

Q. Were there any prominent VEGF blockers that you were knowing about and following at the time?

A. Two of the most prominent VEGF blockers were Avastin, or bevacizumab is the genetic name, and Lucentis, or it was ranibizumab at that time because it wasn't approved when we first started working on it.

Q. Who was developing those molecules?

A. Genentech was the company that was doing that.

Q. And at the time you were working on your project, who was Genentech in the field of biotechnology and in the field of

VEGF?

A. Genentech were really leaders in both of those spaces. They were probably the premier company in protein therapeutics, and they were arguably the premier company in understanding VEGF biology and pursuing drugs that modulate or inhibit VEGF.

Q. Who did you understand to be leading their VEGF development?

A. A lot of the scientific leadership came from a man named Napoleon Ferrara, who is arguably the father of VEGF and Avastin.

Q. How did Regeneron compare to Genentech at the time?

A. Analogous to us being David in the David and Goliath.

Q. Was aflibercept initially being pursued by Regeneron to treat eye diseases?

A. Not originally, no. It was treating cancer.

Q. Did you participate in that work?

A. I did, yes.

Q. Did there come time when Regeneron considered using aflibercept to treat eye diseases?

A. Yes, we did.

Q. And at the time you began the project, did you consider the project of formulating aflibercept to treat eye diseases easy or hard?

A. We considered that it would be a challenging,

difficult problem.

Q. Why is that?

A. First of all, aflibercept itself being a fusion protein was a challenge because there just wasn't that much knowledge on how to formulate and what the behaviors of those types of molecules, of fusion proteins general.

And the second reason was there just wasn't a lot of experience in the industry in developing formulations that were going to be injected intravitreally.

Q. Did the fact that aflibercept Trap VEGF mean that it could be used to treat diseases in the retina?

A. No. It had to reach the retina in order to be able to do that, both block VEGF and reach the site of action.

Q. Now, you mentioned ranibizumab, which was one of the two molecules that Genentech was developing.

What was your understanding about for what diseases Genentech was pursuing ranibizumab?

A. My understanding was they were only pursuing retinal diseases with ranibizumab.

Q. Did you consider aflibercept to be like ranibizumab for purposes of treating eye diseases?

A. It was similar in a very high-level sense in that they're both protein therapeutics, but the chemical nature of these two drugs was very, very different, and they were different classes of proteins.

Q. Did they have any other differences that you considered to be important for purposes of your project?

A. Yes. Aflibercept was considerably larger than ranibizumab was.

Q. What do you mean by larger or smaller in the context of molecules or proteins?

A. So what we mean by larger is molecular weight, kind of the space a molecule takes up. And the ranibizumab molecule was about a third the size of a full antibody. So it's an antibody part. It's in some ways considered an antibody, but it's really a part of an antibody, the FAB domain. And that's about a third of the size of a total antibody.

And the VEGF Trap or aflibercept is much more similar in size to an antibody than it is to ranibizumab.

Q. Was a molecular weight or the weight the only thing you considered in terms of the size?

A. No. So the molecular weight of aflibercept was a little bit smaller than an antibody, but we felt like it behaved more like the size of an antibody. It's kind of like if you -- could make a football analogy where you get somebody who's a fullback might be or a running back might be, this relatively heavy, relatively dense, small, compact person; and then you have a wide receiver who might weigh even maybe a little bit less but be much bigger, might have more trouble fitting in an airplane seat because of their -- they just take

up more space.

Q. And so was aflibercept more like the wide receiver or like the fullback?

A. More like the wide receiver and, therefore, more similar to an antibody in size, despite its actual weight being somewhat less.

Q. And was aflibercept in the same class of molecules as ranibizumab?

A. No. As I mentioned, ranibizumab was an antibody or considered an antibody as it was part of an antibody, and aflibercept was a receptor fusion protein. It had receptor domains on it that were previously in a normal setting on the surface of a cell and bore no resemblance to the structures of an antibody.

Q. Based on your understanding at the time, does a formulation that works to stabilize one protein in a class work to stabilize a separate protein in a class?

A. No, not necessarily.

Q. Why not?

A. The chemical nature of even two antibodies can be very different, and it's the chemical nature of those antibodies, how charged they are, hydrophobic they are -- hydrophobic meaning kind of a dislike of water, if you will. Depending on the nature, they could be very different things that are required to maintain their stability in solution.

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Q. Did you understand that a formulation that stabilizes an antibody could be used to stabilize a fusion protein?

A. Definitely not. The differences between a fusion protein's chemical nature is even more different than an antibody to an antibody.

Q. And I should have asked you this before. When you came to Regeneron in 2002, did you start working on protein formulations immediately?

A. Yes.

Q. Was it your understanding, Dr. Furfine, that you could take an existing antibody formulation, take out the antibody, and put in a different molecule such as a fusion protein?

A. No. That's not how we do formulation discovery. We have a path where we do things that are fit for purpose. You decide what's going to be used for, you decide the nature of the molecule you're formulating, and you design the formulation for that.

Q. Would it even be allowed to make that kind of substitution to make your product that way?

A. Absolutely not. It's a cardinal rule of formulation science and drug discovery generally that you only put things in that you need. You have to actually go through the process of showing that you need something and figuring out exactly not only that you need it but how much to put in, and that includes

the drug itself.

Q. Now, you said a moment ago that you had to get into the proper areas of the eye. I just want to put up a figure on the screen from Exhibit 579. That's PTX 579.

When you were working on the project on aflibercept, what was your understanding about where the molecule had to go to treat the diseases you were targeting?

A. It would help if I had --

MR. BERL: May I approach, Your Honor?

THE COURT: You may.

THE WITNESS: So you see the word "choroid" here. This is the -- roughly the place in the eyeball where you would stick the needle, and it would go through the sclera here and into this kind of like peach-colored area. That's called the vitreous. So you would directly inject the drug right into the vitreous.

Now, the drug will freely over time, maybe about a day, diffuse throughout the vitreous, but the key is you see this lighter yellow-colored part that abuts the vitreous here, that goes here, that's the retina. So it has to be able to get out of the vitreous and into the retina.

It also needs to be able to get past the retina into this next darker red color next to the light yellow. That's called the choroid. Those are the two places where the disease happens, the choroid and the retina. So the drug needs to get

out of the vitreous, needs to penetrate these two tissues in order to work.

BY MR. BERL:

Q. And what was your understanding at the time about what kind of molecules would be most likely to get in significant amounts into the retina and choroid?

A. So there was evidence from our colleagues, competitors at Genentech that said that larger molecules, antibody-sized molecules, essentially stayed mostly in the vitreous and did not penetrate the retina; but smaller molecules, like ranibizumab, which is a third of the size of an antibody, was able to actually get into those tissues where the disease biology happens.

Q. Let's take a look -- it's in your binder as well -- at Exhibit 1848. Can you identify this document for the Court?

A. Yes. This is the paper that I was referring to from Genentech that compared the antibody to the ranibizumab.

Q. And did you read this article when you were working on your aflibercept project at Regeneron?

A. Yes, I did.

Q. And you mentioned Dr. Ferrara earlier. Is he one of the authors of this article?

A. Yes, he is, right here.

Q. Let's take a look at the abstract, and we've highlighted part of the abstract on the first page.

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Can you explain what Genentech was conveying and what you understood about it when you were working on your project?

A. Right. So you can see right here they point out the difference in molecular weight or the size. So you can see it's 150 versus about 50. So it's a third the size; so that's essentially consistent with what I was saying. And that the antibody, the bigger molecule, did not penetrate the retinal tissues whereas the ranibizumab, or the FAB fragment of the antibody, was able to penetrate the tissues in this study.

Q. What was the principle of this -- what was the relevance of this principle to your work on aflibercept at the time?

A. Well, as I mentioned before, because aflibercept was more similar in size to an antibody, we were concerned that we could see the same thing and that, if we gave an intravitreal injection of aflibercept, it might not get to the place where we needed it to go to affect the disease. So we were concerned about that.

Q. Did you understand this issue of size to be relevant to Genentech's development of ranibizumab?

A. Absolutely. I think that's partly why they published this paper too. And they clearly thought that this smaller molecule was the better way to go, and that's what they pushed forward with.

Q. When you read this when you were working at

Regeneron, were you certain that Genentech was correct about what it was saying?

A. I wasn't. I was skeptical of this article. As a scientist, we're often skeptical of articles and not that they think of everything. And I didn't -- I wasn't sure that this was right.

Q. What did you do in view of your skepticism?

A. Usually what scientists do when they're skeptical is they do their own experiment, and we did a study in rabbits.

Q. We'll get to that in a moment.

This issue of getting into the retina and the choroid, is it all or none like a light switch, Dr. Furfine?

A. No. I think there are degrees of penetration, and there can be examples sometimes where there is a sharp cutoff, but I don't think that was the case here. This is a gradient, if you will.

Q. Did Regeneron only have aflibercept to block VEGF, or did it have smaller molecules too?

A. We had small molecules. Well, we had something called a Mini-Trap. Kind of like what the FAB or the ranibizumab was a part of the antibody, we had the Mini-Trap that was a part of aflibercept that, in case I was wrong, then we would have the smaller molecule to move forward with as well.

Q. Just so it's clear, why did Regeneron create the

Mini-Trap?

A. Really in response to this report and other reports that suggested that smaller things do penetrate the retina better than larger things do.

Q. Let's take a look at one of your internal documents at the time. We'll call up PTX 83.

And, Dr. Furfine, is this an internal clinical program strategy meeting from the 14th of June 2003?

A. Yes, it is.

Q. And if we look on the first page, there's a number 4, formulation issues, Eric.

Who is that referring to?

A. That's this Eric.

Q. That's you?

A. Yes.

Q. Let's take a look at page 3 of the document, Dr. Furfine.

THE COURT: For the record, I'm fascinated by this time travel with documents and such. It looks like they were doing MSP. Very excited about this. Go ahead.

MR. BERL: It's probably the dot matrix printer or something.

THE COURT: As an aspiring boomer, I have greatly enjoyed this trip down memory lane.

MR. BERL: I'm with you.

BY MR. BERL:

Q. So looking at page 3, Dr. Furfine, it says "Systemic IV Administration, single-dose escalation IV with full-length VEGF Trap."

Can you explain what that means.

A. So this was -- IV stands for intravenous or the abbreviation for intravenous. So the idea here was to inject the VEGF Trap directly into the vein so you get what we call systemic exposure, and then with that systemic exposure you can penetrate the ocular tissue to treat the disease. And then these are the doses that were tested. You start low, and you go up higher.

Q. What is the full-length VEGF Trap referring to there?

A. That's aflibercept, full-size aflibercept.

Q. Why were you considering intravenous systemic administration to treat AMD with aflibercept?

A. There was evidence preclinically and clinically that the aflibercept -- that drugs could penetrate the retina and aflibercept preclinically could penetrate the retina after a systemic exposure. And so this was a good way to test the hypothesis in humans.

Q. And at this time did you know that you could get aflibercept into the retina by injection into the eye?

A. We did not. And part of the reason for doing the systemic study is that we maintained concern for that.

MR. BERL: I apologize, Your Honor. I think I said this is Exhibit 83. It's actually Exhibit 82.

THE COURT: Understood. Thank you.

MR. BERL: Sorry.

BY MR. BERL:

Q. Now, you had mentioned the Mini-Trap before. Were you considering the Mini-Trap for systemic intravenous administration?

A. No, only intravitreal.

Q. Let's take a look at the two bullets on page 2 of Exhibit 82. It says "Local administration - Full-Length Trap" and "Local administration - Mini-Trap."

What is that referencing?

A. Local administration here refers to an intravitreal injection, so a direct injection to the eye where that needle, as I was pointing out in that eye figure, it goes directly into the vitreous. So this is the possibility of doing both of these treatments using both of these drugs, it being administered intravitreally.

Q. Both of these drugs being aflibercept and the Mini-Trap?

A. Correct.

Q. Let's take a look in that section under "Issues & Risks." And in that section under "Local administration - Full-Length Trap," we've highlighted "intravitreal PK."

What does that mean?

A. So PK stands for pharmacokinetics. That's the science of seeing where a drug goes after you inject it or administer it, could be oral too. In this case we were injecting it. You see where it goes and how long it stays there. So you want to see does it penetrate certain tissues? Does it stay in the place you went? And how long is it in those places?

Q. Why is that listed as a risk or issue?

A. As we discussed a little earlier, we weren't sure that the drug was going to penetrate the retina after we shot it into the vitreous. And so we wanted to do our own study to see whether it did or didn't.

Q. Had Regeneron, at the time you were working on the project, compared the efficacy of aflibercept injected intravitreally in a mouse compared to systemically in a mouse?

A. Yes. There was a study done in the Campochiaro Lab where those things were compared directly.

Q. And if we turn to Exhibit 1785 in your binder -- and we'll put the first page of that on the screen -- is this the publication that you're referencing?

A. Yes, it is.

Q. And is the first author Saishin from 2013?

A. That's correct. And here's the Campochiaro that I referred to.

Q. Just at a high level, what was the result of this study?

A. The high-level result was that, if you inject the drug in the mice to give systemic exposure -- this was not intravenous, it was subcutaneous, but that still gives a big blood level and allows it to go into the retina from the blood. We compared that with an intravitreal injection to see if it could reduce the effects and the disease model that happened in the retina.

Q. What did better, the systemic administration or the intravitreal administration of aflibercept?

A. The subcutaneous injection. So the systemic exposure suppressed the disease model in the retina much more than the intravitreal did.

Q. You mentioned a moment ago a pharmacokinetic study in rabbits.

Was that an important experiment in the course of your project in developing Eylea?

A. Yes, it was a critical experiment.

Q. Let's take a look at Exhibit 1079.

Can you identify this 2005 document?

A. Yeah. This is a clinical investigator's brochure.

Q. And if we move to page 4 of the document, in the table of contents, under "Pharmacokinetics of VEGF Trap," what's Section 8.2 about?

A. That's the study that we did where we administered the Trap in rabbit eyes intravitreally and we measured how long it was there -- as I measured, pharmacokinetics is how long it's there -- and what tissue did it distribute it to. So did it get in the vitreous? Did it get in the retina? Did it get in the choroid? The two tissues, retina and choroid, where the disease would happen.

Q. Let's go to page 46 now, Section 8.2 of the same document, Exhibit 1079. And we've highlighted some language on the screen.

Can you explain, first of all, what is being measured in this study, Dr. Furfine?

A. Yeah. So we developed assays to measure the drug, the VEGF Trap, in the vitreous, in the choroid, and in the retina. And we collected those tissues after we injected the drug, and we measured the drug levels in those drugs. And here, as we say, the bottom-line result is, in fact, the VEGF Trap did penetrate the retina and the choroid.

Q. Let me just back up a moment ago. I want to break that down a little.

You said you developed assays. Is that another word for tests?

A. Yes. Sorry.

Q. No problem. That's okay.

You said you measured in the vitreous, the retina,

and the choroid. Did I get that right?

A. Correct.

Q. Where is it easier to measure how much aflibercept is present, in the vitreous or in the retina and choroid?

A. It's easiest to measure the drug in the vitreous.

Q. Why did you measure in the retina and choroid also?

A. The retina and choroid, as I mentioned, are the sites where the disease biology happens. It's where the VEGF is produced; it's where it needs to get blocked. If the drug does not get to the site of action of the biology, you can't block the biology.

Q. We looked at general results here. I want to look at the more detailed results.

If we could turn to Exhibit PTX 3257. Is this a report about the rabbit pharmacokinetics study?

A. Yes, it is.

Q. Let's turn to page 5 of this report.

When was this study conducted?

A. In July of 2004.

Q. Did you receive the results soon after that?

A. Yes, I did.

Q. And was -- were these data kept confidentially when they received it at Regeneron or was it published when they received it?

A. They were confidential to Regeneron.

Q. Let's take a look at page 100 with the results. And we've highlighted the sentence that begins "despite the differences described above."

What does this sentence convey?

A. The idea here is a comparison of a relatively large molecule, the full-length Trap, to the Mini-Trap, a smaller molecule; and that despite those size differences, both drugs got into the retina and the choroid at respectable and reasonable levels.

Q. What did you call the retina or related structure in this document?

A. The desired site of action. That's the place where the disease biology happens, and you need to get your drug there.

Q. Did you think it was enough for aflibercept just to get into the vitreous?

A. Absolutely not.

Q. Did you think that having aflibercept in the vitreous would somehow get rid of the VEGF in the vitreous and then suck VEGF out of the retina and thereby treat retinal diseases?

A. I can't imagine a way that would work.

Q. Was that finding that we show here in the rabbit pharmacokinetic study, that aflibercept will get to the desired site of action in the retina and related structure, good news or bad news?

A. This was very encouraging to us. It meant that we actually had a potential path forward to move forward with a program where we did an intravitreal injection and could expect that the drug would get to the site of action that we desired and have good effects on the biology of blocking VEGF.

Q. Dr. Furfine, without this information, would you have decided to move forward with intravitreal injection of aflibercept?

A. No, we would not have.

Q. If not enough aflibercept had reached what you call here the desired site of action, what would you have done?

A. We would have probably switched to the Mini-Trap, which would have -- you know, based on this study and on the analogy to ranibizumab, would have worked better to penetrate that tissue.

Q. Now, Doctor, I'd like to move to a different topic now, which is the dose or concentration that was used in your aflibercept project.

What dose did you understand Genentech to be pursuing for ranibizumab?

A. It's a 10 mg/mL solution that results in a 500-microgram dose because you take 50 microliters of that solution and inject it. So 10 mg/mL equals 500 micrograms.

Q. How did you understand that 10 milligrams per milliliter of ranibizumab that Genentech was using to map onto

the aflibercept that you were studying at the time?

A. We were looking at 40 mg/mL solution.

Q. How did you try to -- how did you map -- how would 10 milliliters of ranibizumab correspond or map onto aflibercept?

A. So they would be similar doses in that regard, but because the aflibercept was a more potent molecule, you would expect it might work even better even at the same levels or even slightly lower levels.

Q. If you wanted to make a similar or a me-too version of ranibizumab that had aflibercept instead, what kind of concentration would you have used in the formulation?

A. By the same analogy, given that the drug was somewhat more potent, you would not have to go any higher than 10 and you could potentially go lower, but you would have to prove that in the clinic.

Q. Now, did you follow Genentech's literature regarding ranibizumab when you were working on your project?

A. Yes.

Q. And let's put up on the screen Exhibit PTX 1839, the Gaudreault article from 2005.

Did you read this article when it was published?

A. Yes, around that time, somewhat after.

Q. While you were still working on the project?

A. Yes, near the time when it was published.

Q. Turning to page 2 of the article, can you explain this experiment and how you understood it at the time?

A. Yes. So this was a study where the drug was injected into the animal eyes and they were assessing the pharmacokinetics; so what the tissue distribution was and how long it was staying.

And during that assessment they also looked at if there were any adverse effects of these injections into the eye, and you could see that at the lower dose, the 10 mg/mL solution, there was relatively small amounts of inflammation; it was here absent to moderate.

But at the higher dose the 40 mg/mL formulation or 2 micrograms, that high dose, four times higher now, had substantial and concerning inflammation after this single injection.

Q. Is that the moderate to severe information?

A. Correct, yes.

Q. It says in the next sentence that it had been completely resolved by day eight.

Was that comforting?

A. Not really. I mean, I guess better than being there the whole time, but not good.

Q. How often would you administer a drug like this approximately?

A. So as we know now, these drugs are administered

roughly monthly. And, you know, so to have this happen every time you administer the drug would not be an acceptable tolerability profile.

Q. Now, just so the record's clear, what drug is being administered in this Gaudreault study?

A. It's ranibizumab.

Q. You said it was a pharmacokinetic study. Was there a long discussion of the health findings of the toxicity or was it more of a shorter, minor discussion?

A. It was a more minor discussion, but still it pointed to an issue that we were concerned about.

Q. Was this encouraging or discouraging at the time that you read it for purposes of potentially using a higher concentration?

A. This was quite discouraging for using a higher dose. I mean, we clearly see a lot of inflammation here, an unacceptable amount of inflammation. Apparently Genentech found it to be unacceptable as well because they moved forward with the 10.

Q. We'll look at that in a moment.

Let me just understand, though, Doctor, if you're trying to treat a disease, why wouldn't you just use as much as possible, the highest concentration you could?

A. I think this is the classic example of why you don't do that, is that you can get adverse effects. In drug

discovery almost everything we do is a yin and a yang. There's a benefit to be gotten from having a lot of something, and there's also a downside to be had of those things. And you have to find that balance of safety versus risk, efficacy versus adverse effects. And, you know, the higher you go, the higher the chances you're going to get an adverse effect that may dampen the benefit that you get.

Q. What about stability in formulation?

A. Higher concentration formulations with proteins in particular are much more challenging to do.

Q. What happens when it's challenging? What happens with high concentrations sometimes?

A. High-concentration formulations of proteins often aggregate and precipitate out of solution and cause particles.

Q. Is that a problem?

A. That's a big problem, and it's probably more of a problem for an eye drug than it is for a regular drug.

Q. Why is that a problem for an eye drug?

A. So there's three big reasons why particles are a problem for an eye drug. These are probably somewhat obvious, but one is, if you put particles in the eye, you can imagine obscuring your vision. And, in fact, that can happen.

The other thing is you can induce inflammation, which, in fact, we see inflammation here. We don't know that it was particles, but it very well could have been.

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And the third thing is you can stimulate an immune response to the drug that you've injected. And if you get an immune response to the drug, you can end up neutralizing the drug so it doesn't work anymore.

Q. And when you said we --

THE COURT: I'm sorry. What do you mean when you say "immune response," Doctor?

THE WITNESS: So what happens -- immune response can be a number of things; so it's a good question. So a lot of times you get an antibody response, like to COVID. And if you make antibodies to COVID, you clear the COVID. If you make antibodies to your drug, you clear your drug.

THE COURT: Understood.

Sorry, Mr. Berl.

MR. BERL: Thank you. We're all here to help you understand. Doesn't matter if anyone else does.

BY MR. BERL:

Q. You said in your answer we see inflammation here. I just want the record to be clear. When you said there's inflammation here, were you referring to the Gaudreault reference on the screen, Exhibit 1839?

A. Yes.

Q. Now, let's go back with that in mind to the rabbit PK study that you had mentioned, which is PTX 3257, and the results at page 100. We looked at this paragraph before. I'd

now like to ask you about the language further down in this paragraph about how long the protein can be present in the tissue.

Can you explain what result you obtained in your study?

A. Yes. So as you can see here, the drug was present in the tissue for at least through 28 days. And, again, this is a yin and a yang situation. If you have a lot of drug around for a long time, there's a chance it could have an adverse effect. But if you have a drug around for a long time, it could be having efficacy for that time.

I was a little bit more on the optimist side of things in this case, but nonetheless one has a concern that you can have a problem with it, and you need to do further testing to sort that out.

Q. To be clear, Dr. Furfine, did you expect to obtain this result in the pharmacokinetic study in the rabbits of the protein being present in the tissue for up to 672 hours?

A. No, we did not expect this.

Q. Is that a high number or a low number?

A. It's a high number. This was, roughly speaking, about twice as good as ranibizumab, and that was encouraging to us.

Q. And just again so the record's clear, was this public at the time?

A. It was not.

Q. Now, given all the concerns that you've mentioned, why did you end up using a higher concentration?

A. So when you see one advantage -- in this case, it was how long it was staying in the eye; it was staying in the eye longer than ranibizumab -- you can actually leverage that to your advantage in another way by adding more.

So if you add more of something that's longer-lived, you kind of double down on the longer-lived. So every time you double the concentration that you inject, you get an extra half-life. If your half-life is already longer than ranibizumab and now you're getting more of them, this was an exciting possibility to reduce the number of injections a patient would have to get. And so we were excited about that possibility.

Q. Did you still have all those concerns you mentioned about toxicity and stability?

A. Absolutely.

Q. So what did you do in view of those concerns?

A. We did a lot of experiments to figure out whether we could make a stable formulation and whether we were going to have toxicology that was associated with higher concentrations.

Q. I'd like to discuss some of those experiments with you. Let's turn to Exhibit PTX 81.

What is this document, Dr. Furfine?

A. This is a summary of a lot of the nonclinical work that we did, including the formulation development to support clinical studies.

Q. You've been using the term "nonclinical" or "preclinical." Is that experimentation done before you actually administer something to human beings?

A. Yes.

Q. Now, let's turn to the Bates number ending in 262 which is on page 10 of the document. And this is under -- at the top of the page we can see here 1.3. It's a little faded, but it says "Summary of Formulation Development." And then there's a Table 3.

Can you explain what's shown in Table 3.

A. Yes. This shows four formulations. Two of them are intravitreal formulations, and then the other two are what was used in the cancer programs for systemic, either IV or subcutaneous is SC.

The intravitreal formulation 1 there was the first formulation that we moved forward with into clinical studies.

Q. Why did you start with this formulation, labeled ITV-1?

A. So as I mentioned, you don't want to have anything in your formulation that is, you know, more than what you need or have a reason for having it there. So this was a minimalist approach that we took to this formulation. And we wanted to

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make sure that we were using things that we thought had a high probability of success in the eye because there wasn't a lot of experience with eye formulations.

And so we focused on mostly excipients that we knew actually were there already. Sodium phosphate, of course, is in the eye; sodium chloride, saline, same thing is in the eye. So we used ingredients here that we thought would be reasonably well-tolerated. It was kind of a minimalist approach, if you will.

Q. Didn't you already have formulations of aflibercept that had been developed for systemic treatment of cancer?

A. Yes. The two furthest to the right, IV and SC, were already developed.

Q. Did you consider starting with those in your research on an ophthalmic formulation?

A. That didn't occur to us. That's not how you do science.

When you make a formulation, when you make a drug or a drug product, there's this idea of fit for purpose. You have to decide what you're going to do with the drug, what's it going to be used for, and what are you stabilizing.

And so you don't start with something that was made for something else to use it for something completely different. You have to start over again and ask your question: What's the right thing to do in this situation?

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And so that's what we did. We started over.

Q. Are there considerations that are relevant for intravitreal formulations that are less important for intravenous or subcutaneous formulations?

A. Absolutely. One big one, and maybe one of the biggest ones, was that there's a stress that happens in intravitreal formulations that wouldn't happen in systemic formulations.

So when you do an injection in the eye, you can imagine you want to use the smallest needle you can because who wants a big needle in their eye?

THE COURT: That is well established.

THE WITNESS: See, I don't have to do too many more studies on that. It's already known.

So what you do is you use these really narrow-bore needles. It's a very thin hull. What happens is, when you force solutions, protein solutions especially, through a narrow-bore needle, you create what's called shear stress. It's like a pressure, and that creates a stress that can cause a protein to come out of solution.

So you need to add agents into your formulation, ingredients that stabilize the solution and keep the drug in solution under these kinds of stressful situations. That would not happen for IV and SC.

THE COURT: When you say "in solution," I assume you

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mean still floating in the carrying liquid, for lack of any scientific term.

THE WITNESS: That's exactly right. That's perfectly scientific.

And what happens here, in fact, is if you don't survive shear stress, you see particles that are clearly -- by definition, a particle is not in solution. So, in fact, it's black and white. They're either in solution or they're not.

THE COURT: And in this form, again, because we're using a needle and a syringe, particles might be attached to the syringe itself or --

THE WITNESS: No. The manufacturer of syringe needles and the like has them clear of, really, any detectable particles. And so if you saw particles after shooting the drug through it, it would be solely the result of the protein coming out of the solution.

MR. BERL: I think what Your Honor -- what the Court may have been asking is do the particles get stuck in the needle? Is what you're asking, Your Honor?

THE COURT: Yeah. You're talking about shear stress which I'm envisioning sort of three lanes of traffic merging as one, right?

THE WITNESS: That's right. That's right. That's right.

THE COURT: You have all that there. So when that

occurs and that buildup occurs, if the protein falls out of solution, where does it go? Where do the particles exist?

THE WITNESS: So most -- it's a great question. So most of the time they actually don't clog the needle, but they could. If you had a severe enough response, you could actually clog the needle.

What usually happens is you shoot them into the eye, and that's where you get your trouble.

THE COURT: Okay.

BY MR. BERL:

Q. Do you ever want to shoot a particle into the eye, Doctor?

A. No, no, you don't.

THE COURT: Again, I believe that also has been well established.

BY MR. BERL:

Q. Now, let's take a look at the same page further down, 262 in Exhibit 81.

Was the ITV-1 formulation that you said you started with, was that ultimately a formulation that met your needs for intravitreal administration?

A. No. In fact, it was problematic in this very stability test that we were just referring to. It did not withstand shear stress to the degree that we wanted it to and had a second problem that it didn't stand up -- withstand heat

stress as well.

Q. But let's take a closer look at those data. If you could turn to Exhibit PTX 2223 for a moment.

Are you familiar with this document, Dr. Furfine?

A. Yes.

Q. Is this a protocol for stability study?

A. It is.

Q. And we're looking at the first page here and it talks about data from stability studies indicate that there's a problem with the physical stability of VEGF Trap in the current ITV formulation above 10 milligrams per milliliter VEGF Trap. Do you see that?

A. Yes.

Q. So first of all, when we say current ITV formulation, was this referring to what you've been calling ITV-1 in your testimony?

A. Yes. It was the first clinical formulation we used.

Q. When do you start to have problems with ITV-1, at what concentrations?

A. Concentrations that were above the 10 mg/mL. So if we wanted to go to 20 or 40 or whatever, that's where we started to have issues where it was not surviving this syringe needle test that we do. We have to -- you actually put it through tests that mimic what's going to happen in real life. So we say is it going to make it through without making

particle? We actually do the experiment before we stick it in someone's eye.

THE COURT: Comforting.

MR. BERL: For all of us.

BY MR. BERL:

Q. Doctor, is that consistent with the principle you articulated earlier that you get more instability and aggregation at higher protein levels compared to lower?

A. Yes, it is.

Q. And let's take a look -- let me ask this: Before you did this manipulation where you did the syringe, was all of the aflibercept in the solution?

A. It started in the solution, yes.

Q. Let's go further down this page on 2223. The "in addition" paragraph, if we could pull that up.

Is this another test that you conducted on your ITV-1 formulation?

A. Yes. This is an agitation stress study that we did, and it's kind of analogous to a shear stress. Basically what you do is you whip the solution around for long periods of time and see whether it comes out of solution. It's like an extreme agitation.

Q. Went you say you whip it around, is that referenced on the document on the page as "vortexed"?

A. Vortexed, that's right. That's what we call it.

"Vortex" is another word for whipping around.

THE COURT: Thank you.

BY MR. BERL:

Q. This document says -- Exhibit 2223 -- that the ITV-1 formulation has been shown to be prone to precipitate when vortexed.

What does that mean?

A. That means the protein was coming out of solution. It was precipitating when we stressed it by -- this is exactly what it does, is it goes around in circles at a really high rate. So it's like shaking it up as hard as you can, or even more than that, for two hours.

Q. Before you shook it, was all of the aflibercept in solution?

A. Yes.

Q. And then when you shook it, was it still all in solution?

A. No. It came out as a result of being stressed by the shaking.

Q. Now, is this condition of vortexing or whipping it around, as you've been calling it, is that relevant as to how the drug's actually going to be used?

A. Absolutely. All the tests we do along this line are called accelerated stability studies. The idea is you want to, in a short time, mimic what happens in real life that might

include something that happens over a long time.

So there's a lot of shaking that can happen over the course of time in preparing the drug in the manufacturing, distributing it, bouncing around in the clinic, and so on and so forth. And so you need to -- if you shake it up a lot in a short period of time, you can mimic what happens for longer times.

Q. Did you have any experience while you were at Regeneron with things coming out of solution in actual use?

A. Yes. So with another program that preceded the VEGF Trap was called the IL1 Trap. So we had a formulation that we developed there, and we used a shorter vortex time. We only did 30 minutes, not the two hours. And we thought that was good enough at the time; we didn't know any better.

And what happened, disappointingly and kind of interestingly, is that during a clinical study a few months down the road when the manufacturing facility does its check on how's the drug supply doing, they saw particulates coming out. And we didn't anticipate that because we had never seen it happen. And we, even in the stressful situation, didn't see it happen.

So we instituted a new test in response to that, which was essentially to vortex not for 30 minutes but now for two hours because we didn't want this to happen to us again.

Q. Doctor, it says later on in the same paragraph on 22,

23, "VEGF Trap no longer precipitated upon vortex when the clinical DP was spiked with .03 percent polysorbate 20."

Can you explain what that means?

A. So basically we had to find an ingredient that we could put in the formulation that would make it soluble under the conditions of vortexing. And so one of the ones that we tested is this organic cosolvent, polysorbate. We had prior to that a cosolvent called PEG. We thought this one might be better, and we tested it. And, in fact, it did work superiorly to PEG.

Q. When you said keep it soluble under the conditions of vortexing, are those conditions also relevant to actual use of the product?

A. Yes. Everything we do in an accelerated stability study is intended to mimic what happens in real life over sometimes the same and sometimes over longer periods of time.

Q. So was this ITV-1 formulation that came out of solution upon the needle test and being vortexed, is that something you wanted to move forward with as a product?

A. No. It would have been unacceptable. It would have been very high risk and probably would have failed.

Q. What did you do as a result of that?

A. We started examining new formulations where we put in different ingredients that we thought would make it more stable to this agitation and shear stress and also the thermal tests

that we do.

Q. Dr. Furfine, let's turn to Exhibits 97 and 98 and show them together because they're associated. They're also in your binder, but we'll put them on the screen.

Can you explain what Exhibit 97 and 98 are.

A. Yeah. So these are the stability tests with the new formulations that had excipients or ingredients that we thought would better stabilize the two problem areas, thermal stability, heat, which also translates to shelf life. If you can tolerate heat better, you're more likely to even last longer in cold. There's kind of a correlation there. And then also the agitation stability.

Q. So we'll get to the data in a moment. Is Exhibit 97 an email from November 2005 from Kelly Frye to various people that you received?

A. Yes.

Q. Okay. And it says, "I've attached a chart with the new formulations so that it's clear what the new formulations consist of."

Do you see that?

A. Yes.

Q. And if we turn to Exhibit 98, PTX 98, its says, "New ITV Formulations."

Is that the chart that Kelly Frye attached in the email?

A. Yes, it is.

Q. And I want to take a look at this chart in Exhibit 98. What is this showing?

A. This is showing what formulations we tested. They're listed 1 through 8. Number 1, it says old. That's IVT-1. It's the original one that we drove into the clinic that was insufficient long term.

And then the others, if you look at the top row, the columns show the ingredients we tested and in what concentrations we tested them to see if we could make superior formulations.

Q. So, for example, ITV-1, did that have any sucrose or mannitol?

A. It did not.

Q. And then did you test at least one formulation with sucrose, Formulation Number 41?

A. Yes. 4 was sucrose.

Q. Now, we see all these formulations with ingredients and amounts. How did the formulations actually get made?

A. Laboratory scientists who are easily skilled to do this. It's not a major problem.

Q. What kind of training or expertise or degrees did the people who made these formulations require?

A. Nothing more than a bachelor's degree would be required.

Q. And how much training in making formulations in order to take this information and turn it into something that has a formulation?

A. I think if someone came in fresh out of school, a matter of a week or two would probably be sufficient to get them to know this.

Q. Now, I'd like to go through a couple of the ingredients with you. It says "10mM" -- is that millimolar?

A. Millimolar yes.

Q. -- "phosphate." Was that in all of the formulations?

A. Yes, it was.

Q. And what is that?

A. That's a phosphate buffer. It's -- a buffer is used to maintain the pH of the solution in a narrow range.

Q. And did you understand that other buffers could do that too?

A. Yes, they could, of course.

Q. We have sucrose listed here. What did you understand sucrose to be doing?

A. Sucrose in this case we were using primarily as a thermal stabilizer, so basically make the protein more -- less susceptible to heat and increase the shelf life.

Q. What was your understanding as to whether other stabilizing agents other than sucrose could do that too?

A. They could potentially work. In fact, we tested

mannitol, which is a very similar chemical; it's the same class of molecule. And, in fact, it did work to some degree.

Q. Now, if these ingredients are useful to maintain the pH and to keep the solution -- keep the protein in solution under stress like thermal conditions, why wouldn't you have just included them in the first place?

A. Well, as I mentioned, you know, we take as strategy a fit for purpose, first of all; and, second of all, you can't add things that you don't know you need and you can't add more of them than you need. And so you really need to do an experiment to test what's my problem? And now what am I going to add to solve that problem? And what's the least amount I can add of it to solve the problem? You don't want to give anything in a drug that you don't need to give.

Q. I see PS 20 listed here. Is that polysorbate 20?

A. Yes, it is.

Q. What did you understand that to be doing in the formulations?

A. We refer to it as an organic cosolvent. It helps stabilize and keep the drug in solution under stresses like agitation and shear.

Q. What was your understanding about whether other organic cosolvents other than polysorbate 20 could do that?

A. They can. In fact, PEG is right next to it and was serving a similar purpose.

Q. Let's take a look at PTX 86, Dr. Furfine. Can you identify this document for the Court?

A. Yes. This is a meeting between -- our partner at this time was Aventis, the pharmaceutical company partner. Was a joint meeting between our teams to discuss the development of the VEGF Trap.

Q. Just so the overall story's clear, is Aventis a predecessor of Sanofi?

A. Yes.

Q. And if we go to page 11, did you attend this meeting?

A. I did.

Q. And did you present to Aventis about intravitreal formulation issues relating to aflibercept in 2004?

A. Yes, I did.

Q. Let's take a look at what you said on page 5.

What did you say at the beginning of this paragraph?

A. Basically sort of what the data that we've shown so far is that we needed an organic cosolvent to stabilize the protein against agitation or shear stress induced coming out of solution. We call it aggregation, but it's a forcing a precipitation, not a solution.

Q. And what examples did you provide of organic cosolvents in your 2004 presentation to Aventis?

A. As you can see there, there are PEG and polysorbate, the same two that were on that table that we just were looking

at.

Q. How did you understand organic cosolvents like polysorbate to work?

A. So proteins have a surface, and on that surface there can be patches of different sort of chemical nature. And sometimes there's a patch that we call a hydrophobic patch. Hydrophobic, as I mentioned, means don't like water.

If you have two hydrophobic patches one on one protein, one on the other one, they like to come together because neither of them wants to be in water but they prefer -- hydrophobic likes hydrophobic, doesn't like water.

So when you have two hydrophobic patches, you can get an aggregation that happens, and that's when the protein can come out of solution.

If you have an organic cosolvent in there, that can kind of coat or associate with that hydrophobic patch because there are parts of polysorbate that are hydrophobic as well. So the hydrophobic likes the hydrophobic, and they kind of associate. And that blocks the protein from doing that because it's already got polysorbate there. So, basically, it stabilized it to hydrophobic against intermolecular, what we call molecule-to-molecule, hydrophobic aggregation.

Q. Let's take a look at your testing of the various formulations, Dr. Furfine. If we could go to 2223 in the first instance, and I'm now on page 2. We looked at page 1 a moment

ago.

In the bottom of the page, which is shown here on the left, what conditions are you studying in this test?

A. Yes. These are a classic subset of the accelerated stability that we do. The agitation, which is essentially vortexing that we discussed before, and the thermal stability. So you incubate the tubes of drug formulation at elevated temperatures.

Q. And let's take a look at some of the results of the testing.

If we could go to 2224 and look at page 1. If we could go down just a little more, Mr. Schliesske, and look at the 45-degree data.

Can you explain what these data shown in PTX 2224 reflect?

A. Yes. As you can see, if you look at the yellow lines on the bottom there, the formulations that contain a thermal stabilizer, in this case it's sucrose, are doing pretty well. They're not aggregating, and they're not coming out of solution. But you see the number is higher in Formulation 5 that does not have the sucrose in; it only has the sodium chloride in it. There's some other excipients but no thermal stabilizer, and so the number is higher.

So when numbers go up higher, those are the results of particles forming and light scattering, and the more light

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scatters, the higher the number goes. So particle, light scattering both go up, and that's how you know you're getting precipitation and particle formation.

Q. Let's break that down just a little. The test you're running at the top of it says OD 405. What is that?

A. That's the absorbance at 405. That's a measurement of the scattering of the light in the solution. So when you send a light beam through the solution, if you have particles, it scatters them and then it doesn't make it through the detector. And that's how you measure the 405.

Q. So in laymen's terms, are you measuring how clear or how cloudy the solution is?

A. Essentially, yes.

Q. And the numbers at the bottom that you're showing that are in yellow under 14 day 45 degrees, did I get it right that the higher numbers are worse than the lower numbers?

A. Higher number is worse, like golf, as you say.

Q. Now, what did that teach you with respect to whether you wanted to use a thermal stabilizer?

A. This was an indicator that, in fact, we needed a thermal stabilizer. We needed something more than just the salt that was in IVT-1.

Q. And let's now go to additional data in this test. If we could go -- and we're still in 2224. On the left it says VTX.

A. VTX is going -- it's an abbreviation for vortex. So we're back to this agitation stress. And you can see the times. We started with 30 minutes of vortexing, which was our old way, and then we moved to up to see how much it could do. And we went up the way up to two hours, 120 minutes, two hours of vortexing. And you can see the numbers are not going up at the OD 405.

Q. And just to be clear, did you have organic cosolvents in these formulations?

A. Yes.

Q. And so what did you think about these results?

A. These indicated that the more recent organic cosolvent of polysorbate was going to be necessary and that it was superior to the PEG. The PEG was in the IVT-1. We didn't have polysorbate there.

Q. If we look at the next test or another test also on page 1, there's something a little higher up.

We did that one already, I think, Mr. Schliesske. I think this is 1.9.

There's something called F/T there. Can you explain for the Court what that test is?

A. Yeah. F/T stands for freeze/thaw. So when you manufacture a drug, there are lots of times when you have to freeze it, usually in bulk, to store it until you're going to fill it or modify it in some way to get it towards its final

form.

And so you may several times thaw the drug out to transfer it into whatever its new manufacturing state is and then refreeze it because maybe you don't use it all; you just take part of it. And so you need to be able to make your drug stable to freeze/thaw.

And polysorbate is actually pretty good at stabilizing drugs to freeze/thaw. And as you can see here, it did a nice job both through four or even eight freeze/thaws.

Q. In your testing, Dr. Furfine, out of all of these formulations, which one performed best?

A. The 5 percent sucrose, .03 percent polysorbate. So that's Number 2 there.

Q. What is this formulation called?

A. That formulation is now called Eylea.

Q. Did you also study the ability of your formulations to withstand the shear stress of a narrow needle?

A. Yes, we did.

Q. And what did that testing show with respect to whether your 40 milligram per milliliter formulations you created was able to withstand shear stress of a 30-gauge needle?

A. We required the polysorbate to withstand the shear stress in addition to the agitation stress.

Q. Did the 40-milligram-per-milliliter formulations you

created with polysorbate withstand shear stress of a narrow needle or did they fail?

A. They passed that test.

Q. If your 40-milligram-per-milliliter formulations had not passed that test of getting through a 30-gauge needle, would you have developed it for intravitreal formulation?

A. No, we would not have.

Q. Did you perform additional testing, Dr. Furfine, that we haven't discussed or shown here?

A. Yes. There's a lot of testing needed before you can move a drug into the clinic.

Q. Did you think those tests were important in terms of determining whether you could have a successful 40-milligram-per-milliliter intravitreal formulation with aflibercept?

A. We only do tests that we consider important.

Q. Let's bring your patent up.

THE COURT: You asked, Counsel.

MR. BERL: I deserved that. Sorry.

THE COURT: I tell you what, though, since I've interrupted and my personal comfort schedule usual regimen was disrupted earlier, let's take five and take a personal comfort break and we can come back.

Doctor, we're going to take a few minutes. You're not allowed to talk to anybody. They're not allowed to talk to

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you. So don't mean to be discourteous.

THE WITNESS: Can I sit here?

THE COURT: You're welcome to, but you're free to not aggregate as a particle.

See, I'm learning. How about that?

You do not have to remain there, Doctor. If you need to use the restroom, whatever, feel free. But no one can talk to you.

THE WITNESS: Thank you.

(A recess was taken from 4:16 p.m. to 4:23 p.m.)

THE COURT: Counsel, you may proceed, sir.

MR. BERL: Thank you, Your Honor.

BY MR. BERL:

Q. If we could put up PTX 2 again. That's your patent.

Dr. Furfine, what did you think you and your coinventors had invented when you filed the patent application?

A. We thought we'd invented two things. One is Eylea, the drug that's on the market now; and the second thing is a set of principles and guidelines on how to formulate aflibercept into an intravitreal formulation.

Q. As you look back on your career, Dr. Furfine, how long have you worked as a scientist in the pharmaceutical field?

A. Since 1989. I'm sorry. I can't do that math.

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Q. In that time that you've been working in this field since 1989, how does the invention described and claimed in this product patent, the '865 patent, fit in?

A. This is something that I remain very proud of. I guess maybe just to give a little context, you know, I've always wanted to make medicines, and that's what kind of gets me up in the morning, is knowing that everything we do in the lab or in designing strategies for experiments is with the goal of making a medicine that's going to make somebody feel better. And that's what motivates me; it's what gets me excited about going to work.

And to know that we actually created something here that became a drug that transformed the way age-related wet AMD is treated and -- it's like night and day, right? I mean, these drugs are amazing. They stop people from going blind. And to have contributed to that with my colleagues is something I'm very proud of.

MR. BERL: Thank you very much, Dr. Furfine.

THE COURT: Cross?

MR. RAKOCZY: May I approach with some binders, Your Honor?

THE COURT: You may.

MR. RAKOCZY: Good afternoon, Your Honor. William Rakoczy for Mylan and Biocon. May I proceed?

THE COURT: You may. Sorry. Go ahead.

CROSS-EXAMINATION

BY MR. RAKOCZY:

Q. Good afternoon, Dr. Furfine.

A. Good afternoon.

Q. I represent Mylan and Biocon. I have just a few questions for you.

Now, you testified quite a bit at the beginning of your direct testimony about the aflibercept molecule, correct?

A. Correct.

Q. Now, you don't purport to have invented the aflibercept molecule, correct?

A. That's correct. It was before my time at Regeneron that that molecule was invented.

Q. And your patent doesn't purport to invent the molecule aflibercept, correct?

A. Correct.

Q. The patent is about a formulation of the aflibercept molecule, correct?

A. Correct.

Q. So the molecule was known before your patent, correct?

A. Yes, it was.

Q. Now, you talked a lot about aflibercept penetrating the retina.

Do you recall that testimony?

A. Yes.

Q. There are no studies or tests in your patent about aflibercept and whether it will penetrate the retina or not, correct?

A. That's correct.

Q. There are no PK studies on aflibercept of any kind in your patent, correct?

A. That's correct.

Q. There are no tox studies on aflibercept in your patent, right?

A. That's right.

Q. No rabbit studies, no monkey studies, correct?

A. That's correct.

Q. As a matter of fact, there's no human studies of any kind on the formulations in your patent, correct?

A. That's correct.

Q. Your patent -- the only tests it has are you made formulations, you put them on stability, and then you tested them for native conformation and turbidity, correct?

A. That's correct.

Q. Now, you mentioned some skepticism about 40 mg/mL concentration. Do you recall that?

A. Yes.

Q. Now, your patent doesn't contain any statements about skepticism or insights about 40 mg/mL, correct?

A. It doesn't contain anything about skepticism. That's correct.

Q. As a matter of fact -- I'm sorry. I didn't mean to interrupt.

A. There is data on 40 mg/mL in there, though, but no statements of skepticism.

Q. Correct. Let me rephrase it. I'll make it clear.

Your patent doesn't say anything in there that skilled persons didn't think you could make a 40 mg/mL concentration formulation, correct?

A. Correct. It does not say you can't do that.

Q. In fact, your patent covers any concentration of aflibercept, correct?

A. I don't know what -- whether the claims would be -- cover -- what the range of coverage is. That's kind of out of my field.

Q. Let's pull up PTX 2. It's in your counsel's binder he gave you.

If we could have PTX 2 on the screen, Claim 1, please.

THE COURT: Do you have that, Doctor?

THE WITNESS: I do.

THE COURT: Okay. Go ahead, Counsel.

MR. RAKOCZY: Could we have Claim 1, please. If we could blow up Claim 1, please. Thank you, Mr. Gibson.

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BY MR. RAKOCZY:

Q. You see this is Claim 1 of your '865 patent, Dr. Furfine?

A. Yeah. Hang on just a minute here. Yep, go ahead.

Q. You see Claim 1 is directed to a vial that comprises, and the first ingredient is a vascular endothelial growth factor, VEGF antagonist, correct?

A. Correct.

Q. It doesn't specify any concentration there, right?

A. That's correct.

Q. So it could be below 40 mg, well above 40 mg. That would cover any concentration of aflibercept, correct?

A. You're kind of getting into this space of legal interpretation, I think, of claims, and that's out of my field.

Q. My question is simple. When it says "VEGF antagonist," it doesn't specify a concentration, correct?

A. It's true that it does not specify a concentration.

Q. And if we look at the other ingredients, the buffer, for example, it doesn't specify a buffer either, right?

A. It does not specify a buffer, correct.

Q. So that could be any buffer?

A. I don't think it could be any buffer, but in this case it does not specify the buffer.

Q. And it doesn't specify the stabilizing agent either, correct?

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A. It does not specify it in this specific claim, no.

Q. Let's talk about the formulation. And I want to start with polysorbate 20, as you can imagine. That's a nonionic surfactant, correct?

A. Correct.

Q. And in your formulation development work at Regeneron, you and your colleagues described polysorbate 20 as a stabilizer or stabilizing agent, correct?

A. Yes.

Q. Let's look at some of your formulation work. Let's start at DTX 722. It's in your binder, and I'll also pull it up on the screen for you.

A. This is your binder now?

Q. Yes, sir. My apologies.

So you have my binder, and then I'll always pull the document up on the screen for you as well.

A. 722 you said?

Q. Yes, at page 1. I want to look at the first email.

A. Hang on a second. Okay.

Q. Look at the first email you see. It's from Amy Galluccio to you, coinventor Kelly Frye and others, dated November 8th, 2005, with an attachment entitled "Sucrose VGT formulation help." Correct?

A. Yes.

Q. Now, I want to move to page 2 of this email, and

there's an attachment entitled "Product Composition." Do you see that?

A. Yes.

Q. And below that we see a formulation, right?

A. Correct.

Q. And we see 10 millimolar phosphate, 40 millimolar NaCl, 0.03 percent polysorbate 20, and 5 percent sucrose.

Is that the formulation?

A. Correct.

Q. Now, I want to focus on --

A. The formulation is 40 mg/mL VEGF Trap too and pH .5, but I assumed you were inferring that, but I just want to make sure.

Q. Absolutely. And I want to go to the paragraph above that and look at the first sentence. You see it says, "This is an unstable formulation for VEGF Trap since there are minimal excipients for intravitreal delivery and the formulation contains a high concentration of VEGF Trap."

Do you see that?

A. Yes.

Q. And then it goes on to say that "The drug substance, formulated drug substance, or drug product is held or stored at 25C and should be kept to a minimum during the manufacturing process."

Do you see that?

A. Yes.

Q. And that "Temperatures above 25C must be avoided," right?

A. Yes.

Q. And that it "should be held or stored at less than minus 20C," correct?

A. Yes.

Q. So this was an unstable formulation as of the date of this email, November 8, 2005, correct?

A. I would have to look at this a little more closely to make sure I understood the context at which this was being stated.

Q. We can agree your formulation group attached this product composition memo, and they said this is an unstable formulation, correct?

A. I think that what you stated in the text is absolutely correct, but I think there are -- stable to what? And so you have to take it within the context, and I'd have to think back to things that I don't have the information on here as to what the situation was that we're talking about being stable to, you know.

So it's possible that it could be stated as being unstable in this situation, does not necessarily mean it's unstable to become a marketed product and used in the clinic as we want.

Q. We can at least agree that as of November 8, 2005, this formulation, someone wrote, is unstable, correct? Can we agree with that?

A. It is stated as such in the text, yes, absolutely.

Q. Now, let's look at the table on that same page, and here we have the ingredients of the formulation. And we can see that the solvent in this formulation is the WFI, or the water for injection, correct?

A. That's correct.

Q. And that's used to dissolve the aflibercept, correct?

A. Yes.

Q. And the buffer is phosphate, correct?

A. Yes, it's a mixture of two different salt forms, but yes.

Q. And then the sucrose is identified as a stabilizer, correct?

A. Correct.

Q. And then the polysorbate 20 is identified as a stabilizer as well, correct?

A. Yes, it is.

Q. It's not identified as a solvent, correct?

A. It is in this document not identified as a solvent.

Q. And polysorbate 20 is not used to dissolve aflibercept, correct?

A. It is not used to dissolve aflibercept.

Q. And this document also does not identify polysorbate 20 as a cosolvent, correct?

A. In this document it does not.

Q. And, in fact, in your development of the Eylea formulation, you did not use polysorbate to remove or dissolve aggregates, correct?

A. That's correct. We did not use it to remove or dissolve aggregates.

Q. And it doesn't do that, right? Once there's an aggregate in the formulation, you don't put polysorbate in there to dissolve it, right?

A. That is typically correct, yes.

Q. Now, let's go to another one of the formulation development memos. I believe even after 2005 we'll see representations of polysorbate as a stabilizer.

So let's look at DTX 736 in your binder, and it's also on screen. And you see this is an email dated April 21st, 2006, now, with attachments from coinventor Dr. Graham and copied to you and coinventor Dr. Dix, correct?

A. Correct.

Q. And if we go to page 3 of this exhibit, we see a memo from coinventor Dr. Graham that he signed and actually dated April 21, 2006, correct?

A. Yes, I see -- you said page --

Q. Page 3 of the exhibit. So it would be --

A. I have -- it's weird. It says page 1 of 1, 1 of 2, 2 of 2.

Q. I apologize. I'm referring to the exhibit number. So DTX 736.0003.

THE COURT: The bottom right-hand corner in bold typeface, Doctor.

THE WITNESS: Okay. Yeah, 0003. Got it now.

BY MR. RAKOCZY:

Q. So just for the record, on page 3 of DTX 736, we have Dr. Graham signing and dating this memo, April 21, 2006, correct?

A. Yes.

Q. It's entitled "Revised pH for 40 mg/mL VEGF Trap for ITV in a 0.03 percent polysorbate-containing formulation," correct?

A. Yes.

Q. And the first sentence, obviously, identifies this as a formulation of VEGF Trap for intravitreal delivery, correct?

A. Yes.

Q. And if we look at the formulation here, we can see a formulation identified as 10 millimolar phosphate, 135 millimolar NaCl, 0.03 percent polysorbate 20, 40 mg/mL of VEGF Trap pH 6.3, correct?

A. Correct.

Q. Now, I notice there's no sucrose stabilizer in this

formulation, correct?

A. That's correct.

Q. So let's look at the table below that and let's see what folks said about these ingredients. And, again, water is the solvent, correct?

A. Yes, it is.

Q. That's what's dissolving the aflibercept in this formulation, correct?

A. It's not dissolving the aflibercept because the aflibercept is already in a solution prior to adding the WFI.

Q. So aflibercept is already in solution. Then you add the water?

A. Yes.

Q. And then we have the other ingredients. We see the phosphate buffer again, correct?

A. Yes.

Q. We have the NaCl, salt, correct?

A. Yes.

Q. We have no sucrose stabilizer this time, right?

A. Correct.

Q. So this formulation as of April 2006 does not have the sucrose stabilizer, right?

A. This specific memo quotes a formulation that does not have the sucrose in it, correct.

Q. And this memo identifies the function of

polysorbate 20 as stabilizer, correct?

A. Yes, it does.

Q. It doesn't say solvent; it doesn't say cosolvent. Correct?

A. It does not say solvent or cosolvent.

Q. All right. Now, let's jump back to the formulation on DTX 722, if we could very quickly.

THE COURT: That's on page 2, Counsel?

MR. RAKOCZY: Yes. And, Your Honor, I apologize.

THE WITNESS: This is .0002? Is that the right one?

MR. RAKOCZY: Yes.

Your Honor, I neglected to move to admit DTX 722 into evidence.

THE COURT: Any objection?

MR. BERL: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 722 was admitted.)

MR. RAKOCZY: And I also neglected to move to admit DTX 736 as well, please.

THE COURT: Any objection to 736?

MR. BERL: No objection.

THE COURT: Without objection, DTX 736 is hereby admitted.

(DTX 736 was admitted.)

BY MR. RAKOCZY:

Q. Now, this formulation does have the 5 percent sucrose, correct?

A. Yes, it does.

Q. So this is similar to the Eylea formulation, right?

A. Yes, it is.

Q. So let's take a look at that. I'd like to go to PTX 1519, pull it up on screen for you.

A. Is this now back in my --

Q. This is in the same binder I gave you.

A. I thought you said -- there are Ps here. Sorry.

Q. There should be PTX 1519 in the binder I gave you.

A. I got it now.

Q. Or my colleague. I apologize.

A. I got it now.

Q. And this is the drug product section from the Eylea BLA, and I'd like to focus on components of Eylea, which are on page 5 of PTX 1519.

A. This is your 1519.0005?

Q. Yes, sir.

A. Okay.

Q. We can see on screen we have a Table 1.

A. Yes.

Q. And you see it is entitled "Nominal Composition of VEGF Trap-Eye DP Formulation," correct?

A. Yes, it is.

Q. And this identifies the ingredients of Eylea and the functions, correct?

A. Yes, it identifies the ingredients and the functions.

Q. So we have aflibercept, the active ingredient, correct?

A. Yes.

Q. We see the buffering agents, the phosphate again, correct?

A. Correct.

Q. We see the sucrose stabilizing agent, correct?

A. Yes.

Q. And the BLA then identifies polysorbate 20 as stabilizing agent, correct?

A. Yes.

Q. It does not say solvent or cosolvent, correct?

A. It does not.

Q. And you know what a BLA is, don't you?

A. Yes.

Q. So a BLA, they're supposed to be truthful and accurate, correct?

A. They must be truthful and accurate, yes.

Q. Because you're making representations to the FDA to seek approval for your drug, correct?

A. That's correct.

Q. So in this BLA identifies the ingredients and the function. It represents to the FDA the polysorbate 20 functions as a stabilizing agent, correct?

A. Yes, it does.

Q. Now, let's look at the same exhibit, page 5. I'm sorry. Let's go to the same exhibit, page 6, sir. My apologies.

Here we have another table and this one is Table 2 from the BLA, and it says, "Role of Excipients in the VEGF Trap-Eye Formulation," correct?

A. Yes.

Q. And the role of polysorbate 20 here is identified again as "stabilizing agent," correct?

A. Correct.

Q. Not solvent?

A. Correct.

Q. Not cosolvent?

A. Correct.

Q. And it goes on to provide additional description. Do you see there it says for polysorbate 20, "The addition of polysorbate 20 reduces the rate of aggregation and precipitation when the protein is handled and agitated as a liquid," correct?

A. Correct.

Q. And you agree with that, correct?

A. I do.

Q. Now, it says "reduces the rate of aggregation and precipitation." I think we just established polysorbate 20, it doesn't dissolve aflibercept, right?

A. That's correct.

Q. And it doesn't dissolve or get rid of aggregates, correct?

A. That's correct.

Q. And just to be clear, there are no solvents identified in this formulation to the FDA other than water for injection, correct?

A. That's correct.

Q. All right. I'd like to talk a little bit about some of the information that you were tracking from your competitors like Genentech.

Do you recall testifying about that?

A. I do.

Q. Let's look at a couple documents. Let's pull up the first one, DTX 710.

MR. RAKOCZY: I apologize, Your Honor. I need someone to pass me some notes.

Move to admit PTX 1519, Your Honor.

THE COURT: Any objection to 1519?

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

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(PTX 1519 was admitted.)

MR. RAKOCZY: Let the record reflect Mr. Salmen did not hand me the note he was supposed to hand me.

THE COURT: You may now ask for notes, Counsel, and I suspect you shall receive.

BY MR. RAKOCZY:

Q. All right. Apologize, Dr. Furfine. So we have DTX 710. Are you with me?

A. I am.

Q. On page 1 you see this is an email from Jesse Cedarbaum, dated March 1, 2004, to you and others including cofounder Dr. Yancopoulos, correct?

A. Correct.

Q. Here Mr. Cedarbaum is circulating an abstract that Genentech had published for Lucentis, correct?

A. Let's see. Just give me a second to read it.

Q. Absolutely.

A. Yes, it is a pharmacokinetic study for ranibizumab.

Q. Yes. The abstract title was "Pharmacokinetic Study of Ranibizumab (Lucentis) Following Subconjunctival" --

A. Conjunctival, yes.

Q. -- "Intracameral and Intravitreal Administration in Rabbits."

A. Yes.

Q. So this is consistent with your testimony you were

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following Genentech and what they were doing with intravitreal delivery of that molecule, correct?

A. Yes.

Q. This is March 2004. Let's look at January 2005 and see what else you got your hands on.

MR. RAKOCZY: That time, I did get a note.

THE COURT: Noted for the record.

Good job, Counsel.

MR. RAKOCZY: Move to admit DTX 710, Your Honor.

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 710 was admitted.)

BY MR. RAKOCZY:

Q. Dr. Furfine, on screen should be DTX 714.

A. 714. Yes.

Q. This is an email dated January 27, 2005, to you and others at Regeneron, again including cofounder Dr. Yancopoulos, correct?

A. Yes, it is.

Q. And the subject is "Lucentis ITV PK," correct?

A. Correct. Yes.

Q. And if we go to page 2 of the document, this email was forwarding the Gaudreault paper entitled "Preclinical Pharmacokinetics of Ranibizumab (rhuFabV2) After a Single Intravitreal Administration." Correct?

A. Yes.

Q. And this is the Gaudreault paper you mentioned earlier, right?

A. Yes, it is.

MR. RAKOCZY: And, Your Honor, we will get you and Madam Court Reporter a list of all of these terms. I realize we're ripping them off pretty quickly.

THE COURT: Much appreciated.

MR. RAKOCZY: Move to admit DTX 714, Your Honor.

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 714 was admitted.)

BY MR. RAKOCZY:

Q. Now, in this paper, in addition to the part you cited or testified about, you also got your hands on the actual formulation of ranibizumab in this paper, correct?

A. I believe it is in here somewhere, though I don't remember exactly where right this second.

Q. Let's go to page 3 of DTX 714, left-hand column below the table, the fourth line.

A. Got it, yep.

Q. Here we see that ranibizumab was "formulated as 10 millimolar sodium succinate, 10 percent trehalose, and 0.5 [sic] percent Tween 20 (pH 5)," correct?

A. Correct.

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Q. I'll read it again. I apologize.

Again, we're in DTX 714 on page 3. And here we see that ranibizumab "was formulated as 10 millimolar sodium succinate, 10 percent trehalose, and 0.05 percent Tween 20 (pH 5)," correct?

A. Yes.

Q. And Tween 20 is another name for polysorbate 20, correct?

A. Correct.

Q. And trehalose here is the stabilizer, correct?

A. Trehalose is known as a stabilizing agent. It can be used that way. Because I did not develop this formulation and were not aware of the testing they did, I can't say for sure that that's what it was used for here.

Q. So you wouldn't know what the function of that ingredient is unless you actually had test data on it, correct?

A. That's correct.

Q. And sodium succinate, would it be the same answer? That might be a buffer, but you would actually have to see testing data to know. Am I right?

A. I don't know for a buffer -- I guess in a perfect world, yes, you would want a pH test done.

Q. Now, same answer for the Tween 20, the 0.05 percent. You would need to see test data to know exactly how that was behaving and how it was functioning in the formulation,

correct?

A. You would, though these would be relatively easy tests to perform.

Q. Okay. That's fair. But you would want to do that test to know what it was doing, correct?

A. I think it's slightly different than that. If you don't mind my -- so science is done a little bit differently than that. Basically, you have a challenge that you're trying to solve, and you add things to try and solve those problems.

And so it's really kind of -- you're kind of putting the cart before the horse a little bit in the way you're describing it. So, really, like, you decide what you want to test because you're trying to solve a problem. Then you run that test.

Q. My question is much simpler. We're looking at a formulation of ranibizumab. You don't have any data on it. To know the functions of those ingredients, you would want to see test data on them, correct?

A. I would.

Q. Okay. And this article is what ran the PK study on -- can you pronounce it for me? Is it cynomolgus monkeys?

A. Cynomolgus monkeys, correct. You pronounced it correctly.

Q. Now, this publication, would it advance the skilled person's knowledge, at least to some degree, regarding the

tolerability of polysorbate in an intravitreal injection? Correct?

A. It would have advanced the knowledge and would have actually been potentially concerning, given their information results.

Q. We'll get to that. But my question is it would have advanced the skilled person's knowledge at least to some degree?

A. That's correct.

Q. Now, in fact, Genentech here had beat you to the punch, right, in measuring or attempting to evaluate tolerability of polysorbate in a formulation? Is that right?

A. I don't know that we were in a race with Genentech to test polysorbate. That wasn't really a competition that was going on. So I would say no to that.

Q. Well, you were tracking Genentech's work, at least. That's fair, right?

A. We were.

Q. Now, Genentech was proposing to use five times the amount of polysorbate 20 in this formulation than you were proposing at around this time; is that right?

A. I think we tested .1 to .03; so this is not five times those.

Q. At the time of this article, isn't it true that you were proposing to limit the amount of polysorbate 20 in the

formulation to 0.01 percent?

A. Oh, yeah. That's a function of a manufacturing process where we had to add a little bit to stabilize it to the stringencies that happened during manufacturing.

And the idea there was that, if we didn't want polysorbate in there, we would have to be able to state what the minimum that was in there was.

So we were first making formulations that didn't have polysorbate. As you saw, IVT-1 did not have polysorbate in it. But, in fact, it had a small amount because that got carried through in the manufacturing.

So that's what that was about. We didn't go with polysorbate until later when we required it because it worked better than PEG.

Q. Let's take a look at DTX 711. And I want to look at the first email on the page.

You see this is an email dated December 8, 2004, around the same time as you received that Gaudreault paper. And this is from named coinventor Dr. Graham on the subject of "Specification for intravitreal VEGF Trap," correct?

A. Yes.

MR. RAKOCZY: Move to admit DTX 711, Your Honor.

THE COURT: Any objection?

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 711 was admitted.)

BY MR. RAKOCZY:

Q. All I want to do is confirm here lower in the email at the end of the second -- or the last paragraph, you see here that Dr. Graham is proposing a limit for the polysorbate as not to exceed 0.01 percent in the specification, correct?

A. Yes, that's what it states.

Q. So the ranibizumab formulation you saw in Gaudreault was using five times that amount of polysorbate 20, correct?

A. Yes, it was five times the amount -- well, five times the maximum amount that could have been in the solution, yes.

Q. Correct. Thank you.

So in April 2005 I believe you received information on Genentech's Avastin formulation.

Do you recall that?

A. Not off the top of my head, but --

Q. Let's take a look. DTX 714 on screen. It's also in your binder.

A. So this is still the -- the Gaudreault paper is 14.

Q. I'm sorry. DTX 716. My apologies.

Do you see this?

A. Yes.

Q. This is an email dated April 12, 2005, from you to your coinventors, Dr. Dix and Dr. Graham, correct?

A. Correct, yes.

Q. And the subject is "Avastin EMEA discussion," correct?

A. Correct.

Q. Now, Avastin was the name of Genentech's bevacizumab; isn't that right?

A. Yes.

Q. Now, if we look at who forwarded this, you see there's a forward from the CEO, Leonard Schleifer, correct?

A. Yes, that's correct.

Q. And you see he says, "This is single-most comprehensive discussion of Avastin all in one place. The European approval discussion document!" Correct?

A. That's what it says.

Q. Now, you then forwarded this to your formulation team?

A. Yes.

Q. Dr. Dix, Dr. Graham, and Kelly Frye. And you instructed them to take a close look at the protein characterization, manufacturing, and stability part of this document, correct?

A. Yes, I did.

Q. And you pointed out that there may be some other things Regeneron should consider based on what Genentech had done, correct?

A. Correct.

Q. Now, the attachment, the EMEA report, actually discloses the Avastin formulation, correct?

A. Yes, it must. I haven't read it in a long time; so --

Q. Let's --

A. -- I'll trust you on that.

Q. Let's go to page 9 of DTX 716, under the drug product section. Do you see that?

A. Yes.

Q. And if we go to lines 4 to 5, you see the bevacizumab or the Avastin formulation there, correct?

A. Yes. 10 mg/mL.

Q. It's a formulation containing 51 millimolar sodium phosphate, 60 mg/mL trehalose dihydrate, and 0.04 percent polysorbate 20, correct?

A. Maybe I'm looking at a different one. I'm sorry. Say it again just to make sure I'm in the right place.

Q. It's highlighted on screen as well; so...

A. I'm sorry. I was looking at the one above that. Yeah. Okay. 51 millimolar.

Q. The Avastin formulation had phosphate --

A. Yes.

Q. -- trehalose, and 0.0 [sic] percent polysorbate 20?

A. Correct.

Q. So four times the amount of polysorbate that your

specification topped out at, correct?

A. Correct, though this is for cancer treatment, systemic exposure, not eye.

Q. Now, you understand this formulation was used in the eye, though, correct?

A. At later points in time, there were people who administered off-label -- unapproved, off-label -- bevacizumab to the eye, yes.

Q. A lot of off-label use, right?

A. A lot, yes.

Q. Now, I want to ask you about this formulation and the functions, and I don't need to spend a lot of time on it. I just want to confirm your answer would be the same.

Looking at the formulation, you don't know the function of those ingredients unless you had test data on it, correct?

A. I wouldn't know for sure. I could suspect, but I wouldn't know for sure.

Q. Now, let's look at page 4 of this document, DTX 716.

MR. RAKOCZY: And I apologize if I neglected to move to admit -- move to admit DTX 716.

THE COURT: Any objection?

MR. BERL: No objection.

THE COURT: Without objection, motion, in note form, granted.

MR. BERL: I have no objection to him just doing it at the end too.

BY MR. RAKOCZY:

Q. All right. If we look under the introduction, I want to look at the size --

A. Which tab are we on now?

Q. So we are on the same exhibit.

A. Okay.

Q. DTX 716 at page 4.

A. Oh, page 4.

Q. It's the first two lines right under the introduction.

And Avastin is a big molecule, isn't it?

A. It has a molecular weight of 150,000, like most antibodies, yes.

Q. It's bigger than aflibercept, correct?

A. Depends how you want to measure it. If you measure it in absolute molecular weight, yes, it's a little bit bigger. If you measure it kind of like we talked about before and its function, it's more similar in size.

Q. We want to look at kilodaltons, at kDa's. Aflibercept is, I think, 115 you mentioned?

A. That's correct.

Q. And bevacizumab, or Avastin, is 149 kilodaltons, correct?

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A. That's correct.

Q. So bigger. And used in the eye successfully, correct?

A. It has at later points, than I think when this document came out, been used in the eye successfully.

Q. Now, let's look at -- I want to go back to your instructions to your team in the email. You told them to take a close look at the stability part of the document?

A. Yes.

Q. And let's go to the stability part of the Avastin report, which I believe is page 10 of DTX 716. And if we look at the third-to-last line --

A. Third-to-last line.

Q. -- we can see that the Avastin report concluded that "The submitted stability data support the proposed shelf life of 24 months when stored at 5 degrees C plus or minus 3 degrees C," correct?

A. Yes.

Q. So this formulation containing the trehalose, the polysorbate 20, and the buffer was stable for 24 months at 5 degrees C, correct?

A. Yes, it was.

Q. Now, the EMEA discussion document for Avastin was not the last information that you obtained on Genentech's Avastin, correct?

A. No, I doubt it. I don't remember everything I received, you know, 20 years ago on this topic, but probably not.

Q. Let's look at DTX 718.

A. Okay.

Q. And this is an email from Kelly Frye on your team to you and others dated April 18, 2005, with the subject line "Avastin and Macugen formulations," correct?

A. Yes.

Q. And if you look at the bottom half of the email, she provides the formulation for Avastin?

A. Yes.

Q. Apologize. We need to go down further in the email. There it is.

A. I see it.

Q. And so we see the Avastin formulation again -- the phosphate, the trehalose, and the polysorbate 20, correct?

A. Yes.

Q. And then the Macugen formulation there as well, correct?

A. Correct.

Q. And below that she says, "Both of these formulations would be iso-osmolar," correct?

A. Yes, she says that.

Q. That's the same thing as isotonic, correct?

A. Yeah, they're synonymous.

Q. So the Avastin formulation, even though it was for cancer at 10 millimolar phosphate, 6 percent trehalose, and 0.04 percent polysorbate 20, was isotonic, correct?

A. Yes.

Q. Now, by July of 2005 it was also known that Avastin, or bevacizumab, a much larger molecule than aflibercept, had actually been used in the eye, correct?

A. So, first of all, it's not a much larger molecule. It's actually functionally about the same. So I would disagree with that assessment.

And I don't know when the Avastin was started to be used off-label in people's eyes instead of ranibizumab. I don't remember when that started. I started tracking it more when it was after the ranibizumab approval, so after Lucentis was approved, when it became an issue and more in the news because Genentech was not happy about it.

Q. We'll take a look.

MR. RAKOCZY: Before we do, move to admit DTX 718, Your Honor.

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 718 was admitted.)

BY MR. RAKOCZY:

Q. Let's pull up DTX 3058 on Avastin.

A. Sorry. Say the number again.

Q. DTX 3058. And you see this is a paper dated July-August 2005 entitled "Optical Coherence Tomography Findings After an Intravitreal Injection."

Do you see that?

A. Yes.

Q. Does this refresh your recollection that Avastin, or bevacizumab, had been used by intravitreal injection?

A. Yes. This is a publication on the topic, yes.

Q. So by July or the summer of 2005, someone had used bevacizumab, or Avastin, off-label in the eye, correct?

A. That's correct, yes.

Q. All right. I want to talk briefly about this ITV-1 formulation, the PEG formulation.

Do you recall that?

A. Yes.

Q. And just to clear up, some of the documents say ITV and some say IVT. Can I assume that's the same thing?

A. Yes.

Q. Okay. So the IVT-1 was the PEG formulation, and that was the first one that you put into the clinic at Regeneron, correct?

A. That's correct.

Q. And so that did not use polysorbate, correct?

A. That's correct. That did not use polysorbate.

Q. Let's pull up DTX 719 and look at page 1.

And you see this is a memo. It's copied to you, dated August 16th, 2005, from --

A. Yes.

Q. It's from coinventors Dr. Dix and Kelly Frye, correct?

A. Yes.

Q. And the subject is "VEGF Trap intravitreal formulation storage and shipping conditions," correct?

A. Yes.

MR. RAKOCZY: Move to admit DTX 719, Your Honor.

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 719 was admitted.)

MR. RAKOCZY: I apologize. Also move to admit DTX-3058.

THE COURT: Any objection to 3058?

MR. BERL: No objection.

THE COURT: Without objection, that is also admitted.

(DTX 3058 was admitted.)

BY MR. RAKOCZY:

Q. Let's look at the formulation identified on DTX 719. And we can see this is a 10-millimolar sodium phosphate, 135-millimolar sodium chloride, and 0.1 percent PEG 350, correct?

A. Yes, that's correct.

Q. Now, I think you mentioned that this formulation, in your view, was somehow inferior, but this is the one that was actually moved into the clinic first in Phase I and Phase II trials, correct?

A. It was moved into the clinic first, but we didn't know, when we moved it into the clinic, that it was inferior.

Q. But it was actually used in Phase I and Phase II clinical trials, correct?

A. Yes, it was.

Q. I'd like to look at another study on this IVT-1 PEG formulation, and it's at DTX 723.

A. Organic cosolvent. Got it.

Q. This is a memo from Laura Pologe copying you --

A. Pologe, yes.

Q. I apologize.

This is a memo from Laura Pologe copying you to coinventors Dr. Graham and Dr. Dix, dated March 10, 2006, entitled "Syringe compatibility of 10 mg/mL and 40 mg/mL VEGF Trap," correct?

A. Correct.

Q. And this study actually tested the PEG formulations, correct?

A. Give me a second to look. Yes, it appears to be the PEG.

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Q. If we look at the first paragraph, last two lines on page 1 of this exhibit, we see the formulation. 0.1 percent PEG, correct?

A. Correct.

Q. And so this test was using the same amount of PEG, 0.1 percent, but testing it in 10 mg/mL and 40 mg/mL, correct?

A. Yes.

Q. So you don't have to add more PEG to dissolve aflibercept or the other ingredients in here, correct?

A. When we make a formulation, the aflibercept is already in solution; so we don't use the PEG to dissolve it.

Q. Thank you, sir.

MR. RAKOCZY: Move to admit DTX 723, Your Honor.

THE COURT: Any objection?

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 723 was admitted.)

BY MR. RAKOCZY:

Q. Now I'd like to move on to the polysorbate formulation, or, I believe, IVT-2, correct?

A. Hang on a second. Say which one you are again.

Q. The IVT-2 formulation was the polysorbate formulation.

A. Yeah, but which page are you on?

Q. Oh, I'm moving to a new exhibit now.

A. Okay. Can you just restate the number?

Q. I just had a quick question to confirm. IVT-2, that denoted the polysorbate formulation without PEG?

A. Sorry. Yes. Correct.

Q. Okay. So let's go to DTX 725. And this is an email you're copied on from coinventor Dr. Graham?

A. Yes.

Q. Dated May 8, 2006, with the subject "VEGF Trap formulations for ITV," correct?

A. Yes, correct.

Q. And in the email below on this page, you are asking Dr. Graham to provide the formulations moving into the tox study, correct?

A. Yes.

Q. And this email is dated May 8, 2006, correct?

A. Yes, correct.

Q. And let's look at the formulations above that very quickly. We see that he sent along a lead formulation and a backup formulation, correct?

A. Correct.

Q. And the lead formulation had phosphate, NaCl, polysorbate 20, and 5 percent sucrose, and 5 to 40 mg/mL VEGF Trap, correct?

A. Correct.

Q. And the backup formulation had phosphate, NaCl,

polysorbate 20, and also 5 to 40 mg/mL VEGF Trap, correct?

A. Correct.

Q. Now, this email does not contain any tox data, correct?

A. It says we're going to use it in a tox study, but it does not show the data from that study, correct.

Q. So you didn't have that tox data yet. You were moving these into the study, correct?

A. That's correct.

Q. And this email does not provide any stability data on these formulations either, correct?

A. It does not, no.

Q. And you agree that the purpose or the role of the 0.03 percent polysorbate in this lead formulation and the backup formulation was as an agitation stabilizer, correct?

A. It does serve that purpose, yes.

MR. RAKOCZY: Move to admit DTX 725, Your Honor.

MR. BERL: No objection.

THE COURT: Without objection, 725 admitted.

(DTX 725 was admitted.)

Counsel, may I inquire? Where are we in the grand scheme of things?

MR. RAKOCZY: Your Honor, I'm terrible at time, but I may have a decent amount. If you want me to break, I'm happy to break.

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THE COURT: Are we at a good spot in that to do so?

MR. RAKOCZY: Yes, we are. We're moving to a new module.

THE COURT: Why don't we do that then, given the hour.

MR. RAKOCZY: Did I move to admit DTX 725? I did, right?

THE COURT: Yes. Based on affirmative head nod from Madam Clerk, yes.

MR. RAKOCZY: Thank you.

THE COURT: Doctor, this may come as good or bad news to you. In the back of the room to the right, just you and I hear that. You're midstream on your testimony. So my admonition about being a man without a country applies to you this evening as well. So have dinner on your own and perhaps decompress a little bit. But formally, for the record again, because you are midstream, so to speak, on your testimony, you're not permitted to interact with anyone. They're not allowed to talk to you, vice versa. So I'll offer that as protection for you or an excuse as to why folks may run from you during this evening.

But you're free to step down, sir. Go right ahead. You can leave those materials right there.

THE WITNESS: Thank you.

THE COURT: No, thank you. And have a pleasant

evening in solitude.

THE WITNESS: Still okay to, like, get a ride back to the hotel?

THE COURT: I will give you special dispensation. Someone will give you a ride. Turn the radio up really loud.

Good question, though, Doctor. Good question. You don't have to stay in the courthouse. That's reserved for other people.

We'll pick up with the doctor's testimony tomorrow morning at 9:30, unless there's anything else we need to take up at this point.

MR. RAKOCZY: Nothing from Mylan.

MR. BERL: Nothing from us.

THE COURT: Any additional exhibits plaintiffs expect to seek to introduce for Dr. Furfine?

MR. BERL: We have a list from what happened on direct. I can just do that at the end of the redirect.

THE COURT: That's fine. Just make sure that's kept in updated condition, and we'll do that.

MR. RAKOCZY: That's fine with us, Your Honor.

THE COURT: Great.

With that, everyone have a pleasant evening, and we'll resume tomorrow morning. Thank you all very much.

(Proceedings concluded at 5:16 p.m.)

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CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 13, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 13th day of June 2023.

/s/Cindy L. Knecht

_____

Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 3

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 14, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

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Proceedings recorded utilizing realtime translation.
Transcript produced by computer-aided transcription.

Wednesday Morning Session,
June 14, 2023, 9:30 a.m.

- - -

THE COURT: We all reconvene for day three of trial. Happy Flag Day to everyone.

A couple things to start with. I will remind everyone, counsel and spectators, local rule 85.01 of the Northern District of West Virginia absolutely prohibits any recording or photographs of the courtroom or in the areas immediately adjacent to the courtroom. There was a report yesterday that there had been photographs being taken. If that gets confirmed, if that happens again, violators will be dealt with accordingly. But everyone is hereby reminded of that local rule as an FYI.

I'm aware there's been a flurry of filings this morning. Regeneron's motion to exclude. And there was also a letter emailed to Ms. Marcum this morning on Steptoe & Johnson letterhead. The Court will order that filed and made part of the record as well. We have not had a chance to read that; so we'll take that up after we do.

If we're ready to resume with our current pending witness, we can proceed.

Yes, Doctor, there you are. I'm sorry. Good morning, sir. Go ahead and resume the stand. I'll remind you you remain under oath. Good morning. I hope you enjoyed your

evening of solitude.

THE WITNESS: I did.

THE COURT: Good.

(Witness resumes stand.)

THE COURT: You're welcome.

Counsel, go right ahead.

MR. RAKOCZY: Good morning, Your Honor. William Rakoczy for Mylan and Biocon.

CROSS-EXAMINATION

BY MR. RAKOCZY:

Q. Good morning, Dr. Furfine.

A. Good morning.

Q. Let's jump back to your '865 patent, if we could, go over just a few items. It is PTX 2 in your binder. If we could go to page 7, please.

Go to the beginning of the examples. I believe if you start on page 7, Dr. Furfine, you'll see that your patent has eight examples. Do you see that?

A. I see the examples list.

Q. And if you look through the next couple pages, you'll see it runs through eight total examples, correct?

A. Yes.

Q. Now, let's look at Examples 1 and 2 quickly, please, on page 7. And you see both of those examples are directed to a formulation containing 50 mg/mL VEGF Trap, correct?

A. Correct.

Q. So those examples would not be covered by a claim that required 40 mg/mL of VEGF Trap, correct?

A. I don't think I'm qualified to decide what claims cover what.

Q. You agree 50 is different from 40 mg/mL, right?

A. I would indeed.

Q. Now, if you could quickly look at Examples 7 and 8 on page 9 of the exhibit, and you see both of those examples are directed to 20 mg/mL VEGF Trap, correct?

A. Correct.

Q. So, obviously, not 40 mg/mL VEGF Trap, correct?

A. Correct.

Q. And if you look at Examples 4 and 6, do you see those are liquid formulations in a refilled syringe, not a vial, correct?

A. Correct.

Q. Now, Examples 5, 6, and 8, can you confirm for me those do not contain a sugar stabilizer? Is that right?

A. 5. What were the other ones?

Q. Excuse me. 5, 6, and 8 do not contain a sugar stabilizer; is that correct?

A. Correct.

Q. Now, you did not invent any new or novel excipients in your '865 patent, correct?

A. No, there were not novel excipients.

Q. The excipients used in your patent were known and available before the patent, correct?

A. Yes, that's correct.

Q. Can we look at Example 3, please, on page 9. And you see that's a liquid formulation in a vial, correct?

A. Sorry. Example 3 on page 9?

Q. Yes, sir.

A. My page 9 has Examples 7 and 8.

Q. I'm sorry. Page 8. My fault. Example 3 on page 8 is directed to a liquid formulation in a vial, correct?

A. Correct.

Q. And liquid protein formulations in a vial, they were known before your '865 patent, correct?

A. Generally speaking. Is that what you're asking, liquid formulations?

Q. Yes.

A. Yes.

Q. And we saw yesterday, we discussed the Lucentis and the Avastin formulations were liquid formulations known, correct?

A. Yes, they were liquid formulations known.

Q. And your Example 3 also contains 10 millimolar phosphate, correct?

A. That's correct.

Q. You didn't invent a phosphate buffer for a protein formulation, correct?

A. I'm not sure exactly how to answer that. I didn't invent a phosphate --

Q. Let me back up.

A. I invented the use of a phosphate buffer in this formulation to stabilize aflibercept.

Q. But phosphate buffers were known before your patent, correct?

A. That's correct. Phosphate buffers were known.

Q. Now, your Example 3 also contains 5 percent sucrose, correct?

A. Yes, that's correct.

Q. And sucrose stabilizers were known before your '865 patent, correct?

A. They were known generally as a class of molecules that could stabilize proteins, yes.

Q. And Example 3 also contains 0.03 percent polysorbate 20, correct?

A. Yes.

Q. And polysorbate 20, I believe you said yesterday, was a known excipient before your patent, correct?

A. That's correct.

Q. Now, we discussed yesterday, I believe, Lucentis formulation we looked at was for intravitreal administration

and that had used sodium succinate, trehalose, and polysorbate 20, correct?

A. That's my recollection.

Q. So you would agree those excipients would be suitable for intravitreal administration, correct?

A. So depends whether you mean at the time that I was inventing this or what eventually became true.

Q. Before your patent, you would agree it was known that excipients used in Lucentis would be suitable for use in an intravitreal injection, correct?

A. I don't know that there was enough data to make that claim at that point.

Q. So you would have needed more test data at the time to know that?

A. I think so, yes.

Q. And would the same answer be true for the excipients in the Avastin formulation for your patent? You would have needed more test data to know whether those would have been suitable for intravitreal administration?

A. Yes, probably.

Q. And that's true even though Avastin had been used in the eye by intravitreal administration, correct?

A. One patient and also animal studies suggesting that it could be problematic.

Q. So you wouldn't have known before your patent whether

you could use the Avastin excipients in the eye?

A. Not for sure. No, you wouldn't.

Q. Now, let's talk about buffers. Can you confirm for me, sir, that every example in your patent, 1 through 8, they all use a phosphate buffer, correct?

A. Correct, they all use a phosphate buffer.

Q. And you didn't personally develop a histidine buffer aflibercept formulation when you were at Regeneron, correct?

A. I'm not sure the timing of when the histidine buffer was developed, whether it overlapped with my time or not. I don't recall working on it. I think I stated that previously in deposition. But I can't tell you for sure that it didn't happen and I'm just not remembering.

Q. I think you testified at your deposition you couldn't recall seeing a histidine buffer formulation during your time at Regeneron. Is that right?

A. I did not recall it, that's correct.

Q. Now, I'd like to switch gears -- yesterday you talked about the Gaudreault reference from Genentech.

Do you recall that?

A. Yes.

Q. And I believe you testified that there was -- the results from Gaudreault, the transient ocular inflammation, I believe you used the words, were concerning or discouraging at the time to you.

Do you recall that?

A. I do recall that, yes.

Q. Now, to be clear, there was nothing discouraging about those results to Genentech, correct?

A. Actually, I think there probably was, but it would be me inferring things. The fact is that they didn't go with a 40 mg/mL formulation and they could have, and perhaps that was part of the reason why they didn't.

Q. They continued to develop their Lucentis formulation despite the Gaudreault results, correct?

A. The 10 and lower, not the 40.

Q. But they continued to develop despite the results, right?

A. They continued to develop the lower concentrations despite the results, yes.

Q. Now, Regeneron wasn't discouraged by those results from pursuing Eylea either, correct?

A. We thought that it was possible that there could be something specific to Eylea -- excuse me -- specific to ranibizumab and it could be possible for us to find something better, yes.

Q. And you actually continued developing Eylea even after seeing the Gaudreault results, correct?

A. Yes, we did.

Q. And, in fact, you saw similar results of transient

ocular inflammation in your own monkey studies, correct?

A. It's been a while since I've looked at that data, but I believe that's correct.

Q. Let's pull up PTX 3255. Should be in your binder. And let's look at page 4.

A. Say the number. 5 --

Q. Yes, sir. PTX 3255.

THE COURT: 3255, Counsel?

MR. RAKOCZY: Yes.

THE COURT: Thank you.

THE WITNESS: 3255, yes.

BY MR. RAKOCZY:

Q. You see this is the nonclinical overview from the BLA, correct?

A. I do.

Q. If you look at page 4, there's a reference in that sentence to a comprehensive toxicology program, including a treatment schedule of every two to six weeks.

Do you see that?

A. This is page 4?

Q. Yes. It's on your screen as well.

A. Yes, I see the paragraph now.

Q. So if we go to page 19 of this exhibit, you see a reference to a repeat-dose toxicity study, correct?

A. I do.

Q. And we see there that the chronic toxicity of VEGF Trap was evaluated in the -- I'm going to mispronounce it again -- cynomolgus monkey, correct?

A. That's correct.

Q. Let's look at -- a little further down in that paragraph we see the results. We see Regeneron told the FDA that the "ocular findings were consistent across all GLP IVT studies and consisted primarily of mild and transient ocular inflammation."

A. Correct.

Q. Is that correct?

A. Yes, that's what it states here.

Q. And then if you go a couple sentences down, Regeneron concluded that "these ocular findings were mostly or completely reversible before the next dose or during the recovery periods." Correct?

A. I'm just trying to find where you're reading this.

Q. It's in that same paragraph, fifth line down.

A. Yes.

Q. Now, these results did not discourage Eylea's development, correct?

A. They did not.

Q. And when you said the results from Gaudreault were concerning, you're not suggesting that moderate to severe inflammation would somehow outweigh vision loss, are you?

A. Moderate to severe inflammation -- repeated moderate to severe inflammation might cause vision loss.

Q. So your view is that moderate to severe vision loss that could resolve in a week would be enough to stop development of a drug that can prevent vision loss. That's your testimony?

A. My testimony is not exactly that. It's that a repeated moderate to severe inflammation could have consequences that might result in vision loss. You would have to do the experiments.

Q. But that inflammation, that transient inflammation that resolved in a week or two, was not enough to prevent Lucentis development or Eylea development, correct?

A. It prevented -- well, by inference, because they did not develop the 40 mg/mL formulation, it would suggest that they were concerned about the same thing because they stuck with 10, which didn't have that finding in that study.

Q. The Gaudreault paper concluded that all the doses they tested had transient inflammation that resolved.

A. The degree. It's a severity. You have to include the severity when you make your judgment of what you want to do.

Q. All right. Let's actually -- I forgot to mention something in your patent. Let's toggle back to your patent.

A. Okay. Remind me.

Q. PTX 2. If we go to page 2. And I'm going to focus -- and I'll put it on the screen -- on the application number and date.

A. Yes.

Q. And you see that the --

If we could go down, Mr. Gibson, to the application number in the middle.

You see this patent issued from Application Number 16 --

A. -- 739 --

Q. -- 739,559, filed January 20 -- let me back up. Let me strike that. I'll start over.

Your '865 patent issued from Application Number 16/739,559 filed January 10, 2020; is that right?

A. That's correct.

Q. I want to look further down on this same page to the related U.S. application data.

A. Yes.

Q. You see that section?

A. I do.

Q. And I want to focus on paragraph 60 where it says "Provisional Application."

Do you see that?

A. I do.

Q. And so the provisional application, number 60/814,484

was filed on January 16, 2006, correct?

A. Say that number again, which one you were...

Q. Yes. So it's highlighted on the screen.

A. Sorry.

Q. The U.S. Provisional Application Number 60/814 --

A. Right.

Q. -- 484 was filed on June 16, 2006, correct?

A. That's correct, yes.

Q. Are you okay if I refer to that as the provisional application just for short?

A. Yes.

Q. Now, let's look at PTX 8. I'm sorry. Strike that.

Let's look at PTX 3249, which is in the small binder right in front of you.

A. Sorry. It's not another tab on here?

Q. No. The small binder right there. Go to PTX 3249. If we go to page 8, please.

A. Okay.

Q. You see this is the provisional application for patent. Do you see that?

A. I do.

Q. And you're listed as an inventor right there. Do you see that?

A. Yes, I do.

Q. And you see the title is "VEGF Antagonist Formulation

Suitable for Intravitreal Administration," correct?

A. Yes, I do.

Q. And if you go to the bottom of this page, you see dated June 16, 2006, correct?

A. Yes.

Q. Did you review this provisional application before it was filed on June 16, 2006?

A. I presume that I did, but, honestly, I don't remember that far ago. That was, like, 20 years ago or something.

Q. How about before your testimony yesterday? Did you review this provisional application before yesterday?

A. I reviewed the patent application, but I'm trying to remember if I reviewed the first -- I think I might have reviewed the provisional, but I can't remember for certain.

Q. So do you remember doing a side-by-side comparison of this provisional application with your issued '865 patent before your testimony yesterday?

A. I don't recall doing a side-by-side comparison, no.

Q. Let's look at page 11 of your provisional application. So that's PTX 32 --

A. It doesn't mean that I didn't. I just don't recall.

Q. I'm asking, before your testimony yesterday, did you do a line-by-line comparison?

A. No, not that I remember, no.

Q. So let's look at page 11 of your provisional

application. And I've got it on screen, PTX 3249.

A. Yes.

Q. And I'd like to focus on paragraph 8 and the sentence that starts "more specifically, the ophthalmic formulations comprise."

Do you see that?

A. I see in paragraph 8 is "in several embodiments," right, "more specifically," yes.

Q. So you see that sentence that starts "more specifically, the ophthalmic formulation comprises," and then it continues on, correct?

A. Yes.

Q. So I want to toggle back to your issued '865 patent, which is PTX 2 --

A. Right.

Q. -- at page 4. And we'll put it on the screen. And I want to focus on Column 2, lines 53 to 57. And we'll put it on screen.

A. Okay.

Q. You see here in your '865 patent, it says, "more specifically, stable liquid ophthalmic formulation." So you see the words "stable liquid" have been added.

Do you see that?

A. I see this "stable liquid" in this one. I haven't looked to see if it's not in the other one.

MR. RAKOCZY: Mr. Gibson, can we please pull up that paragraph 8 from the provisional. If we put it next to the paragraph from PTX 2, please.

BY MR. RAKOCZY:

Q. All right. So you see on screen in the provisional paragraph 8, you see it says "the ophthalmic formulation."

Do you see that?

A. Correct, the top one.

Q. Yes, that's the provisional. And in your '865 patent, it says, "the stable liquid ophthalmic formulation," correct?

A. Yes.

Q. Did you add "stable liquid" to the '865 patent specification?

A. I don't recall personally doing that. I don't write the applications.

Q. Did you authorize someone to add the words "stable liquid" to your '865 patent specification?

A. I do not believe I -- I didn't -- I didn't authorize or not authorize. I wasn't involved in that, to my recollection.

Q. Your '865 patent claims are all directed to stable liquid formulations, correct?

A. Yes.

Q. Now, I'd like to put up a demonstrative for you of

your PTX 2, and we'll call up DDX 5 at page 5.

What I've done here is I've highlighted in yellow parts of Columns 3 and 4 from your issued '865 patent at PTX 2 at page 5.

Do you see that on your screen?

A. I see it here. It's easier for me to look at the book here, but yes.

Q. Are you aware that everything that is highlighted on this demonstrative in Columns 3 and 4 of your '865 patent -- so it's Columns 3, line 11, extending through Column 4, line 10, of PTX 2 -- is not found in your original provisional application? Are you aware of that?

A. I'm not aware of that. I've not done the head-to-head comparison, as you suggested.

Q. So at no time before your testimony today or yesterday did you do the comparison to see that this is all new matter added to your '865 patent, correct?

A. I did not -- I did not do the comparison to be able to detect that that was the case.

Q. Did you authorize anyone to add all this new material to your '865 patent?

A. Again, I didn't authorize or not authorize. I don't recall being involved in that process.

Q. Let's stay on DDX 5, page 5, and I'd like to look at Column 3, lines 36 to 40. If we could blow that up. And I'd

like to focus on -- I apologize. I'm pointing to the wrong -- I'm sorry.

Column 3, lines 36 to 40. And do you see here in the third line it says "about 0.013 to about 0.1 percent polysorbate"? Do you see that?

A. Can you just tell me -- I'm having trouble finding this. Is this in the Column 3?

Q. Yes. Column 3, lines 36 to 40.

A. I see it now.

Q. And do you see there is a range there for the polysorbate? It says, "about 0.3 to about 0.1 percent polysorbate." Do you see that?

A. I do see that, yes.

Q. Do you know whether that exact range is found in your provisional application?

A. I do not recall if it is or isn't.

Q. I would like to look at one more portion of this highlighted document. If we could look at Column 4, lines 36 to 44.

A. Yes.

Q. And you see this is a paragraph directed to a lyophilizable ophthalmic formulation. Do you see that?

A. I do.

Q. Are you aware of whether this paragraph in this formulation appears in your provisional application?

A. I don't recall it being in there or not. I don't remember everything that's in that provisional application.

Q. And assuming it wasn't in your provisional, did you authorize anyone to add this paragraph to your issued '865 patent?

A. I didn't authorize or not authorize that.

Q. All right. Thank you, sir.

MR. RAKOCZY: I believe I have a couple exhibits to move in, Your Honor.

Move to admit PTX 1519, PTX 3255, and PTX 3249.

THE COURT: Any objection to those three exhibits?

THE WITNESS: I'm sorry. Can you say that --

THE COURT: We're just tidying up, Doctor. I'm sorry, sir. That wasn't a question for you.

Any objection to any of those exhibits?

MR. BERL: Oh, sorry. No. That was a question for me?

THE COURT: That was a question for you.

MR. BERL: We're all confused. I can be better at this. I've been here before.

No, I have no objection, Your Honor.

THE COURT: Without objection, so admitted.

I'll repeat something that I shared at home. For those of you unfamiliar with the sports calendar of West Virginia middle school and high school sports, we're in what we

call three-week period, which means school, even though it's out, the various teams will have workouts and play in tournaments and the rest. The time-old adage from when I was younger, Wednesday of camp week is always the hardest day of basketball camp. That applies to trial as well.

So with that, those exhibits, so admitted with no objection and pass the witness.

(PTX 1519, PTX 3255, and PTX 3249 were admitted.)

MR. RAKOCZY: Pass the witness.

THE COURT: Understood.

Mr. Berl, recognize it's Wednesday of basketball camp week, sir. You're up, redirect.

MR. BERL: It's been a great basketball week for me, Your Honor. I've waited 40 years for my favorite team to win a championship, and it finally happened.

THE COURT: Congratulations, sir. Congratulations.

MR. BERL: Thank you.

REDIRECT EXAMINATION

BY MR. BERL:

Q. Dr. Furfine, I'd like to start with where Mr. Rakoczy left off with your provisional application, which is PTX 3249.

Can we put page 11 on the screen, the same page that Mr. Rakoczy just asked Dr. Furfine about.

And Mr. Rakoczy asked you various questions about

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paragraph 8.

Can we blow that up.

And do you recall questions in which Mr. Rakoczy was suggesting that the provisional application does not include a disclosure of the words "stable liquid" before formulation.

Do you recall that?

A. I do.

Q. Now, let's take a look at paragraph 7, same page, higher up. Did Mr. Rakoczy show you this paragraph, Dr. Furfine?

A. He did not.

Q. And can you read the first four words of that paragraph.

A. "The stable liquid ophthalmic formulation of the invention."

Q. Now, Mr. Rakoczy also showed you PTX 3255.

Let's pull that up on page 19.

Do you recall he asked you some questions about toxicology studies that were conducted at Regeneron?

A. Yes.

Q. And he asked you various questions about the particular data, including evidence of inflammation. Do you remember that?

A. I do.

Q. Just to be clear, was this information public as of

the time of your invention?

A. I don't believe it was, no.

Q. And is this information the same information that Genentech published in Gaudreault or is it more detailed and additional information?

A. This is much more detailed and a much more detailed and extensive study of animals than their study was.

Q. And, now, if we go back to the Gaudreault reference, which he was asking you about in purported comparison to this exhibit -- this is Exhibit 1839.

And if we could go to the portion that we talked about on direct examination about the toxicity of the 40 versus 10 mg/mL ranibizumab injections into the eye.

Now, Doctor, were the results that you obtained with your Eylea formulation the same as the results that Genentech obtained with their 40 mg/mL ranibizumab formulation?

A. No. These results seem less severe than what's stated here.

Q. Sorry. "These" and "these" won't come up on the transcript?

A. I'm sorry. You're right. I'm sorry.

The aflibercept data appears to be less severe than what is noted here in the ranibizumab paper.

Q. And in the ranibizumab paper they found inflammation that was from absent to moderate at 500 micrograms per eye; is

that right?

A. That's correct.

Q. Is that the same as the 10 mg/mL?

A. That's correct.

Q. And then it was moderate to severe for 40 mg/mL?

A. That's correct.

Q. And what was your understanding about whether Genentech continued to develop this 40 mg/mL that was indicated publicly to cause moderate to severe inflammation?

A. They did not progress anything beyond the 10 mg/mL formulation.

Q. Is that surprising to you in view of the data that they published?

A. It's not.

Q. Now, I'd like to go back and discuss a few things that Mr. Rakoczy talked about yesterday.

He asked you various questions about whether polysorbate dissolves aflibercept. When you formulate proteins, Dr. Furfine, do they start out as a solid, like a powder, or are they in liquid?

A. They're liquid at all times unless they become lyophilized at some point.

Q. So when you're doing a liquid formulation, do you dissolve the active ingredient like aflibercept like someone would dissolve sugar in their coffee?

A. No, you do not.

Q. You were asked various questions about whether polysorbate dissolves protein aggregates. Do solvents dissolve protein aggregates?

A. No.

Q. What do they do instead with respect to aggregates?

A. They protect against degradation and precipitation and falling out of solution.

Q. So does water dissolve protein aggregates?

A. No.

Q. Does water remove protein aggregates?

A. No.

Q. Do solvents remove protein aggregates generally?

A. No.

Q. Okay. Now, you were shown documents yesterday by Mr. Rakoczy in which you called polysorbate a stabilizing agent, including in the BLA. Do you recall that?

A. I do recall that, yes.

Q. When you call something a stabilizer, is that an indication that it's not increasing solubility?

A. No. They're two separate things, and it can do both.

Q. Did you also call polysorbate an organic cosolvent in your documents at the time?

A. Yes.

Q. Let's pull up PTX 86 again.

If we go to the front, is this again a document that you -- that reflects meeting minutes from February 2004?

A. Yes.

Q. And if we go to page 5. And if we put up -- you said here in 2004, "VEGF Trap" -- is that referring to aflibercept?

A. It is, yes.

Q. -- "requires the presence of an organic cosolvent to stabilize the protein against agitation-induced aggregation."

Do you see that?

A. Yes, I do.

Q. And you see further down in the paragraph, what organic cosolvents are you providing as examples in 2004?

A. PEG and polysorbate.

Q. Are you saying that those aren't stabilizers because you called them organic cosolvents?

A. No. We're saying they are. They serve both purposes.

Q. There was some suggestion yesterday, when Mr. Rakoczy was showing you a lot of Genentech articles from the 2005 time frame, that you got the idea of using an organic cosolvent like polysorbate from Genentech. Was this written before 2005 or during or after 2005?

A. This was written in -- before.

Q. Now, you answered some questions yesterday about whether various ingredients like trehalose were being used, how

they were being used in Genentech's program. Do you remember?

A. I do recall, yes.

Q. Do you recall your testimony that you couldn't be sure what they were doing in Genentech's formulations without seeing data?

A. That's correct.

Q. What if someone who was participating in Genentech's program told you how they were functioning in Genentech's formulations? Then would you know?

A. Yes, you would, absolutely.

Q. In your patent do you tell the public what trehalose and other sugar stabilizers are doing?

A. We do.

Q. Now, a few more points.

There was a suggestion yesterday that bevacizumab, the active ingredient in Avastin, is much bigger than aflibercept. Do you recall those questions?

A. Yes.

Q. In terms of how much space aflibercept occupies compared to bevacizumab, is bevacizumab bigger?

A. Not substantially, if at all.

Q. Now, you were asked at the beginning of the cross-examination about whether you invented aflibercept. Do you remember that?

A. I do.

Q. Can aflibercept be administered by itself with nothing else?

A. No.

Q. How is it administered?

A. It's administered as the formulation called Eylea.

Q. And did you help invent that?

A. I did.

Q. Thank you. No further questions, Dr. Furfine.

MR. BERL: I do have some exhibits to read in, though.

THE COURT: At a measured pace.

MR. BERL: I absolutely will. I didn't need a reminder, but thank you.

PTX 2, PTX 579, PTX 1848, PTX 82, PTX 1785, PTX 1079, PTX 3257, PTX 1839, PTX 81, PTX 2223, PTX 97, PTX 98, PTX 86, and PTX 2224.

THE COURT: Any objection to any of those, Counsel?

MR. RAKOCZY: One moment, Your Honor. It's a long list.

THE COURT: Certainly.

MR. RAKOCZY: No objection, Your Honor.

THE COURT: Without objection, Mr. Berl's lists are all deemed hereby admitted.

(PTX 2, PTX 579, PTX 1848, PTX 82, PTX 1785, PTX 1079, PTX 3257, PTX 1839, PTX 81, PTX

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2223, PTX 97, PTX 98, PTX 86, PTX 2224 were admitted.)

THE COURT: Recross?

MR. RAKOCZY: Nothing from us, Your Honor.

THE COURT: Nothing.

Doctor, you may step down, sir. And, unfortunately, I now must lift my ban of anyone speaking to you; so you're fair game. Thank you very much. You can leave all that there. Someone will tidy up. Thank you very much.

If I could ask counsel to clean up and get whatever Madam Clerk requires to her, please. Thank you.

Call your next witness.

MR. BERL: Thank you, Your Honor. Plaintiffs call Dr. Bernhardt Trout.

THE COURT: Doctor, good morning.

BERNHARDT TROUT, PLAINTIFF'S WITNESS, SWORN

THE COURT: Thank you so much, Doctor. Once you're seated and comfortable, if you wouldn't mind adjusting that mic so everyone can hear you. Take a pause for a few seconds while we distribute binders. Thank you, sir.

Counsel, you may proceed whenever you're ready.

MR. BERL: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. BERL:

Q. Good morning, Dr. Trout.

A. Good morning, Mr. Berl.

Q. Could you please introduce yourself to the Court.

A. Yes. My name is Bernhardt Trout.

Q. And what do you do, Dr. Trout?

A. I'm a professor of chemical engineering at MIT in the Boston area.

Q. And can you briefly describe your educational background.

A. Yes. I was an undergraduate at MIT, also got a master's degree both in chemical engineering. And then I went to University of California at Berkeley also for my PhD in chemical engineering. And then I did a postdoctoral engagement at the Max Planck Institute in --

THE COURT: Could you spell that for us.

THE WITNESS: Yes. M-A-X P-L-A-N-C-K.

THE COURT: Thank you very much.

THE WITNESS: Yes, sir.

An institute in Stuttgart, Germany.

BY MR. BERL:

Q. What did you do after that?

A. After that, I returned to MIT but this time on the faculty at the beginning of 1998 also in chemical engineering.

Q. And have you been there since?

A. Yes, I have been.

Q. Can you briefly describe the research you conduct at

MIT.

A. Yes. In a word, I describe it as pharmaceutical development and manufacturing research.

Q. And does your research include both small molecules and proteins?

A. Yes, it does.

Q. And what are you doing with formulation research generally?

A. Well, that's a major aspect of what I've been doing since I started in 1998. So I do research in order to advance the field in formulation -- excuse me -- in formulation, better understand formulations and formulizing, and also developing algorithms to try to make predictions.

Q. Have you worked on any biologic therapeutics?

A. Yes, I have. I've worked on quite a few biologics, again, starting in 1998 when I began as an independent researcher.

Q. Approximately how many biologic therapeutics have you worked on?

A. Probably roughly around 50.

Q. Have you worked on any molecules administered to the eye?

A. Yes. I have worked on bevacizumab, which we've been talking about in this case.

Q. Do you teach?

A. Yes, I do.

Q. And who do you teach?

A. Well, I teach primarily at MIT. I teach undergraduates, graduate students, classes, fundamental classes in chemical engineering. And then I also teach researchers, graduate students, postdoctoral researchers. I should say undergraduates are also in my laboratory.

And then I also have a professional short course every year that I teach on bioformulation to professionals in the industry, which, as a matter of fact, I just taught last week.

Q. And can you describe who attends that course and what they learn.

A. Yes. There's a variety of professionals. I would say roughly half, perhaps a bit more than half, are junior formulation scientists. And then the other half are scientists in other aspects of pharmaceuticals discovery, manufacturing, and also managers who want to learn about bioformulation.

Q. Where do people who take this course from you work?

A. Well, they work at -- typically at a variety of companies, from large companies, big pharma, to medium to small, even startup. We also have sometimes people from government, from national labs, and other organizations.

Q. Do you consult with industry?

A. Yes, I do.

Q. Can you describe generally what that involves.

A. Yes. It generally involves two types of engagements. So one is more strategic. For example, I'll be invited to be on a scientific advisory board, and then I'll go to the company and provide general advice on their strategies, like their formulation strategies.

And the other is more targeted. A company might have a problem, a problem with protein stability, for example. And then they'll ask me to try to help them to solve that problem.

Q. Do you work with governments?

A. Yes, I do. I've worked with the FDA for some time, since approximately 2007, but I also work with other regulatory agencies around the world. And we actually just convened a conference in April. For the first time since COVID, reengaging the community on regulations and also development of pharmaceutical manufacturing technologies.

Q. Have you published?

A. Yes, I have.

Q. And approximately how many papers have you published in the field of protein formulation?

A. Well, I've published over 200 papers total, and I would say over 50, maybe close to 60, are in protein formulation.

Q. Have you won any awards of note?

A. Well, I've won some awards.

Q. Any in particular that stand out?

A. Well, the one, I guess, that most stands out is a recent award from my peers at the American Institute of Chemical Engineers. It was an award on drug product quality or advancing drug product quality.

Q. We've talked about protein formulation and stabilization in this case. Is that your only area of expertise?

A. No. I also work in the area of pharmaceutical manufacturing and the interface between the two, between protein formulation/development and manufacturing.

Q. Have you been qualified as an expert in federal court before?

A. Yes, I have.

Q. Have you testified for both patent owners and patent challengers?

A. Yes.

Q. If you could turn to PTX 66C in your binder, and we can maybe put the first page up on the screen.

Doctor, what is this?

A. This is my CV.

Q. And does this summarize your professional experience?

A. Yes.

MR. BERL: We offer Dr. Trout as an expert in formulation and stabilization of protein therapeutics and

small-molecule therapeutics.

THE COURT: Any voir dire or objection to the motion?

MR. RAKOCZY: No objection, Your Honor.

THE COURT: Without objection, then, the doctor is so qualified.

You may proceed, Mr. Berl.

MR. BERL: Thank you, Your Honor.

BY MR. BERL:

Q. Now, before we get into the details, then, of the infringement testimony you're going to give today, Dr. Trout, I'd like to discuss a little background with you.

You said you do research on formulations. What is formulation research?

A. Well, formulation research is kind of a key part here. I'm sure the Court and others remember the pictures from Dr. Csaky yesterday in terms of actually how the eye is injected.

THE COURT: I do.

THE WITNESS: I figured you would, Your Honor. We all do.

So doctor -- I guess my job is -- so professionals, doctors like Dr. Csaky, doesn't have to be concerned about various aspects of injecting the pharmaceutical. And, for that matter, the patient doesn't either. For example, the product is stable, doesn't form particulates which might go in the eye.

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The other is of course we talked -- we don't want the needle clogged while doctors or any doctor is giving an injection.

And then another aspect is what we call viscosity or the thickness of the formulation. It goes through a very thin needle. And, again, I don't think it's hard to convince everyone that we don't want the needle in there for a long period of time; so it has to be a thin enough fluid so it can go in pretty quickly.

BY MR. BERL:

Q. Is formulation research as simple as taking a formulation and substituting it into a new molecule?

A. No, sir. That's not what we do. That's not how formulation works.

Q. Now, I'd like to discuss the concept of solubility with you. What does solubility mean in the context of protein formulations?

A. Well, with -- many protein formulations are formulated as liquid in aqueous or water solutions. And solubility is the concept of keeping it in solution under whatever condition it might be subjected to.

Q. And is there one solubility for a given protein in a formulation?

A. No. Even for a given formulation, that solubility will depend on conditions, for example, temperature and pressure, including shear.

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Q. Is there such a thing as a protein simply being fully in solution without regard to the temperature or pressure conditions?

A. No. Those are essential conditions in determining and defining solubility.

Q. Dr. Trout, have you prepared demonstratives to help explain the scientific principles relevant to your testimony today?

A. Yes, I have.

Q. Let's take a look, starting with Demonstrative Slide 3.

MR. BERL: And, Your Honor, this has demonstratives as well as portions of documents that we'll be using with Dr. Trout today --

THE COURT: Understood.

MR. BERL: -- so it's useful to follow along compared to the binder, I hope.

BY MR. BERL:

Q. We've shown PDX 5-3.0003, Dr. Trout. Can you explain what's shown here?

A. Yes. Here I just show a comparison between a typical small-molecule pharmaceutical aspirin and a biologic or large-molecule pharmaceutical like aflibercept. This is more or less to scale. Hopefully, the Court can see there's a little speck there which is represented as aspirin. And you

can see here is the molecular weight. And that's 0.18 kilodaltons. That was brought up yesterday in court. And it's just a measure of the weight but in molecular units like pounds or kilograms. And then the aflibercept is about 115 kilodaltons. So it's about 1,000 times bigger in terms of size, which is reflected in the relative scale here.

THE COURT: Just so I'm clear, when we say aspirin, we're talking about aspirin?

THE WITNESS: Yes, sir. Well, in a certain sense we're talking just about the molecule aspirin, not the formulation aspirin.

THE COURT: A singular molecule of aspirin?

THE WITNESS: Yes, sir. Correct.

THE COURT: Understood. Thank you.

BY MR. BERL:

Q. So these proteins like aflibercept, do they come in solution, in a liquid state, or are they in a powder state like something like aspirin?

A. Not like aspirin. They're in a liquid state from manufacturing. And, again, the idea is to maintain them in a liquid state. Aspirin I think we're familiar with is typically formulated into a tablet, and it comes from manufacturing as a powder and is made into a tablet.

Q. So what do solvents do for proteins if it's already a liquid to start with?

A. Well, solvent does what solvents do to molecules that keep it in solution. For example, water will interact with the protein around the surface of the protein and will orient itself to keep it in solution.

Q. Are solvents added to dissolve or remove aggregates in protein formulations?

A. No. Typically, aggregates are irreversible. So once they form, they don't go backwards.

Q. So is making a protein formulation, is it like what I talked about a moment ago, like taking sugar and dissolving it in your coffee?

A. No, on the contrary. Again, aspirin, we could make an analogy with sugar. That can be dissolved and then formed a solid again, a powder. But proteins, typically, we want to keep them in solution. Again, they come in the liquid state from manufacturing. And if they start precipitating or becoming insoluble, it's typically irreversible.

Q. I'd like to discuss now with you how that happens and how those aggregates can form.

If we could go to Exhibit PTX 1556.

Is this an article by Wang in 2005 that you reviewed in connection with your work in this case?

A. Yes, it is.

Q. If we look at the abstract on the first page, it says, "Protein aggregation is arguably the most common and

troubling manifestation of protein instability encountered in almost all stages of protein drug development."

Can you explain what Wang is conveying here?

A. Yes. This is the first sentence of the abstract, so really the first sentence in the paper. And it talks about, right here, protein aggregation. That's the protein molecules coming together, which we don't want. That's a manifestation of the instability. And it's omnipresent is what Wang is saying here.

Q. Let's go to page 3 of the article. And we have blown up a paragraph that begins with "protein aggregation has been observed frequently."

Can you explain what Wang is saying here?

A. Yes. Well, again, Wang is talking about protein aggregation, as I just mentioned from the abstract.

And specifically I've highlighted, Your Honor, two places, shearing/shaking. So that's an example of a pressure or pressure disturbance which is going to be omnipresent in --

THE COURT: And shearing would refer to the propulsion, if you will, of the solution through the needle.

THE WITNESS: Yes, sir, that can be it. But also during shipping, for example, during usage when the doctor or the medical professional takes it out, it can slosh around, to use a better term. So certainly that's the case. And then also just during storage, to name two examples.

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BY MR. BERL:

Q. Are there particular conditions that scientists would think about in assessing intravitreal formulations?

A. Yes. So, again, for intravitreal we want the needle to be as thin as possible, typically, a 30-gauge needle, which has a very thin bore, which means that the solution has to get through that bore. And it can -- it is -- the bore exerts significant shear, a great amount of shear, because of the very small diameter.

Q. Doctor, what is the connection between this protein aggregation that Wang is discussing on the one hand and the concept of solubility that you discussed a moment ago?

A. Well, protein aggregation is, first of all, the first stage of solubility, and then it also -- or first stage towards insolubility I should say, and it also describes the insoluble particles which can be called insoluble aggregates.

Q. Can a protein come out of solution without aggregation?

A. No.

Q. What does it mean for a protein to stay in solution?

A. Well, it means that it is in solution. It is surrounded by the solvent molecules, primarily water molecules, and it doesn't aggregate and eventually come out of solution and precipitate.

Q. What's the problem with a protein not staying in

solution?

A. Well, there are several problems. One problem is that, if it comes out of solution, it's typically inactivated so it's not going to be useful to the pharmaceutical or at least the material that comes out of solution.

But above and beyond that, it can cause serious reactions. We talked about inflammation even earlier today, but then even the most serious one is immune response, which means that the body's immune system can actually attack the molecule which is meant to be a therapeutic.

Q. Let's take a look further down on page 3 of Wang, under the Subsection 2 in the paper "Protein aggregation and its influencing factors."

What is Wang writing here?

A. Well, Wang is just talking about two categories of aggregation, which I've highlighted in yellow. The first category is physical aggregation. So that's molecules coming together, for example, through hydrophobic, hydrophobic effects. I'll have some pictures of that shortly. But that does not involve the breaking of formation of chemical bonds.

And the second is the chemical aggregation, which can involve the breaking or formation of chemical bonds, for example, sulfur-sulfur bond forming.

Q. Doctor, in terms of assessing or determining the solubility of a protein, does it make any difference which of

these mechanisms that Wang is describing caused the protein to come out of the formulation?

A. No. It just matters the degree to which it's soluble or not soluble; it comes out of solution.

Q. How does a scientist know how much of a protein stays in solution under a particular set of conditions?

A. Well, in the extreme case, a scientist can, for example, experiment or do experiments under certain conditions; and if the solution gets cloudy, which one can see visually, then it's come out of solution, it's insoluble, that part that's cloudy.

But that's really an extreme case. Long before one can visually see the cloudiness, we can use analytical techniques, such as probing it with lasers and whatnot to determine the degree of insolubility.

Q. What kinds of conditions are used in these tests of solubility?

A. Well, the kind of conditions at which the protein might be subjected to during its lifetime as a pharmaceutical product, conditions such as shear, shaking, going through the needle as we just talked about, and potential temperature excursions.

MR. BERL: Your Honor, at this point I'm going to start getting into the claims and Mylan's product. I think Mylan has requested that the balance of the examination have a

sealed courtroom.

THE COURT: Understood.

MR. COPLAND: Yes, Your Honor. I discussed with Mr. Berl, and he'll need to go back and forth repeatedly to confidential information. The cross-examination will as well. So we ask the courtroom be closed for the remainder.

THE COURT: Understood. Consistent with -- is there any objection to that, Mr. Berl? I'm sorry.

MR. BERL: No objection.

THE COURT: Consistent with this Court's prior protective order and our prior practice during this trial, I would ask anyone who is not covered under that protective order to step out of the courtroom at this point in time.

(The following proceedings (581/16 to 711/16) were sealed and are filed under separate cover.)

THE COURT: I believe we're ready to hear from our next witness. If we are, go right ahead and hit play.

MR. GREGORY: Your Honor, I think we're all set to play this next deposition.

THE COURT: Thank you so much. Whenever you're ready, sir, you can go ahead and hit play. Thank you.

(Deposition of Vanessa Smith played.)

MR. GREGORY: And I believe that is the end of the video deposition testimony that we're prepared to present today. I'm happy to work with Mylan's counsel and the court

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staff after the end of the day to figure out the exhibits that need to be moved in.

THE COURT: Sure. That sounds acceptable to me.

Where are we at overall, then, today, Mr. Berl?

MR. BERL: Your Honor, plaintiffs rest their case in chief.

THE COURT: That answered my question.

Counsel.

MS. MAZZOCHI: Good afternoon, Your Honor. This is Deanne Mazzochi speaking on behalf of the Mylan and Biocon defendants. At this time defendants move for entry of judgment on partial findings of noninfringement on all asserted claims pursuant to Federal Rule of Civil Procedure 52(c). Granting this relief now would also streamline significantly the invalidity portion of this case.

The defendants -- I also note that in the -- I'm sorry. The defendants also move for entry of judgment on partial findings for noninfringement as to all of the asserted claims of the '572 patent, Claims 6 and 25; '601 patent, Claims 11 and 19; and '865 patent, Claims 4, 7, 9, 11, and 14 to 17.

With regard to the asserted dosing patent claims, first, the defendants respectfully move for judgment on partial findings of no direct infringement on all asserted dosing patent claims.

Regeneron has introduced no evidence at trial that defendants will directly practice any of the claimed methods. Regeneron's expert admitted that he was not contending that defendants directly infringed. Regeneron thus has failed to prove by a preponderance of the evidence that defendants will directly infringe any asserted dosing patent claim.

Second, the defendants respectfully move for judgment of partial findings of no induced infringement for all asserted dosing patent claims. An active induced infringement requires first a predicate act of direct infringement, and Regeneron's expert has not satisfied Regeneron's burden of proof in that regard.

All of the dosing patents' asserted claims require a fixed-dosing schedule, including a specific number of monthly doses followed by a very precise eight-week dosing schedule.

Regeneron has failed to prove by a preponderance of the evidence that doctors in the real world actually do adhere to this schedule, let alone by any appreciable degree, and certainly not to the extent that this Court should be justified in inferring a specific intent by the defendants to induce doctors to follow this specific label -- I'm sorry -- this specific method of treatment.

While Regeneron has -- and Regeneron also has not thereby met its burden of proof to show that the defendants do, in fact, have the requisite specific intent to induce

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infringement of the claimed precise fixed-dosing regimen.

Regeneron has relied primarily on defendants' Yesafili labeling, but their expert did admit that noninfringing regimens such in the Yesafili labeling include, for example, monthly dosing or every-eight-week dosing. Dr. Csaky was unequivocal that doctors have their own discretion to administer the drug at a dosing schedule of their choice and their control.

In addition, the supposed real-world evidence that Regeneron has presented with their expert having admitted that he did not attempt to quantify any -- the number of infringements that would be potentially in existing if the product were approved -- what he presented that was tied to actual medical records -- likewise cannot cause Regeneron to meet their burden of proof because, again, even in the dosing regimen that was designated as IAI 2q8, the dosing regimen does not fall within the scope of the claims given the wide variation that was permitted both on the, quote/unquote, monthly schedule, which was allowed to be anywhere from three weeks to five weeks, as well as a seven-week or nine-week dosing interval.

Thus Regeneron has not met its burden of proof to show evidence of direct infringement of each and every element of the asserted dosing patent claims, which is required to prove infringement, induced infringement under *Limelight*

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Networks, Inc., v. Akamai Technologies, Inc., 134 S.Ct. 2111, 2117 (2014), noting that inducement liability may arise if, but only if, there is direct patent infringement.

And while the internal quotations are omitted, it also was citing *Aro Manufacturing Company v. Convertible Top Replacement Company*, 365 U.S. 336, 341 (1961), for that premise.

Accordingly, the Regeneron has failed to prove, one, that there will be actual direct infringers; two, that defendants will actively encourage direct infringement; and, three, that defendants have the requisite specific intent to infringe, especially where, as here, that intent cannot be inferred, given the overwhelming noninfringing uses of both Eylea and the defendants' Yesafili product, the existence of all of the noninfringing regimens in the label, which Dr. Csaky admitted, which also can be accompanied by the physician's own discretion and clinical judgment to make the choice of which label indication to use.

Thus, Your Honor, the defendants respectfully move under Rule 52(c) for a judgment of partial findings that all asserted claims of the '572 and '601 patents are not directly infringed by defendants and that defendants further do not induce infringement under 35 U.S.C. Section 271.

With regard to the '845 formulation patent, defendants also respectfully move for a judgment on partial

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findings of no direct infringement with respect to the '865 formulation patent's asserted Claims 4, 7, 9, 11, and 14 to 17.

All of the '865 patent's asserted claims depend directly or indirectly on independent Claim 1, which requires a, quote, organic cosolvent element, as that term has been construed by this Court.

Regeneron has failed to prove by a preponderance of the evidence that defendants' Yesafili product includes the required cosolvent.

More specifically, under Your Honor's claim construction an organic cosolvent must increase the solubility of the drug substance solute, which here is the VEGF antagonist protein aflibercept.

We simply do not have that here. Plaintiffs have only alleged that the polysorbate 20 may be, could, under particular molecular model involving other products, could meet this element.

The evidence you have heard thus far was no disputes that the polysorbate 20 in Yesafili is a surfactant, a surface-active agent. By name and by definition, polysorbate 20 is acting as a stabilizing agent to protect the protein.

Polysorbate 20 indisputably does not dissolve the protein under this Court's claim construction, and Dr. Trout's effort today to try to reconstrue your definition under what he

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claimed was an understanding of the person of ordinary skill in the art is improper.

Polysorbate 20 does not work in conjunction with water to help dissolve aflibercept in the Yesafili formulation. Because there is no evidence that the polysorbate 20 is actually increasing solubility of the aflibercept protein in Yesafili through the use of polysorbate 20, plaintiffs have presented the Court with a theory that fundamentally is unsupported and, in fact, contradicted by the very evidence it presented in its case in chief on infringement.

First, you heard Dr. Trout explain that polysorbate prevents aggregation and protein formulations. Assume that that's true and accurate. It doesn't change the ultimate analysis. Surfactants are well known in the art to be stabilizing agents. Surface active agents that protect the protein from denaturing or degrading and aggregation may be one of those phenomena that can happen in a protein formulation.

Second, you heard Dr. Trout rely on data that Regeneron's counsel characterized as the most important document he was going to show you, but again, there are two problems for Regeneron.

One, this most important document of plaintiff's infringement theory presents data for a different formulation that Mylan and Biocon do not use for Yesafili. No true head-to-head comparison was done at the correct concentration

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with the correct ingredients; and, ultimately, the data are specifically for a formulation that uses the components of Eylea, not the formulation components of Lucentis, which we know Yesafili follows, which was that prior art model, not the Eylea model.

Two, Dr. Trout's theory that inhibiting aggregation somehow equals -- or perhaps he says effectively equals -- increasing solubility simply cannot bear any fruit on their infringement analysis.

Why?

Because the actual data of the histidine-buffered trehalose-stabilized formulation used in Yesafili indisputably confirm that no aggregation occurred in that formulation, both with and without the presence of polysorbate. That same data also showed that the components in Eylea, however, do aggregate.

Thus Dr. Trout's model was built on a fundamental flaw. But even assuming Dr. Trout's theory, all he has attempted to do is redefine the meaning of a cosolvent in violation of your Court's *Markman* order. Thus a judgment of noninfringement on partial findings is appropriate because plaintiff has not proven and indeed cannot prove, given the testimony of Dr. Hana Chang you heard and the Integrity Bio report, that the Yesafili formulation is prone to aggregation and thus needs the polysorbate to inhibit aggregation.

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Furthermore, Your Honor, at the outset of this litigation, Regeneron did assert a variety of claims that are no longer asserted. So defendants also further respectfully move for judgment on partial findings of no infringement for all of those patents and claims that were asserted against the defendants in the complaint that were supposed to be designated for this part of the case and which are no longer asserted.

Thank you very much, Your Honor.

THE COURT: Thank you, Counsel.

Counsel.

MR. BERL: Good afternoon, Your Honor. I'm happy to respond to as much of that as you'd like.

Obviously, Mylan has made its record of filing a motion for partial findings. Actually, this was a nonwritten motion that they've made here. Obviously, it's a bench trial. We disagree with everything that Ms. Mazzochi just said.

THE COURT: Noted.

MR. BERL: I'm happy to explain why. Your Honor listened to the evidence. We obviously went through the claims in painstaking detail, explaining with expert testimony why Mylan induces infringement of all of the asserted claims of the method patent.

The notion that somehow not enough people will actually practice the claim is legally irrelevant. This is a claim of infringement under 35 U.S.C. 271(e). The issue here

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is Mylan's label and whether Mylan's label induces infringement. That's the issue, always has been the issue from the Warner-Lambert case, which is the seminal case on induced infringement under 271(e) in the filing of an FDA application, continuing down through the *AstraZeneca v. Apotex* case, and all of the inquiries that Ms. Mazzochi rested on are essentially not relevant to the proper legal question before the Court.

Those questions before the Court were repeatedly answered by Dr. Csaky over and over and over again. You saw those two questions that were on the screen where he said yes and yes to each one. Claim by claim, limitation by limitation, this infringement case was set forth and made convincingly. And crediting that evidence, there can be no doubt but that a case of infringement was made.

With respect to the '865 patent, Dr. Trout just got off the stand, and you've now heard from multiple witnesses who have experience in protein formulation that the whole notion that Mylan is trying to advance to avoid infringement in this case, that something has to dissolve a protein as if it's some kind of sugar that you put in water and that that's what a solvent means in this context, is just wrong. That's not what anyone thinks. That's not the reality of the world.

And so Mylan is trying to reinterpret this claim to be a claim that never could be infringed because nothing solubilizes a protein under their definition, nothing is a

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solvent under their definition, not even water.

And so Mylan basically advances two noninfringement arguments, it appears. One, that Your Honor somehow held that you have to dissolve a protein as if it's some sugar that you're dissolving in water. That's just not true. The evidence shows that that's not true.

And the second proposition that they appear to be advancing is that we have to show that there's aggregation and that, if you have something in solution just sitting on a shelf, that you can't increase its solubility.

That's not right either. We heard repeatedly that solubility is a function of temperature and pressure so that, if a formulation comes out of solution, for example, when you agitate it and then you add polysorbate and it doesn't happen, you've obviously increased the solubility. You're keeping things in solution.

The notion that the documents didn't show that, respectfully, is not true. What Mylan's doing is they're asking for judgment because they have no evidence on the other side. Their expert failed to address the most important evidence in the case, their own testing of their BLA.

You don't have to take it from me; you don't have to take it from Dr. Trout. Their own documents said in black and white what it was attributed to, what was going on with the formulation when they didn't have the polysorbate in it. And

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it said it -- I'm happy to repeat it even though the courtroom's open -- but it said that it's protecting --

MR. RAKOCZY: Can we --

THE COURT: I've seen that evidence.

MR. BERL: So it cannot possibly be the case that, when you keep things in solution, you are not increasing the solubility. Their case requires someone to hold otherwise, which, honestly, makes little sense on this current record or given the facts of science that are at issue here.

So again, I'm happy to answer any questions, but given the posture of the case, we think that any judgment at this point or any other judgment with respect to noninfringement is completely unwarranted.

THE COURT: Understood. Thank you, Counsel.

It's your motion, Counsel. You get last word if you'd like one.

MS. MAZZOCHI: Just very briefly, Your Honor. We do believe that the case law has been clear out of the federal circuit, and it was actually in some of the cases we cited in our summary judgment brief in connection with the dosing patents that, if the doctors are allowed to exercise their clinical judgment under the label, your label can describe an infringing use; but if it's not a required, mandatory use and the doctors have the option to exercise their clinical judgment to use another method, then that is not enough for them to be

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able to meet their burden to prove induced infringement.

With regard to the '865 patent cosolvent, Your Honor, what -- if I had to basically colloquialize what it seems like Regeneron's argument is is that, well, once you've decided to get married, if you go out and you renew your vows, that somehow means it's adding something to the scope of your legal obligations as a husband and wife. You're really not.

They're talking about -- the whole point of a cosolvent is that it is doing something more to the formulation. Under the Court's claim construction, it has to be increasing, helping to increase the -- I apologize. I don't have the construction in front of me; so I don't want to misquote it. Mr. Salmen will kill me if I do. Fine. He won't kill me. He'll chide he if I do, mercilessly.

THE COURT: I can't do anything about that.

MS. MAZZOCHI: But the ultimate point, Your Honor, is that what they're basically trying to do is suggest that the cosolvent doesn't -- their idea of a cosolvent is that it can be there and not do anything, and if it's not actually causing the formulation to do anything new, if it's not actually increasing the solubility of the aflibercept, then it's not acting as a cosolvent because the whole point is it's supposed to be helping the water to dissolve.

And, furthermore, this notion too that they've been saying is that, oh, it's not like sugar that you put in your

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coffee, well, you can have proteins that are -- you heard it from Dr. Furfine earlier. He said, yeah, you can have lyophilized proteins, where they're proteins, they're solids. Then you can use water to help dissolve them, and sometimes you might want to use a cosolvent to help them dissolve.

That is not what we have here because it is undisputed that Mylan's product starts in water, stays in water, and it doesn't need any type of dissolution aid in the form of a cosolvent to either get it there or keep it there. So that's why again --

THE COURT: This is that chiding in writing?

MS. MAZZOCHI: No, but I --

THE COURT: Sorry, Counsel. I couldn't resist.

MS. MAZZOCHI: No, but again, Your Honor, I think that the ultimate point is is that they have only asserted literal infringement in this case, and it sounds like what they're trying to do is say, well, a surfactant is really equivalent to how a cosolvent works. And that's not the way in which they have presented this case. That would be a completely different theory that they have not raised in their contentions, did not do in their expert reports, which requires a different legal standard.

So they're basically to have their cake and eat it too, saying this is something that's equivalent without actually meeting the standards of the doctrine of equivalents,

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and that's not appropriate either.

So with that, Your Honor, that's why we believe judgment is appropriate.

THE COURT: No, understood. Thank you. Thank you, Counsel.

Under 52(c) the Court is going to decline to render judgment at this point until the close of the evidence, considering the evidence the Court has heard, the context of a bench trial, of course, and the counterclaims and the rest, I think that's the appropriate step at this juncture.

I'm going to make an assumption, and make it a strong assumption, that Mylan would like to call its first witness tomorrow.

MR. RAKOCZY: That would be correct, Your Honor.

MS. MAZZOCHI: And, actually, Your Honor, two quick housekeeping matters that you did mention this morning.

There is an issue with regard to Regeneron has made the assertion that Dr. Rabinow's obviousness combinations were not set forth in his report. Because Dr. Rabinow is one of the witnesses we would like to try to get done in the next day or two, we're happy to actually provide the Court with the evidence that, yes, it is, in fact, in his expert reports -- it was even disclosed in our original contentions -- so that we can get that issue resolved because, if there is going to actually be a change to the scope of his opinions, we'd

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certainly rather know that sooner rather than later. But we don't think that it is.

And I'm happy to turn the floor over to Mr. Hunt to confirm that for you if you would like.

THE COURT: I'd like, sir, if you wouldn't mind filing that sometime this evening or sometime tomorrow morning in response to Regeneron's motion. And it would be my strongest suggestion that a copy of the particular disclosure of that combination again of the Fraser, Dix, Lucentis, which is the Shams and Gaudreault prior art along with Liu where that was previously disclosed.

And I'd also touch upon, assuming it has been previously disclosed -- well, I'll leave it at that at this point, but we'll receive that in writing.

MS. MAZZOCHI: In addition, Your Honor, the defendants were planning on also playing the deposition testimony. I was hoping we were going to have time today; I think we'll do a different one so we can get done roughly before 5:00. But it's the deposition -- the 30(b)(6) deposition testimony of Karen Chu. So here, again, that was part of the letter that went to you this morning. I don't know if you want to take that up tomorrow or --

THE COURT: We're going to take that up tomorrow. I've not had a chance to digest that. And in all candor, I'm making an assumption -- and I don't know who all participated

in Ms. Chu's deposition. I'm making an assumption that there was no clean break between the 30(b)(6) deposition and her testimony as a fact witness. Is that correct?

MR. GREGORY: I don't think that is correct, Your Honor.

Your Honor, part of our problem here is that we think that, while certainly the lines can be blurry in many 30(b)(6) depositions, as you well know, between what is individual capacity testimony and 30(b)(6) testimony, this is actually one of the rare ones where it's pretty clear. I'm not sure if Mr. Schliesske can put it on the screen for me.

THE COURT: So there were two separate depositions of Ms. Chu, one where she served as a designee? No? I'm going to stop assuming. Tell me what happened.

MR. GREGORY: So there's one deposition, Your Honor. I believe it was December 16, 2022. We're looking here at, I believe, page 83 of her deposition transcript, and Mr. Schliesske can put it on the screen.

So you see there's a question from -- right before this there's a question from Mylan's counsel.

Regeneron's counsel, Mr. Oberwetter, says, "Is this a 30(b)(6) question?"

Mylan's counsel replies, "This is just her," i.e., individual capacity.

Ms. Oberwetter replies, "Do you want to tell me when

you go back," that is to 30(b)(6).

THE COURT: The changing of the hats.

MR. GREGORY: Exactly.

And then lest there be any confusion, Ms. Oberwetter asks again -- this is Regeneron's counsel -- "I'm sorry. Are you going to tell me went you go back to asking 30(b)(6) questions?" And Mylan's counsel says, "Sure."

She does not go back to asking 30(b)(6) questions until approximately page 113 of the transcript. And if Mr. Schliesske can put that up. And you see there she flags that we're moving back into 30(b)(6) testimony.

The next break appears at -- there's just two more -- page 123 of the deposition transcript. And, again, there's a question preceding this. And Ms. Oberwetter says, "Is that a 30(b)(6) question?" And again Mylan's counsel says, "That's her"; i.e., this is individual capacity.

And Ms. Oberwetter says, "Can you tell me when you go back to asking 30(b)(6) questions?" And again Mylan's counsel says unequivocally, "Sure."

And she does not go back to asking 30(b)(6) questions until page 273 of the transcript, where there's a question and Ms. Oberwetter says, "Object to form, foundation." And if we're back into 30(b)(6) questions; she poses a 30(b)(6) objection on scope.

So this is one of these situations where we actually

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have a pretty clear delineation in the transcript of what's personal capacity, individual capacity, and what is 30(b)(6).

Now, the problem we have here is that they have represented they are only trying to choose 30(b)(6) testimony. That's the only exception to both the rules and the argument, arguably, the joint pretrial memoranda, which was heavily negotiated by the parties and says that "The parties agree that they shall not be permitted to play deposition testimony from witnesses who are testifying live."

Now, frankly, I think that should control above all else. That was negotiated in the context of the federal rules --

THE COURT: Even more so than Federal Rules of Civil Procedure.

MR. GREGORY: We negotiated with that in the background, Your Honor. But setting that aside, if their point is that this is not Ms. Chu's testimony but rather Regeneron's and they should be allowed to play it, they should only, at the very most, be allowed to play Regeneron's corporate testimony. And here we have clear representations from counsel that we relied on, and more importantly that the witness relied upon, when she was giving these answers, she was answering she, I'm sure, believed on behalf of herself, not Regeneron.

Now --

THE COURT: What position does Ms. Chu hold with

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Regeneron?

MR. GREGORY: I should have addressed that at the front, Your Honor. I apologize.

Ms. Chu -- her exact title is escaping me. She is within the clinical development team. And we are bringing her next week. You will hear from her live. They'll have the opportunity to take her personal capacity, individual capacity testimony at that point, and we've told them that.

But they're seeking to play over an hour of her testimony today, as you saw in the letter, large swaths of which fall within the breaks that I just showed you where it's just personal.

Now, and my final point, Your Honor, and I hate to have to break this up, but I think I'm compelled to do so.

The joint letter that went in this morning was not a joint letter. That letter was served to the Court or submitted to the Court without Regeneron having the chance to first review it and approve it and sign off on it.

And now setting aside whether or not it's improper or from a procedural standpoint -- I can set that aside. The problem here is that it's substantively misleading in a couple of respects that we could have corrected had we had a chance to actually look at it. It's misleading in the fact that they kind of marched through various pieces of her testimony and made arguments about, well, this relates to Topic 17 and this

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relates to Topic 4.

But, again, we would have -- if we knew they were going to do that and we had seen the final letter, we would have showed you in the letter what we just showed you before, the clean breaks in her testimony where they are just explicit that they're doing personal individual capacity, not 30(b)(6).

The other respect with which this is misleading is that one of the documents attached to the letter that went in this morning that we did not have a chance to review and that we did not know would go in with it was a list of the purported topics on which they designated Ms. Chu.

So even if the Court is inclined to go designation by designation -- and, again, we don't think you have to because we have these clean breaks in her testimony. But if the Court were inclined to do that, they put in this list of purported topics, but what they don't tell the Court is that that list was subject to a 25-piece -- 25-page piece of correspondence from Regeneron to Mylan within the days before Ms. Chu's testimony explaining all the problems that we had about the scope and the overbreadth of the 30(b)(6) topics, the ways that we felt they should be limited, and then designating Ms. Chu subject to those objections. And you don't have any of that record.

So, respectfully, Your Honor, I think there are a number of problems with their attempts to play Ms. Chu's

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testimony. At the very least I think this Court should not allow them to play individual capacity testimony from Ms. Chu who will be coming live next week.

THE COURT: Counsel.

MS. MAZZOCHI: Yes. First, Your Honor, this is -- it was precisely my concern that Regeneron just wanted a standing objection as to whether something was 30(b)(6) testimony or not. I declined that.

At page 52 of the deposition testimony, Ms. Oberwetter specifically said, "I would like a running objection."

I said, No. I want to know when you're going to object that this is something that is not her -- you know, she's not speaking on behalf of Regeneron precisely so I then have the opportunity to know and follow up on that.

Now --

THE COURT: Why not two separate depositions, though? It makes this incredibly clean.

MS. MAZZOCHI: Well, I can't answer that, Your Honor. I mean, I would have loved to have had two days with Ms. Chu, but they were only offering one. So to try to --

THE COURT: Subpoenas and the rest. She's a high-ranking official within the plaintiff's hierarchy.

I'm sorry. Go ahead.

MS. MAZZOCHI: Sure. But, Your Honor, I do want to

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say this, that at the point where she said, oh, will you tell me when you're seeing to go back to 30(b)(6) testimony, yes, in the very next question, I said, "What is your understanding?" relating to the exclusion criteria in the VIEW 1-VIEW 2 studies, asked her one more follow-up question, then asked the question of Regeneron. "Did Regeneron ever consider putting the black box warning in this?"

So two questions later I asked her a question of what is Regeneron's position on one of these issues?

THE COURT: How many questions after that are we going back to individual fact witness capacity?

MS. MAZZOCHI: What I was trying to do was, if I was asking her a question that was in your individual capacity, I would say "do you have any personal knowledge" or "in your individual capacity," and then there were many instances where I would -- like are you aware of this change versus what is your understanding -- so page 131: "Was it your understanding that Regeneron was attempting to file patent applications on all of these methods?"

So I was clearly, I believed, attempting to elicit what was Regeneron's position. And I understand, Your Honor -- so that is replete throughout all of these pages that they're complaining about is not -- somehow not Regeneron testimony.

And, furthermore, Your Honor, if we're going to start doing this, she was designated for a whole lot of topics. She

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was designated on conception and reduction to practice, which -- of the '601 and '572 patents. So she's not a named inventor; it was Dr. Yancopoulos. They designated her on that.

A lot of the documents that we are putting into evidence do, in fact, relate to some of those conception issues because they're going to influence the priority date analysis that may have to come up with regard to some of the claims in the patent and whether they can swear back to one of their earlier references.

She was designated to talk about the clinical studies and investigations. So a lot of -- again, that is a large amount of what she was designated to testify to.

So I believed I was asking questions in her corporate capacity, and because I had told Ms. Oberwetter I was not going to agree to a standing objection, I expected her to object if she wanted to say "that's not Regeneron's corporate position" because Ms. Oberwetter is in the best position to know if what she's saying is a position Regeneron wants to take or not. I'm not in that position.

THE COURT: You drafted the designations, and it was noticed as a 30(b)(6).

MS. MAZZOCHI: Yes.

THE COURT: She was produced as a designee. There is no question in my mind that under Rule 32 Mylan may use any 30(b)(6) testimony for any purpose during this trial. As an

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adverse party designee, that that is not even up for dispute.

The question becomes, particularly because Regeneron has represented to this Court repeatedly now Ms. Chu will appear to testify during this trial -- I don't think she's considered unavailable under the rules as to whether testimony in her own individual fact witness capacity can be used from this -- I think even the transcript said hybrid deposition.

And so you-all need to get together this evening and figure out, line by line, which goes in which bucket because the 30(b)(6) bucket, Mylan may use for any purpose during trial, without question. I'll note the objection. But I think Rule 32 is clear on that.

I would anticipate, frankly, under 52(c) not rendering any judgment on behalf of anybody until the close of evidence in this case given the significant factual disputes that I believe were apparent in the cross-motions for summary judgment and remain apparent even though we've only heard the plaintiff's case in chief at this point.

So I guess my ultimate question is what is the practical difference if Mylan waits until Ms. Chu is called to question her then?

MS. MAZZOCHI: The practical difference -- there's two, Your Honor. Number one is we did ask Regeneron -- so let me take a step back.

Originally, Ms. Chu was not even on our radar screen.

She was on a may-call list. All of the indications that we had had from Regeneron is that they were not going to be calling her live. It was only about a week ago-ish -- I don't want to be held to a specific date -- that they decided they were going to call her live.

We don't know why. We asked what would be the scope of what she was going to be testifying to? Because, again, what we're worried about is that we have the adverse admissions against them. They're going to have her come in and try to change something, and now we're going to have to have a cross-examination that's going to be twice as long because we're going to have to be -- is she -- was this answer given in her personal capacity and can I impeach her with her testimony or can I -- am I doing this in a 30(b)(6) capacity where I can actually just play the testimony?

I, frankly, believe it's going to be a lot more efficient and time-saving if we do our deposition designations and, if there's a particular issue where they want to say, No, this is something that we are 100 percent clear; this was her alone and she couldn't possibly fit into one of the topics within their letter, okay, I'm happy to have that discussion. But they won't even tell us what she's going to be here to testify about.

THE COURT: You should have asked her that during her deposition. That's the point of fact discovery.

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MS. MAZZOCHI: I did. I asked her --

THE COURT: Then you can cross her on it. You can impeach her and the rest.

You all have to get together this evening and work through this list and see what's left in dispute. We'll handle it one at a time in the morning of whatever's left.

30(b)(6) testimony, Mylan may use under Rule 32 for any purpose during the course of this trial. Non-30(b)(6) testimony is a different story. Counsel needs to get the buckets straight which is which, and then we'll deal with the personal testimony issue tomorrow morning.

MS. MAZZOCHI: That's fine, Your Honor. Thank you.

THE COURT: Thank you.

MR. GREGORY: Thank you, Your Honor.

MS. MAZZOCHI: Then with that, Your Honor, our first witness, who we would also like to call by deposition testimony, is Abby Cahn, who is a marketing individual within Regeneron.

THE COURT: How long is that?

MS. MAZZOCHI: I think it's about 35 minutes.

THE COURT: I'm going to exercise Article III privilege, and we're going to play that tomorrow morning.

MS. MAZZOCHI: I do have a shorter one.

THE COURT: Actually, no. I have a summer league high school basketball game up the road that I have, with all

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due respect to everyone in this room, more interest in at this point. You all are welcome to attend.

We will hit play on whichever one you'd like to start with tomorrow morning, Counsel.

MS. MAZZOCHI: Then, Your Honor, what we may try to do then because, as we had informed counsel, Dr. Albini does have some scheduling issues. We may call Dr. Albini because we do want to make sure that he can get on the stand tomorrow, off the stand, and doesn't have to be held over for any meaningful period on Friday.

THE COURT: That's fine. And then if that gives you all more time to work through the issues with Ms. Chu's testimony, that's fine by me. I'm not eager to start that --

MS. MAZZOCHI: I understand.

THE COURT: -- first thing; so if there's a witness you'd like to call first, that's fine, other than Ms. Chu. That will be fine.

MS. MAZZOCHI: We'll work on that, Your Honor. Thank you very much.

THE COURT: The best of luck to you all working through that. I'm going to go watch my Fighting Hawks of University High in their summer league game instead.

Anything else we need to take up this afternoon, then?

You've got the mic, Counsel. Go ahead.

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MS. MAZZOCHI: Not that I'm aware of, but Mr. Rakoczy did stand up. So if he's got something in mind, I'll defer to his judgment.

MR. RAKOCZY: Nothing, Your Honor.

THE COURT: Understood.

MR. BERL: Nothing from plaintiff, Your Honor.

THE COURT: I don't mean to rush anybody for tip-off. I've got plenty of time to make tip.

Okay. Nothing?

You guys have plenty to do this evening. We'll reconvene tomorrow morning at 9:30 and go from there.

You all have a pleasant evening. Thank you very much.

(Proceedings concluded at 4:50 p.m.)

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CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 14, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 14th day of June 2023.

/s/Cindy L. Knecht
_____
Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 4

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 15, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

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Thursday Morning Session,

June 15, 2023, 9:30 a.m.

- - -

THE COURT: We convene for day four of trial. Good morning, everyone.

Everyone's curious, the University High Hawks played well yesterday, and rising junior combo guard Noah Kleeh at 12 and 18 points in two games yesterday. So summer league is off to a good start. And while sitting at the Marion County Armory, I was reading the Federal Circuit's thoughts on many things as well.

Okay. Let me ask this initial question so we can most efficiently use our time today. What witnesses does Mylan plan to call first?

MR. McLAUGHLIN: We plan to call Dr. Thomas Albini first.

THE COURT: Outstanding. Are there any issues with Dr. Albini that we need to take up before he testifies that anyone's aware of at this point?

MR. McLAUGHLIN: None that I'm aware of.

THE COURT: Counsel.

MS. OBERWETTER: No, Your Honor.

THE COURT: Outstanding. Let's do that.

Yes, Counsel.

MR. HUNT: Your Honor, just a brief administrative

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matter. Thank you for taking care of the updating us on the Hawks. I was going to check in on that.

With regard to Dr. Rabinow, we have an outstanding motion to exclude. Defendants filed an opposition, I suppose early this morning.

THE COURT: Yes.

MR. HUNT: In the event that the Court is prepared to take up that issue, I think it would be beneficial to the parties and most notably the defendants to assist in witness preparation. So if there's a particular time that the Court would be willing to take that up today, it would be much appreciated.

THE COURT: Why don't we do that -- because Dr. Albini has a travel issue. Is that correct? Or travel schedule, I should say, not issues.

Hopefully, Doctor, wherever you are, you don't have issues, but I know you have a travel schedule.

Let's take that up at morning break or so, and we'll go from there.

MR. HUNT: Appreciate it. Thank you, Your Honor.

THE COURT: Yes, ma'am.

MS. MAZZOCHI: And, Your Honor, the additional administrative matter to bring up has to do with the deposition designations for Karen Chu. So one of the things that we do have -- I'm happy to hand it up to Your Honor -- is we actually

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went through --

THE COURT: I believe I have that.

MS. MAZZOCHI: What got filed was the -- that was our letter that we had previously sent where we -- under the pretrial order where we had specified this was Regeneron's objection; this is ours.

In response to your instructions yesterday, we did have a meet-and-confer. My understanding is that Regeneron's position is that they believe we had an agreement that, therefore, all of Ms. Chu's testimony was converted from 30(b)(6) even if it fell within the notice topics to 30(b)(1). We obviously disagree with that position.

So what we -- we do have a copy of the transcript where we basically have gone through and marked these are the different --

THE COURT: I have the color-coded -- red, green, yellow. I've not had a chance to review that. So we're going to put a pin in that.

MS. MAZZOCHI: I just wanted to know if there was a -- because, again, we were hoping we could play Ms. Chu's deposition testimony today as a 30(b)(6) witness. So I didn't know if that was already something you'd like to take up --

THE COURT: We will when we get to it.

MR. GREGORY: I'm not -- not seeking to argue this right now, just want to clarify.

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THE COURT: Not going to, but go ahead.

MR. GREGORY: The deposition transcript that I believe you have is actually one from Regeneron. I think it's probably very similar to the one that Mylan's counsel has prepared. We received the email request this morning for those transcripts.

We have a machine time limitation on the small printer across the hall. We're running copies. I believe we have provided the Court with two. The next one out of the printer will go to Mylan's counsel. The fourth one will be mine.

THE COURT: Understood.

MS. MAZZOCHI: Your Honor, how about to the extent let's make sure everybody's got copies so nobody's surprised. I'll give this to counsel.

Your Honor, how many copies would you like?

THE COURT: Two, please.

MS. MAZZOCHI: Thank you, Your Honor.

THE COURT: I know we've got some pins on things to deal with. We will take them as they come.

Mylan may call its first witness.

MR. McLAUGHLIN: Your Honor, I believe we have some binders. Permission to approach to pass out those binders, documents Dr. Albini is going to be relying upon.

THE COURT: Granted.

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MR. McLAUGHLIN: Good morning, Your Honor. Neil McLaughlin on behalf of Mylan Pharmaceuticals, Inc., and Biocon Biologics, Inc. Biocon/Mylan would like to call Dr. Thomas Albini as its first witness in its invalidity case.

THE COURT: Good morning, Doctor, sir. If you want to make your way to the front of the courtroom.

THOMAS A. ALBINI, MD, DEFENDANTS' WITNESS, SWORN

THE COURT: Thank you, Doctor. Once you're seated and comfortable, sir, if you wouldn't mind adjusting that microphone. Don't worry; you can't break it.

THE WITNESS: Okay.

THE COURT: Does everyone have all their binders, slides, and the rest?

If you're settled, Counsel.

MR. McLAUGHLIN: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. McLAUGHLIN:

Q. Good morning, Dr. Albini. Can you please state your full name for the record.

A. Thomas Arno Albini.

Q. You're here testifying on behalf of Biocon and Mylan, correct?

A. That is correct.

Q. Did you prepare demonstrative slides to assist the Court with your testimony today?

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A. That's correct.

Q. And looking at the screen -- this is DDX 6 -- are these the slides that you prepared?

A. Yes.

Q. So, Dr. Albini, I'd like to first talk about your qualifications and experience that are relevant to this case.

What is your area of expertise?

A. I am a vitreoretinal surgeon who, among other things, treats patients with angiogenic eye disorders on a routine basis. And I've been doing that now for over 15 years as faculty at the University of Miami Bascom Palmer Eye Institute.

Q. Could you describe your academic experience that led to your eventual appointment to Bascom Palmer Eye Institute.

A. I finished medical school in 1999 at Johns Hopkins University in Baltimore. I then went to Los Angeles to the University of Southern California Doheny Eye Institute, where I finished a three-year residency in ophthalmology. I also undertook a one-year fellowship in intraocular inflammation and ocular pathology.

Subsequent to that, I went to the Cullen Eye Institute at the Baylor College of Medicine in Houston, Texas, where I undertook two years of training as a fellow in vitreoretinal surgery.

And immediately subsequent to that, I was hired as an assistant professor at Bascom Palmer, University of Miami.

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Approximately six, seven years later, I was promoted to associate professor. And back in 2018 I was promoted to a full clinical professor of ophthalmology at Bascom Palmer.

Q. You made a reference to the term "vitreoretinal."

Can you describe for the Court what vitreoretinal disorders are?

A. Vitreoretinal disorders are a number of diseases within the back part of the eye behind the lens involving surgery and medical -- and/or medical treatment of the retina and the nearby tissues in the back of the eye.

So these would be things that people might have heard of, like retinal detachments on the surgical side, epiretinal membranes, and on the medical side, most of the diseases that we'll be talking about, such as macular degeneration and diabetic macular edema.

Q. And looking at the next slide, Slide 3 of DDX 6, can you tell the Court a little bit about your experience working as a medical doctor in the field of vitreoretinal disorders.

A. Sure. So as I mentioned, I started as an assistant professor back in 2006. I've been a staff ophthalmologist at a fully equipped eye hospital, the Anne Bates Leach Eye Hospital, and at Jackson Memorial Hospital, which is the county health system at University of Miami.

Since 2016 I've been codirector of the vitreoretinal surgery fellowship, and then in 2018 I was promoted to full

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professor of clinical ophthalmology.

As of this morning I have decided to become the medical director of the retinal division within Bascom Palmer Eye Institute.

Q. Congratulations.

Now, turning to the -- your next slide, Slide 4, can you describe some of the things that you do on a day-to-day basis in your roles at Bascom Palmer?

A. We have a number of educational conferences for fellows and surgical and medical retina. I routinely participate in those. I have fellows and residents who are with me in clinic virtually every time I'm in clinic. And part of my responsibilities are not only to manage patients as best I can but also to help educate younger doctors who are becoming vitreoretinal specialists themselves.

I also have fellows with me in the operating room, either watching me operate or me watching them operate, and that's also on a routine basis. And I've been doing that for years.

Of course, my primary emphasis is on diagnosing and treating vitreoretinal diseases in patients. I have a very busy clinical load. I see somewhere between 4,000 and 5,000 patient visits per year, and I operate every week.

And as part of those responsibilities, I administer a lot of vitreal anti-VEGF agents such as the ones that we'll be

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discussing the rest of this testimony.

Q. And turning to the next slide, can you describe some of the other contributions and roles that you have within the vitreoretinal specialist community.

A. I've participated in a lot of national and international societies, professional societies, within retina and ophthalmology. I've been given the Senior Achievement Award by the American Academy of Ophthalmology, the Senior Honor Award by the American Society of Retina Specialists. And these awards reflect scientific contributions that I've made to the meetings over the years.

I'm a member of The Retina Society and serve on the nominations committee for The Retina Society.

I'm a member of The Macula Society, serve on the bylaws committee for the Macula Society. And I'm a founding member of the Vit-Buckle Society, which has now become a large organization focusing on mentorship of young surgeons in their residency and fellowship and in the first part of their careers.

I'm codirector now for the last, I think, five years of the annual Angiogenesis meeting that was started by my colleague Dr. Phil Rosenfeld, and I do that along with Dr. Harry Flynn. The three of us are codirectors of one of the largest scientific meetings dealing with angiogenic eye disorders.

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I've been editor on the *Journal of Vitreoretinal Diseases*, although I stepped down recently due to time constraints. And I've been an editor for a professional magazine called *Retina Today*, I think, for about 12 years.

Q. In the context of providing your opinions in this matter, did you provide a definition for a person of ordinary skill in the art?

A. Yes, I did. I believe it's on the next slide.

Q. Is that definition shown here on Slide 6?

A. That's correct.

Q. Now, I'm just going to take some time to read this into the record so we have a clear record of what that definition was.

THE COURT: Slowly, please, Counsel.

MR. McLAUGHLIN: Understood.

BY MR. McLAUGHLIN:

Q. So from paragraph 91 of your expert report it begins:

"After considering the above-mentioned factors, it is my opinion that a person of ordinary skill in the context of both the '601 patent and the '572 patent would have:

"1. Knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and

"2. The ability to understand results and findings presented or published by others in the field, including the

publications discussed herein.

"Typically, such a person would have an advanced degree, such as an MD or PhD, or equivalent or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field with practical academic or medical experience in:

"1. Developing treatments for angiogenic eye disorders, such as AMD, including through the use of VEGF antagonists; or

"2. Treating of same, including through the use of VEGF antagonists."

Did I read that correctly?

A. That's correct.

Q. And in your opinion, do you meet the definition of a POSA with regard to the '601 and '572 patents?

A. I believe I do. I hold an advanced degree; I think I can understand a publication result; and I diagnose and treat those disorders.

Q. Would you have met that definition in the 2010 time frame?

A. Yes, I would have.

Q. At this time could you please turn to DTX 8205 in your -- set of binders you've been provided.

A. I'm not sure where the binders are. Maybe I should have grabbed that.

THE COURT: Of all people, the witness does not have a binder.

One second, Doctor.

THE WITNESS: I apologize.

You're directing me to Volume 1?

BY MR. McLAUGHLIN:

Q. DTX 8205.

A. I recognize that document. Yes, I see it.

Q. Is that a copy of your current CV?

A. That's correct.

MR. McLAUGHLIN: So, Your Honor, at this point we would like to move to admit DTX 8205, Dr. Albini's CV, into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 8205 was admitted.)

MR. McLAUGHLIN: At this time we also proffer Dr. Albini as an expert in the diagnosis and treatment of vitreoretinal disease.

THE COURT: Any voir dire or objection?

MS. OBERWETTER: Yes, Your Honor, as follows. We don't have any objection to him being offered as a treater of angiogenic eye disorders. We have some concern there are going to be opinions elicited today on formulation topics. We do not

believe that Dr. Albini is an expert on formulation issues. And if he intends to speak on his own account about what certain references do or do not disclose about formulations, we do have voir dire from that standpoint, Your Honor.

THE COURT: We'll take that up if and when we tread into those grounds.

But no objection to the present motion as a treater of these certain eye disorders, correct?

MS. OBERWETTER: Correct, Your Honor.

THE COURT: Without objection, that motion is granted, and the doctor is deemed so qualified.

MR. McLAUGHLIN: Thank you, Your Honor.

BY MR. McLAUGHLIN:

Q. Turning to Slide 7. Dr. Albini, before we get to the substance of your opinions, did you conduct your analysis from the perspective of a person of ordinary skill in the art as you described it as of January 2012?

A. I did. And I reviewed the subject matter of the dosing patents and of the asserted claims, the prior art prosecution histories, the technology at issues. And I bring to that my 20 years of experience as described.

Q. In the context of formulating your opinions, did you review Dr. Csaky's responsive expert report in this case?

A. I did.

Q. And did Dr. Csaky provide a definition of a person of

ordinary skill in the art that is different from your definition?

A. He did.

Q. Would your analysis change under Dr. Csaky's definition of a person of ordinary skill in the art?

A. No.

Q. Let's turn to a little bit of a background about this case, just starting with Slide 9.

Have you assessed in this matter the issue of invalidity with respect to U.S. Patent Numbers 10,888,601 and 11,253,572?

A. I have.

Q. Is it okay if I refer to those as the '601 and the '572 patents going forward?

A. Yes.

Q. Would it also be okay if I refer to those as the dosing patents in some instances today?

A. Yes.

Q. You'll understand I'm referring to the '601 and '572 patents?

A. I will.

Q. So let's talk about the asserted claims. Do you understand that the claims shown here on Slide 10 are the claims that are being asserted in this matter by Regeneron?

A. That's correct.

Q. Those include Claims 11 and 19 of the '601 patent and Claims 6 and 25 of the '572 patent?

A. That's right.

Q. Are you rendering opinions on the anticipation and obviousness of each of those patents?

A. Yes.

Q. Do you understand that other experts will be opining on certain elements of one or more of those patent claims?

A. Yes.

Q. And one of those, you understand, will be Dr. Rabinow --

A. That's correct.

Q. -- writing opinions with respect to Claim 6?

A. That's correct.

Q. Did you rely on Dr. Rabinow for opinions regarding Claim 6?

A. Yes, I did. I do not see myself as an expert in formulation, just in vitreoretinal disorders and their treatment. So I did rely on him in that regard.

Q. If we flip ahead to Slide 11 here, can you briefly provide a description to the Court of the opinions that you're going to be presenting today?

A. The basic arguments are going to be that these claims, as you outlined -- the DME, DR claims -- are anticipated by the September 14th, 2009 Regeneron press release

and the 1999 '747 patent; that they are also obvious through those prior art pieces in combination with others; and that the patent Claim 6 of the '572 patent as regards formulation is anticipated and obvious.

Q. Dr. Albini, I would like to start by talking about a little bit of scientific background before we delve into your opinions and the ways of treating various angiogenic eye disorders before 2011.

Let's start with the anatomy of the eye. Can you -- and the Court has heard a lot of this already, but can you briefly describe what you've shown here on Slide 13?

A. Sure. This is a cartoon cross section of the eye, showing the front parts of the eye, the cornea -- the clear part that you see when you look into somebody's eyes -- and the lens.

And the -- shows deeper into the eye. You have the vitreous gel, which occupies most of the volume of the eye, especially that back component. And then that orange-colored tissue that you see there is sort of the wallpaper lining of the inside of the eye called the retina. This is neurologic tissue that connects to the optic nerve and sends visual impulse information back to the brain for you to be able to see.

And if you want to progress the slides, this cartoon starts to move.

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When light comes into the eye, it goes -- it's focused by the cornea and the lens onto the fovea. The fovea is a specific part of the macula, the center part of the macula, and the macula is a part of a retina in general.

And that's the part where you have your highest definition vision. That is the part that's affected by the diseases at issue here, both diabetic macular edema and exudative, or wet, macular degeneration.

In those disease states, either because the blood vessels are leaky, as they are in diabetic macular edema, or because they're leaky because of abnormal growth of vessels that develops in macular degeneration, the retina becomes distorted which, in turn, distorts your vision.

And the miraculous discovery over the last two or three decades is that a lot of that disease process is driven by a molecule called vascular endothelial growth factor and that blocking this vascular endothelial growth factor not only causes some of these immature blood vessels to disappear, but it decreases the fluid buildup and consequent distortion of the retina; and, even more miraculously, it improves patient's vision. And this blockage has been responsible for greatly reducing cases of blindness due to macular degeneration and diabetic macular edema over the last few decades.

Q. Thank you, Dr. Albini.

Now, I'd like to shift to a discussion of state of

the art and the background with regard to what was known prior to 2011, including with respect to some of these VEGF inhibitors that you just made reference to.

Do you understand first -- we'll be filling in this timeline as we go along, but do you understand that 2011 to be the year the patents-in-suit were filed?

A. That's my understanding.

Q. Let's start by talking about the VEGF drugs that were being administered in trials -- or the clinic prior to 2011.

Would that have included ranibizumab?

A. Ranibizumab and bevacizumab -- a very similar molecule to ranibizumab but different in many ways -- were the two main agents that were in use prior to the 2011 date.

Q. And was aflibercept also being tested in clinical trials prior to 2011?

A. It was available for clinical trial use only, that's correct.

Q. So if we flip to Slide 21, can you describe what's shown here on this slide, Dr. Albini.

A. This is a review article that was published in 2009 by Dixon and coauthors, and it describes the -- what became known as the aflibercept molecule. It's VEGF Trap-Eye, which was a scientific name, as Dr. Yancopoulos testified the other day, that was used for this molecule prior to the aflibercept name and the Eylea names being given to it. But it is a fusion

protein with key binding receptors of the VEGF receptor 1 and receptor 2 fused with the FC portion of an antibody.

Q. And here on the slide you're referring to DTX 0204, pages 1 and 3 from the Dixon reference?

A. That's correct. Also here there is another reference from Adis in 2008 which makes reference to the same protein.

Q. And Adis, that's DTX 4008 that you're referring to?

A. That's correct.

Q. What's the year of the Dixon reference?

A. 2008.

Q. And was VEGF Trap-Eye also known as aflibercept in the prior art?

A. That's correct.

Q. And is that shown here on Slide 22 in excerpts from DTX 0204 and DTX 4008?

A. Especially in the Adis 2008 article. The title of the article itself is "Aflibercept."

Q. In the abstract of Adis, the reference is aflibercept, and it says that Regeneron and Bayer are developing the agent for eye disorders?

A. That is correct.

Q. And turning to the next slide, Slide 23, you've shown the '747 patent on the left hand. Is that one of the patents and references you've relied on in forming your opinions in this case?

A. That is correct.

Q. And did the '747 patent recite a molecule called VEGFR1R2-Fc delta C1(a)?

A. That is correct. That is the name given to the fusion protein of the VEGF receptor 1 and 2 bound with the Fc receptor that was in clinical use.

Q. Is that molecule also known as aflibercept?

A. That is correct.

Q. Flipping ahead to Slide 24, this is another disclosure from the '747 patent that you provided here.

Does the '747 patent disclose a method of treatment for an angiogenic eye disorder?

A. It does. In the specification there are outlined patient visits that should occur when the patients are being treated with this molecule, and it says that after the first 30 days, the patient should return for periodic examinations on a monthly basis thereafter.

It also describes that the patient needs to be continuously monitored through periodic examinations for fluid in the retina. And at the time fluorescein angiography is mentioned as an imaging modality to do that with. And it also mentions that, in a preferred embodiment of what's taught in this patent, the initial treatment is followed by subsequent treatments that are given at dosing intervals ranging from one- to six-month dosing intervals.

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Q. And looking at the face of the '747 patent, do you see the date of the '747 patent's priority application?

A. I'm not so clear on all of the legal terms; so maybe -- but I see the date there, December 4th, 2007, although my recollection is that this patent was first filed in 1999.

Q. Thank you.

And flipping to the next slide, Slide 25, is that '747 patent now reflected on this timeline that you've provided?

A. Yes.

Q. And that '747 patent, that's DTX 2730?

A. That's correct.

Q. Now, moving on to Slide 26, let's talk about some of the other VEGF inhibitors that were known and being used by ophthalmologists before the '601 and '572 patents were filed.

What was the first anti-VEGF antibody approved by the FDA for treating an angiogenic eye disorder?

A. The first antibody molecule that was approved was ranibizumab. There was a prior medicine called Macugen, which was an aptamer. It's a slightly different type of technology. It is a binding molecule much like these others all targeting various subtypes of vascular endothelial growth factor.

Ranibizumab became FDA approved for use in wet macular degeneration in 2006. And what we have here is a picture of the label of the drug with an excerpt describing

dosing frequencies of intravitreal injection once a month and another approved dosing regimen of one injection every three months for the first four injections and quarterly injections thereafter.

The other main drug in use was bevacizumab. Bevacizumab is quite an interesting story. It's another molecule that also targets vascular endothelial growth factor. It was also developed by the Genentech. Both these drugs were developed by Genentech.

Ranibizumab was developed specifically for use in the eye while bevacizumab was developed for intravenous use in cancer patients. Bevacizumab was available prior to the availability of ranibizumab. And in 2005 a number of physicians began to inject bevacizumab off-label intravitreally to treat angiogenic eye disorders. There was already good data coming from Phase II studies and other studies showing that there was great efficacy with ranibizumab.

And there was a desire to have this efficacy available to patients before the molecule was actually approved by the FDA; so bevacizumab was used. And that quickly in 2005 spread throughout the world, where this became the major drug that was used in this sphere. And it remains to this day probably used just as often as the name-brand drugs in the United States.

One of the main driving factors for the use of

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bevacizumab, even though it's not specifically FDA-approved for this indication, is a huge differential in cost. The ranibizumab was approximately $2,000 per injection whereas bevacizumab, when you bought a bag of drug for intravenous use and you aliquoted it out to inject it into the eye, the cost of a single ocular injection came out to about $50. So it was a great drug to have especially for patients of limited means.

Q. In your discussion of the ranibizumab label that we just had prior to your discussion of bevacizumab, were you referring to DTX 4056?

A. That is correct.

Q. Thank you.

If we flip ahead, can you briefly tell the Court what you've shown here on Slide 27 with respect to ranibizumab and how it was being used in clinical trials?

A. These are three outcomes from trials with ranibizumab that were available in the 2006 to 2008 time frame. And I think these are really important graphs of top-line data from these drugs.

The first to the left is the top-line visual acuity results from the ANCHOR trial of monthly ranibizumab for the treatment of wet macular degeneration.

The line that you see there going down on the bottom is the control arm. And that was treatment with standard of care at the time, which was a type of laser and photodynamic

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intravenous treatment called photodynamic therapy. That was the best treatment that we had when I was a resident. And as seen there, patients continued to lose vision. Although they lost vision less quickly than they might have without this therapy, it just retarded the rate of vision loss, but patients still continued to lose vision.

The really earth-shattering result that was seen in ANCHOR study and other studies, the MARINA study which we'll be talking about later, was this quick rise in visual acuity that was then maintained over time as you see in the other two lines that go up to where patients are gaining about ten letters, what we call ETDRS letters of visual acuity. That translates into being able to read two lines further down on the eye chart, roughly, in that area. So that was really a very welcome and amazing improvement in the treatment of macular degeneration.

In the center box you see the top-line data from a smaller prospective study called the PrONTO study, which just to have institutional pride, was performed at Bascom Palmer Eye Institute. And this study tested the concept whether we could reduce injections, not necessarily inject patients every month as was done in the original ranibizumab study, but make decisions on a monthly basis whether or not a patient needed an injection by considering certain clinical factors and considering the state of the retina, especially as evidenced by

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imaging technologies, newer technologies that were available at the time, especially something called optical coherence tomography, or OCT, examinations, which are now pretty ubiquitous in the retinal world as a way of evaluating the health of the macula.

So this study showed, as you can see there, that you could get very profound benefit and visual acuity results, really very nicely mirroring the benefits that you see in ANCHOR with this as-needed treatment strategy. This is the so-called prn treatment strategy which became very poplar very quickly in that 2007 and beyond range.

And, finally, you have the results of a quarterly dosing study with ranibizumab, the EXCITE study, which showed that monthly dosing, which is the triangle line up on top, outperformed quarterly dosing. So these were initial monthly loading doses and then followed by quarterly dosing. And that although that treatment strategy resulted in a success compared to photodynamic therapy, certainly compared to observation alone and no treatment, it was not as good as monthly dosing.

Q. And when you were referring to these charts here, you're referring to excerpts from DTX 4061?

A. That's correct.

Q. With respect to the PrONTO study, did you also rely in the process of formulating your opinions on DTX 3115, the Fung 2007 reference?

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A. I did.

Q. Now, turning to the next slide, could you tell the Court a little bit about how bevacizumab was being used in the clinic and how it was being evaluated in clinical trials?

A. This is a clinical trial of bevacizumab for exudative macular degeneration, a one-year prospective study, showing that this drug could be used to obtain similar results with that seven- to eight-letter gain by 12 months. And this was also done with initial loading doses and then reinjection of the drug on an as-needed basis going forward.

Q. So flipping back to the timeline now, so just to summarize, by 2006 there was an anti-VEGF agent, ranibizumab, that had been approved for monthly dosing and for every-12-week dosing?

A. That's correct.

Q. And by 2007 the results of the PrONTO study using as-needed maintenance dosing, had that been reported?

A. That's correct.

Q. And by 2008 had data been reported with respect to the use of bevacizumab in the treatment of AMD and is that reflected here --

A. Yes.

Q. -- on the timeline?

I would like to shift focus a little bit. And can you tell the Court how ranibizumab was being used in the

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context of treating DME in that time frame.

A. This is a review article by Dr. Lalwani from 2009 that reviews the results of a early study with ten patients who received injections of ranibizumab at baseline, month one and month two, so essentially three loading doses, and then received q8-week dosing for the month four and six. And it showed that there was good visual acuity gains from this treatment strategy in this small number of patients with diabetic macular edema.

Q. Is that Lalwani reference now referenced on this timeline here at Slide 31?

A. That is correct.

Q. And that's from DTX 2733?

A. That's correct.

Q. Now, turning to the next slide and turning back to that Dixon reference which you've referenced earlier, was aflibercept being used in a Phase II AMD trial prior to 2011?

A. The Dixon article from 2009 describes both -- describes a Phase II study, the CLEAR-IT 2 study, of 2 milligrams for 12 weeks of the -- of aflibercept being used followed by a prn treatment regimen after the loading dose phase of the study.

And it also describes a Phase III study for wet macular degeneration using the 2-milligram dose administered either every four weeks or every eight weeks and compared to

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ranibizumab.

Q. And these are selections from DTX 0204?

A. That's correct.

Q. And flipping to the next slide, Slide 33, can you tell the Court how else aflibercept was being used prior to 2011?

A. This is a Regeneron press release dated September 14th, 2009. And it describes a Phase III study in retinal vein occlusion. That's another angiogenic eye disorder treated -- VEGF-driven and treated with these same agents. And this describes a protocol with six monthly doses and then prn dosing thereafter.

And it also describes a Phase II study in diabetic macular edema with a monthly arm, also an arm where there were three monthly loading doses and then every-eight-week injections and another arm where there were three monthly doses and prn injections going forward.

Q. And those selections are from DTX 3198?

A. That's correct.

Q. Can you tell the Court how aflibercept was being used in the treatment of DME prior to 2011?

A. This is a manuscript from Do in 2009. And it describes a small study of a single injection of 4 milligrams of aflibercept in a small number of patients, and it describes a visual acuity benefit from that single injection.

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Q. And that visual acuity benefit, again, that was nine letters at one month?

A. That's correct, which is an impressive benefit.

Q. And are those Dixon disclosures and the Do disclosures referenced here on the timeline at Slide 35?

A. Yes.

Q. So now we've reviewed what was being done in clinical trials up to now. Let's shift focus and discuss what physicians were doing in actual clinical practice before 2011.

So on this next slide, Slide 36, can you explain what's shown here?

A. These are excerpts from a roundtable discussion that was published in a professional journal called Retinal Physician in 2007. And I think this is a great way to get a snapshot of what the POSA was thinking at that time.

These are three prominent retina specialists in the United States, and they're describing their treatment protocols. The first one there is Dr. Rosenfeld from Miami. He was the lead investigator and designer of the PrONTO study. And he describes his treatment regimen trying to minimize the number of injections but treat the patients until there's no fluid in the retina. And once they're dry, then having the ability to skip those injections.

Dr. Reichel from Boston also says that he's a big believer in prn dosing. He gives only one injection on a

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routine basis, sees the patient four weeks later, and already makes a decision whether or not to re-treat. So this would be a regimen that would be essentially one loading dose, or just a single primary dose, followed by immediate prn protocol injections.

And Dr. Hariprasad from Chicago also gives his opinion that he doesn't necessarily give three full loading doses, but he gives monthly injections until the patient's retina is dry and then presumably stops injecting until there's reaccumulation of fluid.

THE COURT: Counsel, if I could interrupt.

Doctor, when you reference dry, you're referring to the elimination of any leakage or bleeding from the VEGF-spurred blood vessels and the rest; is that correct?

THE WITNESS: Yes. I'm so sorry that I didn't explain that.

So we often use that as a colloquial term for seeing that there's been resolution of fluid. And you're right on point there with what that means. That's right.

THE COURT: When you say fluid, would there be any other fluids that are offshoots of these various diseases of the eye other than blood?

THE WITNESS: So most of the fluid is clear. It doesn't have red blood cells in it. It's a serous fluid that's in there that extrapolates from the vessels. But the red blood

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cells are usually contained within the vessels. You can have blood also. So it can be either blood, but the majority of the time it's actually not full blood.

THE COURT: But it's fluid that's coming from the blood vessels?

THE WITNESS: That's exactly right.

THE COURT: Understood. Thank you.

Sorry, Counsel. Go right ahead.

THE WITNESS: Sorry I didn't explain that better.

THE COURT: Oh, no. That's good.

Go ahead, Counsel.

BY MR. McLAUGHLIN:

Q. The excerpts that you've been referring to, those are coming from DTX 2035?

A. That's correct.

Q. Turning to the next slide, Slide 37, can you describe what's shown here?

A. This is a quote from the same roundtable discussion. This is Dr. Brown from Houston, Texas, another prominent retina specialist. And he says that he uses treat and extend from the start. I'd just like to point out to everybody that this is back in 2007 that he's describing this treatment strategy.

The treat-and-extend strategy is another strategy that came into vogue slightly after the prn strategy, but the concept here was to not only reduce the number of injections

but to reduce the number of visits that patients needed to come back. And so that if a patient established themselves as someone who was -- who could maintain the retina free of fluid for a longer period of time, then the physicians became comfortable with having those patients come in at longer periods to minimize the burden of visits over time.

And so this is just a nice historical document showing that already in 2007 this type of treatment strategy was indeed being employed.

Q. Is that something that you employed in your own practice prior to 2011?

A. Yes.

Q. Was Dr. Brown's description of treat and extend consistent with the general understanding of the treat-and-extend regimen in that time frame?

A. Yes.

Q. And turning to the next slide, Slide 38, can you describe what you've shown here?

A. This is a survey result from a survey that's performed by the American Society of Retina Specialists every year. And it basically serves as a way to communicate amongst the profession what the treatment modalities are, treatment trends are within the community of retina specialists.

So this -- for example, this question is asking physicians to identify what their treatment strategy is for

exudative macular degeneration or wet macular degeneration. And in 2010, out of 337 respondents to this survey, 43 percent said they were using a prn strategy and 34 percent were already using a treat-and-extend strategy.

Q. Turning to the next -- sorry. Flipping back just to confirm, you're referring to DTX 2040?

A. Yes.

Q. Flipping to the next slide, Slide 39, can you explain what's shown here?

A. This is an article showing a study result for intravitreal bevacizumab -- that's Avastin -- for myopic choroidal neovascularization, a short-term and one-year result. And the interesting thing to me was that this is already making reference to the treat-and-extend approach, just to document that this was already something that was seen as a treatment strategy that was well known within the field in 2009 by the time this was published.

Q. And this is from DTX 4113?

A. That is correct.

Q. So are all these references that you've been discussing over the last several slides represented here on Slide 40 of your presentation?

A. Yes.

Q. So let's just wrap this up and summarize what we've gone through and what we've now shown on this timeline.

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So in terms of drugs that were available, would that have included ranibizumab, bevacizumab, and then aflibercept being in clinical trials prior to 2011?

A. Yes.

Q. And what types of dosing regimens had been reported with respect to those agents?

A. There were fixed regimens such as monthly fixed or a number of loading doses, and then every eight -- then every-eight-week injection on a regular basis; a number of loading doses, and then every-12-week injections given on a fixed basis. There were also individualized regimens such as the PrONTO study that sought to evaluate patients and make decisions about whether or not to reinject on a patient basis.

And those included the treat-and-extend protocol that we've discussed, the loading doses and then prn regimens that we've discussed, and continuous injection until the macula is dry as Dr. Hariprasad evidenced in his quote. And this was across the indications of exudative or wet macular degeneration, diabetic macular edema, diabetic retinopathy, and retinal vein occlusion.

Q. Dr. Albini, do you intend to provide testimony today regarding the invalidity of the '601 and '572 patent claims?

A. Yes, I do.

Q. Would that include Claims 11 and 19 of the '601 patent and Claim 25 of the '572 patent?

A. That's correct.

Q. Is it okay if, going forward, I refer to those as the DME-DR treatment claims?

A. Yes.

Q. So can you briefly describe for the Court the anticipation opinions that you're going to be giving in this portion of your testimony?

A. Every limitation within the claims that we're discussing is either explicitly or inherently available within two single references: the September 14th, 2009, press release from Regeneron and also in the U.S. patent '747 that we've discussed that was filed back in 1999.

Q. Let's start -- we're on Slide 46 now. Let's start with a discussion of these claims.

So you've reviewed the '601 and '572 patents, correct?

A. Yes.

Q. Have you reviewed Claim 11 of the '601 patent?

A. I have.

Q. Is that what's shown here on Slide 46?

A. That's correct.

Q. And do you understand that Claim 11 of the '601 patent depends from independent Claim 10 of the '601 patent?

A. Yes.

Q. Can you describe in your own words for the Court the

dosing regimens set forth in Claims 10 and 11 of the '601 patent?

A. Yeah. In these two claims taken together, they describe a dosing strategy using 2 milligrams of aflibercept for treating diabetic macular edema given as five initial monthly loading doses or five initial monthly injections followed with subsequent eight-week injections.

Q. And looking at the language of Claim 11, when it says every 28 days, for example, would you understand that the disclosure of something occurring exactly every 28 days as the type of regimen that would fall within the scope of this claim?

A. Exactly every 28 days would certainly fall within the scope of approximately every 28 days, that's correct.

Q. Turning to the next slide, Slide 48, did you also review Claim 19 of the '601 patent?

A. Yes, I did.

Q. You also reviewed the claim from which it depends, Claim 18?

A. Yes.

Q. Can you describe in your own words for the Court the dosing regimen set forth in Claims 18 and 19 of the '601 patent?

A. This is the same dosing regimen set forth in the 10 and 11 claims. And in these claims the disease state is different. This is being used for the larger disease entity

called diabetic retinopathy, including other types of diabetic disorders of the retina in addition to macular edema.

And here it describes again the administration of 2 milligrams of aflibercept with five initial loading doses followed by q8-week regular dosing.

Q. Can you briefly describe the relationship between DME and DR?

And by the way, is it okay if I refer to diabetic macular edema as DME and diabetic retinopathy as DR going forward?

A. That's fine with me. I hope it's fine with everybody else.

THE COURT: I think I've got those acronyms down by now, Doctor. So if it works for you, it works for me.

THE WITNESS: Fantastic.

So I think that DME is technically a type of diabetic retinopathy. It is a diabetic eye disease of the retina. It is a specific subtype of diabetic retinopathy. It is the most common cause of mild to moderate loss in diabetic patients, very commonly seen. And it is usually described as a complication of diabetic retinopathy or a subtype of diabetic retinopathy.

BY MR. McLAUGHLIN:

Q. Flipping to Slide 49, have you reviewed Claim 25 of the '572 patent?

A. Yes, I have.

Q. And you've reviewed the claim from which it depends, Claim 15?

A. Yes, I have.

Q. Can you briefly describe the -- how you understand the subject matter of Claims 15 and 25 of the '572 patent?

A. These two claims describe an identical treatment strategy for diabetic macular edema, again administering 2 milligrams of aflibercept with at least five initial monthly injections and subsequent eight-week injections.

Q. In your opinion, are there any substantive differences between Claim 25 of the '572 patent and Claim 11 of the '601 patent?

A. No.

Q. If we could turn to Slide 50. So turning to the references that you referred to earlier, I believe what you've shown on the left here is the 9-14-2009 press release. Is that the reference that you relied upon?

A. That's correct.

Q. And shown on the right is the '747 patent. That's patent number 7,303,747, DTX 2730. Is that one of the other references you relied upon in your anticipation --

A. That's correct.

Q. And turning to the next slide, can you explain what you have highlighted here on Slide 51?

A. This is a text from the Regeneron press release describing a Phase II DME VEGF Trap-Eye, or aflibercept, study using the 2-milligram dose. There were three dosing arms or dosing strategies described in this press release for DME. One was a monthly dosing arm or a three monthly injections followed by prn dosing thereafter. And there was a third strategy described of three monthly injections and then every-eight-week dosing thereafter.

Q. When looking at the 2-milligram dose of VEGF Trap-Eye reported here, would a POSA have understood that to refer to an intravitreal dose of aflibercept?

A. Yes. VEGF Trap-Eye, as far as I know, was only available for intravitreal use in clinical trials at the time.

Q. And just another housekeeping matter. We've used the acronym POSA a couple times. Just so the record is clear --

A. A POSA is a person of ordinary skill in the art, of which I believe I am one and was one.

Q. Thank you.

Turning to the next slide, you mentioned a prn dosing scenario mentioned in this 2009 press release. Can you explain how a POSA would have understood a prn dosing scenario in that time frame?

A. So I think that the dosing regimen that's described stipulates that the patient receive three monthly injections at the beginning of treatment. And then thereafter decisions are

made whether or not to inject based on clinical measures and imaging findings for that patient.

One can immediately envision that a patient might require three initial loading doses and might require that a fourth injection when they come in for that visit and then have a subsequent visit where there's no injection required, resulting in an eight-week interval.

Q. And in typical prn dosing scenarios used in that time frame, monthly visits were the norm?

A. That's correct.

Q. You mentioned immediately envisioning a dosing scenario. So is that something you've illustrated here on Slide 53 of your presentation?

A. Yeah. I think this graphic helps greatly to understand the point here. But what's seen there is the syringes represent injections for the patient, those monthly visits. And the first three are with blue needles, and those represent the monthly loading doses that would be described in that treatment strategy.

At Week 12 and Week 16 you see green needles representing doses that are given during the prn portion of the study. At Week 20, presumably, the patient meets criteria by lack of fluid in the retina, does not require that injection, and then comes back at Week 24 and, again, does require an injection.

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So in the end what you have is five regular monthly injections with an eight-week gap and then the sixth injection.

Q. Turning to Slide 54, can you explain how that scenario relates to Claim 11 of the '601 patent?

A. This treatment strategy, this particular iteration of the prn dosing schedule, is identical to the treatment strategy that's laid out in Claims 10 and 11 and 18 and 19. In every real sense the same number of injections are given at the same time periods and are the same treatment.

Q. So the three monthly loading doses given at Weeks 0, 4, and 8 followed by the two prn treatments at Weeks 12 and 16, those would be injections given every four weeks for the first five injections?

A. That's correct.

Q. And then the injection given at Week 24, after having skipped an injection at Week 20, that would be an injection given once every eight weeks?

A. That's correct. I think the POSA would immediately envision this type of a treatment protocol when a treatment strategy of three monthly loading doses and prn dosing subsequently are entertained.

Q. Would that same analysis apply to Claim 19?

A. That's correct.

Q. Turning to Slide 55, would that same analysis also apply to Claim 25 of the '572 patent?

A. That's correct.

Q. Now, the claim language is a little bit different here; so let's just walk through the claim language real quick.

The dose given at time zero, that would be the single initial dose of 2 milligrams of aflibercept?

A. That's correct.

Q. And then the next two loading doses given under that prn scenario followed by the two prn doses at Weeks 12 and 16, those would be the four secondary doses required by Claim 25?

A. That's correct.

Q. And then the injection given at Week 24, that would be the one or more tertiary doses?

A. That's correct.

Q. So turning to Slide 56, can you explain to the Court what you have shown here with respect to the '747 patent.

A. This is the older patent which we were relying upon as a source for anticipation for the DME-DR claims. And it describes improved pharmacokinetics with the use of the aflibercept or VEGF Trap-Eye molecule for age-related macular degeneration and mentions diabetic retinopathy as well.

Q. If we turn to the next slide, Slide 57, you have highlighted here a selection from the '747 patent highlighting that molecule name.

Why do you have that molecule name highlighted from the '747 patent?

A. Yeah, just showing that there's a clear line that can describe to the POSA the exact molecule that's being discussed and that there is no ambiguity in the '601 and '572 specification that this is aflibercept.

Q. Turning to the next slide, Slide 58, what have you highlighted here from the '747 patent?

A. The dosing range of aflibercept that's being taught in the '747 patent is a dosing range of 25 to 4,000 micrograms, and I just wanted to make the point that the 2-milligram dose of aflibercept, which we've been mentioning over and over again, falls within that range. That's 2,000 micrograms. So it's within the range of what's described in the '747 patent.

Q. Does the '747 patent at this selection here at DTX 2730, page 16, also reference an intravitreal injection of the VEGF inhibitor?

A. That's correct.

Q. Turning now to Slide 59, looking again at the DTX 2730, '747 patent, does the '747 patent here describe a dosing regimen for the treatment of angiogenic eye disorders?

A. Yes. As we've mentioned previously, it describes an initial injection given and then relates it in a preferred embodiment and initial treatment is followed by subsequent treatments given within one- to six-month intervals.

Q. Following such a treatment strategy as described in the '747 patent with monthly examinations, would a POSA reading

the '747 patent in 2010 immediately envision a scenario in which a patient received four more monthly injections?

A. I believe that's true. In a very analogous fashion to the discussion we just had, one of the iterations that one immediately would envision is five initial doses given four weeks apart and then a subsequent dose given eight weeks apart.

Q. And then could a POSA reading the '747 patent in 2010 immediately envisage a scenario in which, following a series of monthly loading doses, the patient were assessed at the next monthly visit and a decision was made to not give an injection, for example, at Week 20?

A. The specifications for the '747 patent do describe in some detail the need for continuous monitoring of patients, including for retinal fluid, which is exactly what we do. And so I think that, having read that patent, that would be very easily envisioned, this type of a treatment protocol.

Q. Following the decision to withhold treatment at Week 20, would a POSA, reading the '747 patent in 2010, immediately envisage a scenario where, on the next visit at Week 24, fluid had recurred and the patient required an injection at that visit?

A. Yes.

Q. So turning to Claim 61, is that scenario that you described accurately portrayed here on Slide 61?

A. That's correct.

Q. Can you describe how that relates to Claim 11 of the '601 patent?

A. Yeah. Again, there is a single primary injection that's given at Week 0; and then at Weeks 4, 8, and 12 and 16, a decision is made to reinject. At Week 20 there's no injection required, and at Week 24 there is an injection that's given eight weeks after the prior injection.

Q. So those injections at Weeks 0, 8, 12, and 16 would be injections given every four weeks for the first five injections?

A. That's right.

Q. And then the injection given at Week 24, that would be an injection given once every eight weeks?

A. That's correct.

Q. Would the analysis be the same for Claim 19 of the '601 patent?

A. That's correct.

Q. Turning to Slide 62, can you explain the -- or summarize for the Court the opinions you're going to be giving in this section of your testimony?

A. Yeah. I believe that, largely based on the same sources in combination with some other sources which we'll go through, that these -- all of these same claims that we've been discussing are rendered obvious given what was known at the date -- in the date.

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Q. Turning to Claim 63 -- or Slide 63, did you analyze Claim 12 of the '601 patent in the process of formulating your opinions in this case?

A. Yes. Claim 12 is dependent on Claim 10, and it describes that after 20 weeks there's an administration of aflibercept every four weeks, suggesting a change in the dosing frequency at some points of every-four-week dosing at some point after 20 weeks.

Q. Would your interpretation be the same for Claim 21 as it relates to Claims 18 and 19 of the '601 patent?

A. That's true. Under this claim this particular version of the dosing schedule would be similar to monthly dosing and would be very similar to the monthly dosing regimens which we talked about were the first dosing regimens for ranibizumab that were used back in 2006.

Q. In this case did Dr. Csaky provide his interpretation of Claim 12 of the '601 patent?

A. Yes, he did. While I think there a number of interpretations that could be made of those two claim combinations, he describes a scenario where the initial five loading doses are given, as you see here, at Weeks 0, 4, 8, 12, and 16. And then there's an eight-week loading dose -- there is an eight-week injection given at Week 24, and at that point the injection frequency is reverted back to a four-week dosing schedule, as described here in this graph.

Q. Did you understand Claim 12 to depend from Claim 10?
A. That's correct.
Q. Is it your understanding that, because Claim 12 depends from Claim 10, that Claim 10 also includes within its scope the dosing scenario of Claim 12?
A. That's correct.
Q. Turning to Slide 67, was the monthly dosing of aflibercept for the treatment of DME disclosed in the prior art?
A. Yes.
Q. Where would that disclosure have come from?
A. This was in the Regeneron press release that we've been describing from September 14, 2009. Describes a Phase II clinical trial that included an arm with monthly dosing, as we've mentioned before. And the claimed subject matter of the combination of claims that we just discussed, including Claim 12, are virtually identical to monthly loading doses, certainly easily envisioned having a protocol with monthly loading doses that one might miss a month at one point.
Q. This is an excerpt from DTX 3198?
A. That is correct.
Q. Would your analysis be the same with respect to the '747 patent and the dosing regimen described therein?
A. That's correct. The dosing regimen described in the '747 patent is somewhat broader, encompassing more treatment

regimen possibilities. But it also describes an initial dose with subsequent treatments given between one and six months apart and so that these treatment strategies would fall within the scope of these teachings as well.

Q. And these disclosures are from DTX 2730?

A. That is correct.

Q. So can you provide to the Court your overall opinions on obviousness of Claims 11 and 19 of the '601 patent?

A. I would say that, due to the great similarity between the virtually monthly treatment that's described once Claim 12 is incorporated in that Claim 10 and 11 and Claim 20 is incorporated in the Claim 8 and 19 of the '601 patent, that this dosing strategy is virtually indistinguishable from monthly administration of aflibercept, which is well described prior to 2011.

Q. Just to clarify the record, I think you said Claim 20 of the '601 patent. Would you be referring to -- I'll flip back. Were you referring to Claim 21?

A. I was. I'm so sorry. Claim 21.

Q. No problem.

A. Thanks for catching that.

Q. Then can you -- now we're on Slide 70, and can you describe what you've shown here on Slide 70 of your presentation?

A. I picked a reference to speak to the reasonable

expectation of success that was available, knowing the clinical data from aflibercept in that period prior to 2011.

This is a report of a Phase I study from 2009 by Diana Do that shows the outcomes from a single injection of 4 milligrams of aflibercept with, as I think we mentioned already, a very remarkable result of eight- or nine-letter gains from just a single injection.

So I think that, given this, the POSA would see a reasonable expectation of success moving forward with dosing regimens that involve more injections.

Q. And this is coming from DTX 3102?

A. That's correct.

Q. Now that the Do reference -- Do 2009, that disclosed just a single vitreal injection of aflibercept?

A. That's correct.

Q. After obtaining that data, would a POSA have been motivated to seek extended long-term dosing regimens for aflibercept in the treatment of DME?

A. Absolutely.

Q. And it's your opinion that, based on these results, after a single intravitreal injection of aflibercept, multiple repeated injections of aflibercept would have -- a person of ordinary skill in the art would have had a reasonable expectation of success using such a regimen?

A. Absolutely. I think Regeneron had a reasonable

expectation of success and went forward with this clinical project.

Q. Turning to the next slide, Slide 71, can you explain the data that's shown here.

A. This is from the review article on Lalwani, which we've looked at already, from 2009. And this describes a ten-patient study, the READ 1 study, for diabetic macular edema with injections given at -- three loading injections given at zero, one, and two months and then two-month injection intervals with injections given at month four and month six. And this article also described good visual acuity outcomes amongst these patients.

So, again, given this data in ranibizumab, which is a molecule with an identical mechanism or very similar mechanism of action as aflibercept, one would have a reasonable expectation of success for the injection strategies that are being described in the patents at issue.

Q. Turning to the next slide, Slide 72, are these the visual acuity gains you had referenced regarding Do 2009? I'm sorry. Lalwani 2009.

A. Yes. Patients gained an average of eight letters in the READ 2 study.

Q. This is from DTX 2733?

A. That's correct.

Q. So, overall, what would the disclosures of Do 2009

and Lalwani 2009 tell a POSA about the reasonable expectation of success of using the regimens described in both the press release and the '747 patent?

A. I think that, overall, the POSA would have thought that there would be a reasonable expectation of success in using aflibercept in the described dosing strategies, given its efficacy as described in these studies, the safety that was seen in the preliminary study by Do, and again in the efficacy and safety that was seen in the similar compound, the ranibizumab, in the READ 2 study.

Q. If we turn to the next couple slides here, so prior to this, you've told the Court about your anticipation --

A. That's correct.

Q. -- regarding the press release and the '747 patent?

A. Yes.

Q. Do you rely on these same references to show obviousness of the DME treatment claims of the '601 patent?

A. Yes.

Q. So turning to the next slide, Slide 75, is this an accurate summary of some of those immediately envisaged scenarios that we described with respect to the press release and the '747 patent that you discussed in your anticipation section?

A. That's correct. I think that given the prior teachings, one would immediately envision this type of dosing

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strategy as described in the patents.

Q. Turning to the next slide, can you tell what was known about VEGF level or what was hypothesized about VEGF levels in DME patients in the 2009 time frame as shown here on Slide 76?

A. Sure. The Lalwani review article references a concept that there are higher VEGF concentrations in patients with DME relative to wet macular degeneration, and she talks about strategies that were being clinically investigated at the time to use higher doses of drug in DME relative to macular degeneration. And I think that the POSA would have immediately thought that, if higher doses were not available, it may be more practical to administer more doses of the drug to try to obtain optimal efficacy.

Q. Turning to Slide 7, can you explain to the Court what you've shown here?

A. I wanted to put together side-by-side DME data, as was described in Lalwani, with injections of aflibercept given over a year.

And one sees in this top line data that there is an improvement in visual acuity up to about ten letters at the 12-month mark, but it is a slow and steady rise over that time period, whereas the data that I brought back to remind us of is the MARINA data from Rosenfeld in 2006 in wet macular degeneration treated with monthly ranibizumab, showing that

there is an initial rise with ranibizumab and then it plateaus and is maintained, so again evidencing that the diabetic macular edema visual acuity gains are more difficult to obtain and require more injections until you get there than what's seen in wet macular degeneration.

Q. What did you conclude with respect to loading doses after reviewing this data?

A. I think the POSA would have concluded that more loading doses for DME relative to treatment strategies that are employed in AMD make a lot of sense given that it takes more injections to get a better visual acuity in these patients.

Q. Can you summarize briefly your reasonable expectation of success opinions that you're going to be talking about over the next few slides?

THE COURT: Doctor, if I could interrupt.

We're going to change topics, Counsel?

MR. McLAUGHLIN: We will in a few minutes. Or now. It's up to you, either way.

THE COURT: Why don't we go ahead and take a break at this point. We'll take ten minutes. We'll take our morning break.

Sorry to interrupt, Doctor. Apologies.

As you may have heard over the last few days, no one can talk to you during our breaks, and no one's being rude or discourteous when they flee. But you're a man without a

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country since you're midstream in your testimony at this point. But you can go ahead and step down if you'd like.

THE WITNESS: Great. Thank you.

THE COURT: We'll take ten minutes, and then we'll resume, and then we're going to take up the question of Dr. Rabinow's opinions. Then we can resume with the good doctor's testimony. See everyone in ten minutes.

(A recess was taken from 11:03 a.m. to 11:18 a.m.)

THE COURT: Now, Counsel, before we -- what are you doing there?

MR. BERL: I thought you wanted to address the Rabinow issue. If you don't want to do that --

THE COURT: I'm going to address. I've read all the parties' briefs. I'm going to grant Regeneron's motion. Mylan will be precluded from offering testimony or opinion related to obviousness with respect to the combination of Fraser, Dix, Lucentis, which includes Shams and Gaudreault and Liu, as prior art. The Court is specifically finding, after reviewing the reports and all briefing, that opinion was not disclosed as required under this Court's scheduling order.

The separate and independent basis for granting that motion is that, as required under Federal Circuit precedent, that not only the combination but also the explanation as to why the combination of that prior art would support an opinion

or finding of obvious was likewise not disclosed.

Let me be clear, though. That is the only relief the Court grants with respect to Regeneron's motion, which is Docket Entry 529. The other opinions previously disclosed remain undisturbed, but that opinion, the Court finds, was not timely disclosed and will not be received here at trial.

We will take up the Chu deposition issue at our next break.

Anything else we need to take up at this point before we resume the doctor's testimony?

MR. BERL: Not from Regeneron, Your Honor.

THE COURT: From Mylan?

MR. HUNT: No, Your Honor. Thank you.

THE COURT: I would note the Court will -- recognizing it is a significant issue although a discretionary decision of this Court, there will be a separate order more eloquently stating the Court's reasons for granting Regeneron's motion, again Docket Entry 529.

With that said, Counsel, you can resume your direct examination.

MR. McLAUGHLIN: Thank you, Your Honor.

BY MR. McLAUGHLIN:

Q. Welcome back, Dr. Albini. We were at Slide 78 of your presentation here, and we're about to launch into discussing reasonable expectations of success with respect to

this obviousness ground.

Can you just give a brief summary of the data and the documents that we're about to walk through over the next few slides?

A. Yeah. These are documents dating from 2006 to 2009 that I think demonstrate the known efficacy at the time of both ranibizumab and aflibercept in treating DME and AMD, which would have given a POSA reasonable expectation of success.

Q. Let's go ahead and take a look at some of these articles. We've seen this one before, Do 2009. It's slide 79, DTX 3102.

Can you explain what you've presented here on Slide 79.

A. Yeah. Again, this is the Phase I study report authored by Dr. Do that describes a small study with a single injection of 4 milligrams of aflibercept, resulting in a significant visual acuity gains of eight letters.

Q. Turning to the next slide, Slide 80, can you describe what kind of data was presented in Dixon that would have given a POSA a reasonable expectation of success?

A. In Dixon there is disclosed published results from aflibercept AMD Phase II data showing visual acuity gains from -- in macular degeneration. And I think that, although these are two different diseases, they are both mediated by vascular endothelial growth factor, which is the target of both

of these therapies, and I do think that the success that was seen in macular degeneration was relevant to the reasonable expectation of success in DME regimens as well.

Q. Turning to Slide 81, you've had the opportunity to review internal Regeneron documents --

A. I have.

Q. -- in the process of formulating your opinions?

A. I have.

Q. And is DTX 8190, shown here on Slide 81, one of those documents?

A. That's correct.

Q. And on this document did Regeneron state that "We believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III and DME can be selected based on results of the Phase II study in patients with AMD"?

A. Yes. And I think that evidence is that the POSA as well would have used results from one disease state to infer reasonable expectations in the other disease state.

Q. And this document also states that "We consider this Phase II data as providing an adequate basis for dose selection for the Phase III DME program"?

A. That's exactly right.

Q. Turning to the next slide, Slide 82, can you describe what's set forth here on this slide in terms of the data from ranibizumab?

A. These are the results for the MARINA prospective randomized trial that was published in the *New England Journal of Medicine* with Rosenfeld as the lead author in 2006, and this was really game-changing data within our field, showing great visual acuity improvements with monthly doses of ranibizumab for wet macular degeneration. Again, a different disease but I think relevant across disease states, as evidenced by the Regeneron communication as well.

Q. And just to confirm, when you're referring to Regeneron, you're not suggesting that Regeneron -- that your reasonable expectation of success is coming from Regeneron's statements. Those are just confirmatory in nature for a POSA?

A. Yeah. My point is simply that it's reasonable to include the ranibizumab data when you're trying to make an opinion about the expectation of success of aflibercept. That's all.

Q. If we turn to Slide 83, can you also explain what's shown here and how that's relevant to reasonable expectation?

A. Again, this was a Phase I study, the READ 1 study, describing three monthly loading doses of ranibizumab followed by eight-week injection intervals, showing good visual acuity outcomes in diabetic macular edema.

Q. If we turn to Slide 84, going back now, is this an accurate summary of the data that you just walked through?

A. That's correct. So that there's -- what really,

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historically, were impressive visual acuity benefits compared to what was available for patients prior to the advent of these anti-VEGF therapies, that there was good success with either ranibizumab or aflibercept in either AMD or DME already available to the POSA.

Q. And did you have the opportunity to review Dr. Csaky's rebuttal opinions in this case?

A. Yes.

Q. Is that one -- is this, shown here on Slide 85, one of those rebuttal opinions?

A. That's correct.

Q. And here, do you agree with Dr. Csaky that concerns about overtreatment would have dissuaded a POSA from using five monthly loading doses in the treatment of DME?

A. I don't agree. I think that there were studies already available with ranibizumab with another anti-VEGF agent that showed that larger number of doses in diabetics were well tolerated. There was safety data already available from Phase I study with aflibercept showing adequate safety, and I certainly think that it was a concern, but I think that the addition of one or two more loading doses compared to other treatment regimens would not have dissuaded somebody from trying the regimens that are detailed in these patents.

Q. And do you agree with Dr. Csaky that use of intravitreal injections and potential side effects, like

elevated intraocular pressure, would have dissuaded a person of ordinary skill in the art from using five monthly loading doses in the treatment of DME?

A. I think that Dr. Csaky's comments in this regard were focused on the use of intravitreal steroids, which have a class effect of raising intraocular pressure. And I think they have limited relevance to anticipated complications for anti-VEGF agents, especially by the time that you get to 2010 and '11 when there's been such great experience in multiple trials conducted in thousands of patients with these agents without seeing this type of pressure elevation that's seen with intravitreal steroid use.

Q. And do you agree with Dr. Csaky's opinions that concerns about systemic side effects would have dissuaded a person of ordinary skill in the art from using five monthly loading doses to treat DME?

A. I think that, although there was always concern for systemic side effects, the addition of one or two loading doses would not significantly dissuade the POSA from increasing the number of injections by one or two, especially with the perceptions that we've talked about, the increased efficacy of doing that and the anticipated necessity for more injections that are seen in DME. So overall no, I don't think that this would have dissuaded the POSA from using more injections. And historically that's what happened.

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Q. Was it also the case that at that time there were trials, including trials run with aflibercept by Regeneron, that were including monthly dosing regimens that involved monthly dosing out to one year and more?

A. That's true.

Q. Now, let's talk about some of that data that you talked about regarding the safety and -- the safety of aflibercept and what was known in the prior art.

Can you explain what you've shown here on Slide 88.

A. This is the article by Do from 2009 showing an early phase study with 4 milligrams of aflibercept. We've seen this before. And it evidences that there were no serious adverse effects in this small study. And they had a reasonable expectation of safety that allowed them to move on to a Phase II study following this.

Q. Based on that, would a POSA have a reasonable expectation of success?

A. I believe they would go through the same thought process and would reasonably have a good -- a reasonable expectation of success, yes.

Q. Turning to the next slide, can you -- this is Slide 89. Can you tell the Court what Dixon disclosed about the safety of aflibercept?

A. Again, in this Phase II study of VEGF Trap-Eye and CLEAR-IT, it remarks that the therapy seems to be well

tolerated, with no serious drug-related adverse events.

Q. And do you agree with Dr. Csaky that a person of ordinary skill in the art would have felt constrained to just three to four monthly loading doses when designing a DME treatment regimen?

A. I don't see anything in the science or in the prior art that would limit the comfort with only three or four but not five loading doses.

Q. So is it true, Dr. Albini, that there would have been a range of monthly loading doses that a POSA would have envisioned for use in treating a patient with diabetic macular edema?

A. I think that this slide nicely encompasses that range. It demonstrates it. There were available, as we've seen, the CLEAR-IT 2 data in AMD with four monthly loading doses, the DA VINCI study in DME with three monthly loading doses with prn dosing following three monthly loading doses.

And in a retinal vein occlusion study that is described in the prior art, even six monthly loading doses followed by prn treatment were all already in the literature and tried. And so I think that anywhere in this range would have been obvious to the POSA in that time period.

Q. And, again, you've had the opportunity to review Regeneron internal documents in this case?

A. Yes, I have.

Q. Is this one of those documents, DTX 4129?

A. Yes, it is. And it shows that Regeneron internally claimed that a target scenario for their novel therapy would be no more than three to six doses, including monthly loading doses for the first three months and described an induction period in the first six months; so saying that they were working -- or demonstrating that they were working within the same dosing range.

Q. Thank you.

And now we're going to move on to another obviousness ground. This is on Slide 93 going to Slide 94.

Before we dive into this ground, I just wanted to make clear. You understand -- or you were led to understand and asked to assume for purposes of this ground only that a priority date of July 12th, 2013, applies to the asserted claims?

A. That's my understanding, yes.

Q. So turning to Slide 95 and looking at the Do 2012 reference here, DTX 3105, can you explain what's shown here on this slide?

A. Sure.

Do describes a study in treating diabetic macular edema with VEGF Trap-Eye or aflibercept, meaning that highlighted part of the Claim 10.

Q. What else did Do 2012 disclose?

A. It disclosed an intravitreal injection of the 2-milligram dose.

Q. And turning to the next slide, can you explain what's shown in this graphic here, Slide 97 from DTX 3105?

A. These are the treatment arms for the study disclosing that in the 2-milligram arms there is an arm with regular -- four weekly injections, an arm with three loading doses and then injections given every eight weeks. And there is an arm with prn dosing described where there are three loading doses given by necessity. And then subsequent to that, there are visits at which there may or may not be doses on any particular visit.

In that arm that would include the possibility of five loading doses with a q8-week interval subsequent to that, as we've described a couple times already in this testimony.

Q. If we were to turn to the next slide, does this slide show the results from that Phase II study?

A. Yes. This shows the mean number of injections was 7.4, greatly less than the number of injections that were seen in the Q four months. So this describes a protocol where fewer injections were required.

Q. And the 7.4 injection number you're referring to, that was from the prn --

A. That's correct.

Q. -- group?

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A. That's correct.

Q. This also discloses that in the 2q8 group they required a mean of 7.2 injections over the first year?

A. That's correct.

Q. Did you have a sense for how that compares to the number of injections that patients received in a prn regimen in the AMD clinical trials?

A. Yeah. Dixon teaches that in the AMD VEGF Trap-Eye there was a mean number of 5.6 injections in prn dosing of VEGF Trap-Eye. And for DME it was 7.4, which was in line with the anticipation, as we discussed before, that in DME more intravitreal injections were going to be needed to achieve optimal treatment of patients than there are in AMD.

Q. What conclusion would a POSA draw from that data?

A. One of the conclusions would be that a greater number of loading doses would certainly be likely to be beneficial in developing a treatment strategy for DME.

Q. If we take a look at the data from that Phase II trial displayed here, the visual acuity data, can you explain or walk the Court through what's shown here?

A. So one can see the outcomes of the four arms with aflibercept showing an improvement in visual acuity that is maintained then through the life of this 52-week study. And in the laser control arm there is ultimately a decrease of vision starting at about 28 weeks going on.

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Q. This is on Slide 101, and this data is from DTX 3105?

A. That is correct.

Q. If we flip forward to Slide 102, can you tell the Court what you've shown here on Slide 102.

A. Highlighted in green is the visual acuity outcomes line from the 2q8 arm. This is 2 milligrams given with three monthly loading doses and then given q8 weeks thereafter. And one can see that, in between the injections given at Week 12 and Week 20, at Week 16 there is a drop in visual acuity, suggesting that the addition of a subsequent dose given at that week would improve the visual acuity.

I think this data could have been interpreted and would have been interpreted by the POSA, especially in combination with the other points that we've made, that an additional loading dose would be a very effective thing to try in treatment strategies for diabetic macular edema.

Q. And is that additional loading dose shown here in green?

A. That's correct.

And that would essentially be consistent with the therapy of five loading doses followed by q8-week loading, essentially indistinguishable from that treatment strategy.

Q. So can you summarize or provide your overall conclusion with respect to the DME -- Claim 11 of the '601 patent with respect to Do 2012?

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A. I think that the Do article gives a reasonable expectation of success and that it would be obvious to the POSA, having read that article, that a more robust dosing strategy would be needed with more loading doses than have been used with AMD, given the data that showed that it is more difficult to achieve optimal visual acuity benefits with fewer injections in DME relative to AMD. So I think the POSA would have seen that and designed a strategy with more loading doses and could have designed a strategy with a q8-week loading arm thereafter as well.

Q. Would that same analysis apply to Claim 19 of the '601 patent as well?

A. That's correct.

Q. Would that same analysis apply to Claim 25 of the '572 patent?

A. That's correct.

Q. We're going to switch gears now and leave the DME-DR treatment claims and move over to Claim 6 of the '572 patent.

Can you briefly explain to the Court the opinions you're going to be offering in this section of your testimony.

A. These opinions are largely based -- as I think we mentioned already early on, on the opinions of Dr. Rabinow, who's a formulation expert, regarding the anticipation and obviousness of the claim regarding isotonic preparation of aflibercept.

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Q. Do you understand Slide 108 to summarize Claim 6 and the claims from which it depends?

A. That's correct.

Q. Do you understand that, with its pretrial order submissions, Regeneron provided a compiled version of Claim 6 that incorporated the limitations of the claims from which it depends?

A. Yes.

Q. Is that what you have shown here on Slide 109?

A. That's correct.

Q. Is it okay if we use this version of Claim 6 to conduct your analysis in this section of your presentation?

A. Yes.

Q. Do you also understand that Regeneron has stipulated to the invalidity of certain claims, including Claims 1 through 5 of the '572 patent?

A. Yes.

Q. So is it okay if we mark with highlighting the material -- or the subject matter of Claim 1 and the compiled Claim 6 in yellow highlight as shown here on Slide 111?

A. Yes.

Q. Are you aware also that the Court issued a claim construction, also called a Markman opinion, that held that the visual acuity elements of the claims do not carry any patentable weight?

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A. Yes, I am aware.

Q. And you understand that Regeneron also represented to the Court that the visual acuity limitations also did not carry any patentable weight?

A. That's correct.

Q. So in light of that, is it okay if we highlight in blue that visual acuity element of compiled Claim 6?

A. Yes.

Q. So, with that, can you tell the Court what remains of Claim 6?

A. The text highlighted in green here stipulating that aflibercept is formulated as an isotonic solution.

Q. Turning to the next slide, Slide 116. So even though this material has been stipulated, we're still going to walk through very quickly where these dosing regimen elements are found in Dixon.

Can you explain to the Court what you have shown here on Slide 116.

A. This is the Dixon reference that we looked at numerous times in this presentation. And it does describe a Phase III study for treating an angiogenic eye disorder here. And so we can check off the first check mark there.

Q. And that's -- you're looking at the title of DTX 0204?

A. The "VEGF Trap-Eye for the treatment of neovascular

age-related macular degeneration" is an angiogenic eye disorder, yes.

Q. The Phase III regimen called out there on the bottom of the slide from DTX 0204, that also describes method of treating an angiogenic eye disorder?

A. Absolutely.

Q. Can you describe what's shown here on Slide 117 from DTX 0204?

A. A Phase III study using 2 milligrams of aflibercept, or intravitreal VEGF Trap-Eye, for the treatment of wet macular degeneration.

Q. And then does Dixon also disclose a treatment method that involves sequentially administering an initial dose followed by one or more secondary doses of 2 milligrams of aflibercept wherein each of those secondary doses is administered approximately four weeks following the immediately preceding dose?

A. That's right. It does that in the highlighted text there.

Q. And the highlighted text is the text following three monthly doses?

A. That's correct.

Q. If we go to the next slide, does Dixon also disclose treatment in which those secondary doses are followed by one or more tertiary doses of 2 milligrams of aflibercept wherein each

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of those tertiary doses are administered approximately eight weeks following the immediately preceding dose?

A. That's correct.

Q. And then, again, you understand the visual acuity limitation to not carry any patentable weight in this claim?

A. That's correct.

Q. So if we turn to the last element, can you read for the Court what the last element of compiled Claim 6 is.

A. Aflibercept is formulated as an isotonic solution.

Q. And with respect to that portion of the claim, did you rely on the opinions of Dr. Barrett Rabinow?

A. Yes, I did.

Q. And are those opinions shown here on Slide 121?

A. That's correct.

Q. And does he cite to a Dixon article?

MS. OBERWETTER: Objection. Your Honor, at this point, because I don't know precisely what Dr. Albini is going to say in response to any particular question, we have an objection to this witness testifying about the reference that is listed here, Dixon, insofar as his testimony would be as to whether it discloses an isotonic solution for two reasons.

First of all, his report itself does not contain an opinion that the POSA would have understood Dixon to make such a disclosure.

And, second, we believe, from a formulation

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standpoint, he is not qualified to render such an opinion.

THE COURT: Understood.

Counsel, aren't we going to hear this from Dr. Rabinow?

MR. McLAUGHLIN: You are going for hear all about isotonicity from Dr. Rabinow. Dr. Albini will be talking about his understanding from the viewpoint of an ophthalmologist of how he would read that aspect of Claim 6 in conjunction with --

THE COURT: Has he offered any opinions in his reports on that?

MR. McLAUGHLIN: He has. He's talked about Dixon. He's talked about the language from Dixon. And we can call that up.

THE COURT: I think I'd like to see what he said in his report, his opinions, because references are one thing, but --

MR. McLAUGHLIN: Sure, sure. Permission to approach?

THE COURT: Granted.

Yes, Ms. Oberwetter?

MS. OBERWETTER: I don't know if I'm on or not.

I believe we're going to be looking at that paragraph, or the same version, elsewhere. But there is a longer paragraph. And I believe that is the entirety of the opinions on it. And there is nothing in which he says he is opining on whether Dixon disclosed an isotonic solution from

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the standpoint of a POSA. And it is a confusingly worded paragraph, but that particular statement is conspicuously not present. As you read it, I will flag that for you, Your Honor.

THE COURT: Okay.

Counsel?

MR. McLAUGHLIN: Well, it's a confusingly worded claim, but what I will direct you to is Dr. Albini's opinions at paragraph 556 of his opening report. That should be on the first tab of the binder that we've handed Your Honor. That's on page 196 of the document. It's Exhibit page 197, DTX 7069.

You can see that Dr. Albini, he does cite Dixon about two-thirds of the way down that paragraph. Dixon is an article that's directed to retinal physicians and people in the ophthalmological community, directed to people just like Dr. Albini. This is language that he would have reviewed in reviewing such an article, and it's language that he would understand as a person who administers these types of drugs on a regular basis.

MS. OBERWETTER: Your Honor, it's not that the word Dixon isn't in this paragraph; it's that there's no opinion that the POSA would have understood the disclosures in Dixon. That is a conspicuous and notable absence compared to other portions of his report, and it's obvious the reason why, because at the time he wrote the report he was relying on Dr. Rabinow whose testimony you will hear forthcoming. There's

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a reason they want Dr. Albini now to be offering that opinion, and it's not in his report.

THE COURT: And what is that reason?

MS. OBERWETTER: That Dr. Rabinow's testimony on that point did not hold up, Your Honor.

THE COURT: I guess ultimately I will be the judge of that, but -- I understand there will be a challenge to that, Ms. Oberwetter. I'll flag that as a preview.

MS. OBERWETTER: Mutual previews, Your Honor.

THE COURT: Great. Great. Thank you.

Yes, counsel?

MR. McLAUGHLIN: I just want to reiterate Dr. Albini, he's somebody that's administered these formulations on a regular basis for the last 15, 20 years.

THE COURT: He concedes in the report -- and, again, I just read paragraph 556 of Dr. Albini's report -- that formulations are not his bailiwick, for lack of a better term.

MR. McLAUGHLIN: They're not his bailiwick, but he's certainly somebody that's qualified to at least talk about the administration of these formulations, how you expect patients to respond to these formulations that are being injected into their eyes. And he's got publications where he talks about -- where he compares isotonicity to osmolarity of different formulations.

THE COURT: Well, I guess my question then, Counsel,

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is what is the relevancy to the questions before this Court? Because paragraph 556, again, of Dr. Albini's report concludes that it's his opinion with respect to the VIEW clinical trial, et cetera -- and Ms. Oberwetter is right. There's no reference to what a POSA would think or expect at that juncture.

With all due respect, Doctor, I'm curious as to what his individual opinion is, what its relevance is.

MR. McLAUGHLIN: That's -- and a lot of this is just the nature of this bizarrely worded claim to begin with. But leaving that aside, he does rely on Dr. Barrett Rabinow to then talk about does this language communicate to a POSA that this is an isotonic solution.

So he's not going to say that those words tell somebody it's isotonic. He relies on Barrett Rabinow for that. But then taking that knowledge from a formulation expert as one would -- as a doctor would who is looking to gain more information from a formulation that he's administering, using that knowledge from Barrett Rabinow, which is what he does in his report as shown here in paragraph 556. He clearly refers to Dr. Rabinow's opinion and his opinions about the isotonicity of this formulation. He then relies on an expert's expert opinion --

THE COURT: Which he's entitled to do.

MR. McLAUGHLIN: -- and incorporates it into his own opinions about Claim 6 overall.

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THE COURT: Anything further, Ms. Oberwetter?

MS. OBERWETTER: Only, Your Honor, that he doesn't rely on Dr. Rabinow; he defers to Dr. Rabinow on that question and does not then frame any opinion that he is offering in his report from the standpoint of a POSA on the method of treatment patents. So that opinion is absent, and this is an effort to backfill that.

THE COURT: Understood.

I'm going to overrule the objection at this point with the coming preview with respect to Dr. Rabinow. And the Court will afford this evidence the weight it believes appropriate. But objection noted.

MS. OBERWETTER: My only remaining question is may I voir dire the witness on his formulation expertise?

THE COURT: Yes, you may.

Counsel, if you wouldn't mind abdicating the podium. Thank you.

I would note, Ms. Oberwetter, that the Court has not qualified Dr. Albini as an expert in any fields related to formulation. But with that, a limited voir dire, I think, would be appropriate.

MS. OBERWETTER: Yes, Your Honor.

VOIR DIRE EXAMINATION

BY MS. OBERWETTER:

Q. Good morning, Dr. Albini.

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A. Good morning.

Q. You agree, and I think we've heard you say earlier today, that you are not a formulation expert, correct?

A. That is correct.

Q. And, in fact, in your report you specifically rely on and defer to Dr. Rabinow in connection with the things that you say about an isotonic solution, correct?

A. That is correct.

Q. Okay. You are not an expert in the design of therapeutics, correct?

A. I'm not an expert in the design, although I read material about such designs on a regular basis when treating patients with pharmacologic agents.

Q. Okay. And whatever you may read, you're not an expert in that field, correct?

A. That is correct.

Q. Okay. And, in fact, you've testified several times in other proceedings on behalf of Mylan, correct?

A. That is correct.

Q. Okay. Including in IPR proceedings related to the method of treatment patents, some of which are at issue here; some of which are not, correct?

A. I have. That is correct.

Q. And when you had your deposition -- if I can turn you back in time to a January 20th, 2022, deposition, you were

asked some questions in that proceeding about how the osmolality of a drug could affect its half-life.

Do you remember that from 2022?

A. Not specifically. I'm sorry. No.

Q. Okay.

If we could pull up the page from that deposition page.

Let me just start with the front, Dr. Albini. This was a deposition you testified in on January 20th, 2022, correct?

A. I have no reason to doubt that. Yes. Correct.

Q. You do recall testifying in a case at approximately that time?

A. Yes.

THE COURT: Let me interject just because I saw the word "confidential" on there. Do we need to seal the courtroom for any of this discussion?

MS. OBERWETTER: Thank you for asking, Your Honor. No, this is fine for us to have up on the screen.

THE COURT: I'm not doubting your statement. But in a trust-but-verify mode, I'll ask Mylan if they have any thoughts to the contrary on that.

MR. McLAUGHLIN: With respect to the confidentiality, Your Honor?

THE COURT: Yeah. Do we need to seal the courtroom

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for a discussion of this testimony? It was an IPR proceeding, I believe.

MR. McLAUGHLIN: No.

THE COURT: Okay. All right.

So, Ms. Oberwetter, my apologies for trusting but verifying. Go right ahead.

MS. OBERWETTER: Always appreciated, Your Honor.

BY MS. OBERWETTER:

Q. If we take a look at page 125 of this transcript. And you recall you were being questioned in that deposition by another attorney for Regeneron, correct?

A. That is correct. I do recall that.

Q. And you were asked in that proceeding a question about whether the composition of an intravitreally administered drug, including its osmolality and excipients, can affect the half-life of the drug in the vitreous, correct?

Do you see that question?

A. Let me just take a second to digest that. Hold on one second.

Okay. I've read the question.

Q. And your answer was you're getting into some very technical issues, correct?

A. That is correct.

Q. And then if we scroll down to the next several lines, you said, "It happens that, as I sit here before you today, I

think off the top of my head that osmolality would not affect half-life, although it would have many effects. But I could be wrong on that. And, again, I am not an expert in the design of therapeutics."

Do you see that?

A. That is correct.

Q. And then you said, "But as a clinician that uses angiogenic drugs and that has written these declarations, I don't think that sounds reasonable. But I don't really have a strong opinion or a lot of experience in that area."

Correct?

A. That is what I said.

Q. And those are answers that you gave with respect to the osmolality of the drug you were being asked about, correct?

A. I don't recall if this was in reference to a specific drug.

Q. Okay.

MS. OBERWETTER: Thank you, Your Honor. That is the extent of my questions on this topic.

THE COURT: Understood. Thank you.

The Court's ruling with respect to the objection remains.

Counsel, you may resume your direct.

MR. McLAUGHLIN: Thank you, Your Honor.

DIRECT EXAMINATION (Resumed)

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BY MR. McLAUGHLIN:

Q. So I will resume my direct, but in the meantime I just want to ask you, Dr. Albini, a few questions about your background. I understand that you don't consider yourself an expert in the design of therapeutics, but would you consider yourself to be knowledgeable about the impact of the injection of an isotonic or nonisotonic solution into the eyes of one of your patients?

A. I would consider myself being an expert in the use of these drugs. The question of the importance of the isotonicity and various options for choosing different osmolarity of agents, I'm not an expert in those issues, but I certainly feel myself confident to describe the use of drugs with formulations that have been approved.

Q. In the course of your work and your research, have you published -- did you publish an article in 2014 called "Ziv Aflibercept as a Possible Alternative to Aflibercept"?

A. Yes, I did.

Q. Do you recall publishing that article?

A. I do.

Q. Do you recall who you published that article with, who your coauthors were?

A. I think my coauthors, as I recollect, were Andrew Moshfeghi, and Jonathan Chang.

Q. If you can recall -- but we can also put the article

up for you, if you'd like, but can you recall what the subject matter of that article was?

A. The subject matter was that there was some early interest, particularly in Brazil as I recall, for using Regeneron's product ziv-aflibercept, which is designed for intravenous use as a cancer therapeutic, to aliquot it in a very analogous fashion as bevacizumab is aliquoted for intravitreal use, to use ziv-aflibercept off-label, again with the goal being of obtaining the -- being able to use the VEGF Trap molecule at a reduced price for patients that could not meet the price point for aflibercept.

Q. And is this a copy of your article shown here?

A. That's correct.

Q. And if we could turn to the second page, I don't know if there's a way to -- is there a way to zoom that in?

So in this top paragraph in the upper left of page 68 of that article, do you discuss the osmolality of ziv-aflibercept versus aflibercept?

A. That is correct.

Q. What did you conclude about the osmolality of the two different formulations?

A. I haven't actually read this whole thing in a while, but as I recollect, I remember having a concern that the higher osmolarity of ziv-aflibercept relative to aflibercept that's injected in the eye, I think the numbers are there,

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815 milliosmoles relative to 260 -- or compared to 260 milliosmoles, that this higher osmolarity may cause a clinical problem in that I had been familiar with work that was done by Dr. Marmor in the 1970s -- and, honestly, right now sitting here, I can't remember what the point of this paper was.

But I remember that the higher osmolarity of intravitreal injections given by Dr. Marmor in -- I think it was a monkey study, I want to say; it's been many, many years since I've read this paper -- that in that -- with that higher osmolarity, there was a risk, a very high risk, for retinal detachment.

And I remember that some of us who were pondering this issue, including me and my coauthors here, were wondering whether ziv-aflibercept was produced with higher osmolarity just to avoid the possibility of intravitreal injection.

So that's my recollections on this issue, but I think I was concerned in this particular case about higher osmolarity given my prior familiarity with work done by Dr. Marmor, as was cited in this article.

Q. Okay. Now, a few minutes ago you said you couldn't remember what this article was about.

You were referring to Dr. Marmor's 1979 article, not the one in front of you here?

A. Thank you for the clarification. Absolutely, yes.

The Marmor article that -- I have not read that in -- probably since this article was published.

MR. McLAUGHLIN: Okay. With that, with Your Honor's permission, I'm going to resume my direct. See if I can recall where we left off.

BY MR. McLAUGHLIN:

Q. So Slide 121, we were talking about Dr. Rabinow's opinion. This is his opinion that you relied upon in formulating your opinions with respect to Claim 6?

A. That's exactly right.

Q. Okay. And this passage that he cites from Dixon, that comes from DTX 0204?

A. That's correct.

Q. If we could pull that up so we can show the Court this language.

This comes -- this is language from Dixon. That's that 2009 article regarding VEGF Trap-Eye; is that correct?

A. That's correct.

Q. What does Dixon say about VEGF Trap-Eye and its formulation?

A. He teaches that it is formulated with different buffers at different concentrations suitable for the comfortable, nonirritating direct injection into the eye.

Q. Going back to the slide deck here, turning to the next slide, Slide 122, did you also rely on the Eylea label

when formulating your opinions in this case?

A. That's correct.

Q. And is this a snapshot of that Eylea label, DTX 3316?

A. Yes, it is.

Q. And what's this say about Eylea in DTX 3316?

A. It says that it is formulated as an iso-osmotic solution.

Q. And in your opinion as an ophthalmologist, is the FDA-approved formulation typically the one that was used in the pivotal Phase III trials that were responsible for that FDA approval?

MS. OBERWETTER: Objection, Your Honor. That's a fact question, not an opinion question if he's asking about this trial.

THE COURT: Repeat that question, Counsel, please.

BY MR. McLAUGHLIN:

Q. In your opinion as a treating physician, is the FDA-approved formulation typically the one that's used in a drug's pivotal Phase III clinical trials?

A. That's my --

THE COURT: One second, Doctor. Sorry.

Objection overruled.

Now you can answer. Thank you.

THE WITNESS: That's my opinion and would be the opinion of the POSA.

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BY MR. McLAUGHLIN:

Q. Did you review Dr. Csaky's rebuttal expert report?

A. Yes, I did.

Q. And did you review the portion in which he was rebutting -- he was providing his rebuttal opinions with respect to Claim 6 of the '572 patent?

A. Yes, I did.

Q. Did Dr. Csaky provide any rebuttal opinion indicating that the FDA-approved formulation of aflibercept was not the one used in the Phase III clinical trial?

A. No, he did not.

Q. Now proceeding forward and now relying upon what you learned from Dr. Barrett Rabinow, the formulation expert that's going to be offered by Mylan, can you provide a summary of your final opinion with respect to Claim 6 of the '572 patent?

A. Yeah. I believe that Claim 6 is anticipated by Dixon, given that a suitable, comfortable, nonirritating direct injection of the eye would inherently be isotonic, as taught to me by Dr. Rabinow.

Q. And now we're going to shift focus a little bit and talk about obviousness of Claim 6 of the '572 patent.

So turning to the Slide 126, can you briefly summarize the opinions you're going to provide in this section of your testimony?

A. Given the text that we've discussed and the Dixon

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reference, combined with a source used by Dr. Rabinow, Hecht, it is -- it becomes obvious that the comfortable, nonirritating, safe for intravitreal injection solution described by Dixon for aflibercept would be isotonic.

Q. We're going to be using the same compiled Claim 6 for your analysis in this portion of your presentation?

A. Yes.

Q. And that's shown on Slide 127?

A. Yes.

Q. So in your anticipation opinions you walked through each disclosure from Dixon with respect to these dosing regimen elements of Claim -- compiled Claim 6; so we won't do that again. But you understand -- or you're going to be applying that same reasoning in your obviousness section?

A. That's correct.

Q. You have the same understanding that the visual acuity limitation of this claim does not have -- does not carry patentable weight?

A. That's correct.

Q. Now, with respect to the isotonic solution aspect of Claim 6, in your opinion, would a POSA -- again, you relied on the opinion of Dr. Rabinow in this part of your -- formulating your opinions as well?

A. That is correct.

Q. And you incorporated his opinion regarding the Hecht

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reference?

A. That is correct.

Q. In your opinion, would a POSA have been motivated to administer a formulation of aflibercept that was comfortable and nonirritating?

A. That's correct.

Q. And do you intend to rely upon Dr. Rabinow's opinion and trial testimony regarding the disclosures of the formulation prior art and reasonable expectation of success at formulating isotonic ophthalmic formulations?

A. Yes, I do.

Q. And assuming that Dr. Rabinow's later testimony shows the obviousness of formulating an ophthalmic formulation to be isotonic to be obvious, what is your final opinion regarding Claim 6 of the '572 patent?

A. That Claim 6 is both anticipated and obvious given the Dixon prior art and the Hecht prior art.

Q. Now we're going to shift gears now and talk about the secondary considerations opinions that you provided. So we're now Slide 134.

Do you understand that, in rebuttal to your opinions, Dr. Csaky provided five different opinions on secondary considerations?

A. That is correct.

Q. And are those five different secondary considerations

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listed here on Slide 135?

A. Yes, they are.

Q. That includes long-felt need, failure of others, unexpected results, industry praise, commercial success?

A. That's correct.

Q. Do you understand, when formulating your final obviousness opinions, that you are to consider -- to take into consideration any evidence of secondary considerations?

A. That's my understanding.

Q. But you understand that those secondary considerations must have a demonstrated nexus to the claim elements at issue?

A. That is correct.

Q. Now I'd like to start by reviewing again what was known and disclosed in the prior art before the 2011 -- 2010-2011 time frame.

Could you briefly describe what's shown here in terms of what was known about extended dosing regimens in the art before 2010?

A. This is a roundtable from Retinal Physician from 2007 that demonstrated that, as early as 2007, there was a variety of extended dosing intervals, including treat and extend, the prn dosing, that were already in use by the leading vitreoretinal surgeons at that time.

Q. Can you explain to the Court what's shown here on

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Slide 137?

A. This -- I believe we've seen this study before as well -- is a study documenting the treat-and-extend approach use with bevacizumab but again showing that the treat-and-extend dosing strategy was -- already had a term and was understood to be a certain type of dosing strategy by the POSA in 2009, as evidenced by its mention here in this article.

Q. And is that the same type of treat-and-extend regimen that was disclosed or discussed by Dr. Brown that we saw in a couple slides previous?

A. That's correct.

Q. Turning to Slide 138, can you describe what's shown on this slide?

A. This slide shows a preferences and trends survey from the American Society of Retinal Specialists in 2009, documenting that, in this survey with 433 respondents, 91 percent of practicing vitreoretinal surgeons in the United States surveyed at that time were using prn dosing or an extended dosing interval well before 2010.

Q. And how many doctors were using a fixed dosing regimen at that point?

A. Injection given every four to six weeks regardless of lesion activity was down to 5 percent by 2010.

Q. And just to clarify, what we talked about on this previous slide is from DTX 4192; is that correct?

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A. That's correct.

Q. Now, jumping to Slide 139, can you describe what's shown on this slide?

A. This is a 2010 preferences and trends survey asking similar question, describing treatment strategies for exudative macular degeneration, or wet AMD. And you see that 43 percent of respondents in 2010 are using prn dosing and 34 percent are using treat and extend already.

Q. This is from DTX 2040, page 24?

A. That's correct.

Q. And turning to Slide 140, can you describe what's shown here?

A. This is the 2011 survey, probably data gathered in the first part of 2011. They're usually reported towards the end of the year at the meeting -- well, middle to end, summer to fall. I don't remember exactly when 2011 meeting took place. But most doctors use prn, 32 percent; and treat-and-extend regimen is being used by 60 percent; and, again, less than 5 percent of physicians are using a follow-and-treat-monthly, active or not.

Q. This is from DTX 4194?

A. That's correct.

Q. And turning to Slide 141, can you tell us a little bit more about the PrONTO study that you discussed in your expert reports?

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A. This is a trial result from the two-year data from the PrONTO study, which again was a prospective study using ranibizumab in a prn fashion after loading doses, showing very good visual acuity gains with prn dosing at 24 months, 11.1 letters of visual acuity benefit were obtained; 43 percent of patients improved by 15 letters or more -- which were, I think, very impressive results at the time -- showing that this could be achieved with an extended dosing regimen.

Q. Is that also summarized here on Slide 142, DTX 3131?

A. That's right. But the highlighted text here makes the point that, with fewer than half the number of injections in the PrONTO study as compared to the MARINA and ANCHOR studies, very similar visual acuity gains were obtained.

Q. If we turn to the next slide, this is also a selection from DTX 3131; is that correct?

A. That's correct.

Q. Can you tell us what's shown on Slide 143.

A. This shows a text from the paper detailing that the PrONTO study was designed to minimize the number of treatments but not the number of visits and discussing already other treatment strategies that may yield similar or even better visual acuity outcomes that require fewer visits, and it discusses the treat-and-extend treatment strategy that we've discussed a number of times and that this was in -- published in 2009 already.

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Q. And can you just briefly summarize then for the Court why the PrONTO results were important?

A. I think in regards to this testimony, they were important because they detailed that in 2009 the need for an extended dosing regimen was already met. And in terms of the weight of those secondary considerations, the variable dosing regimen had already been achieved and in use and certainly would have been readily envisioned by the POSA.

Q. And is this study leading the physicians away from using fixed regimens like monthly dosing?

A. I think very quickly after these data were available, there was a shift. Whether that's causation or just coincidence, I guess is debatable. But certainly it seemed that at around the same time period, physicians started to use prn dosing regimens as evidenced by the *Retinal Physician* roundtable that we've discussed a few times already.

Q. If we turn to the next slide, this is Slide 145, the Engelbert reference, DTX 3215, can you explain what you've shown here?

A. Yea. This paper published in 2010 just evidences that PrONTO-style dosing has become popular within the retinal community. That's the extended prn dosing that we've been talking about. And it also details treat-and-extend dosing with fewer patient visits in addition to fewer monthly injections. So that concept was already there and practiced in

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2010.

Q. And to clarify, DTX 3215 also specifies that, as a result of the PrONTO study, PrONTO-style dosing has become popular in the retina community?

A. That is correct.

Q. Is that consistent with your recollection as well?

A. Yes.

Q. Then, again, you've had the opportunity to review internal Regeneron documents in the process of formulating your opinions; is that correct?

A. That's correct.

Q. Are one of those documents shown here, Slide 146?

A. That's correct.

Q. Is this a 2007 email from George Yancopoulos?

A. Yes.

Q. Is one of the statements that he makes in this email "published prn approaches, which are being widely adopted as current standard of care"?

A. That's correct.

Q. Now, did you review Dr. Csaky's secondary considerations opinions in the process of formulating your reply opinions in this case?

A. Yes, I have.

Q. Is one of those opinions shown here regarding long-felt need from Dr. Csaky?

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A. That's correct.

Q. So in your opinion, as of the 2010 time frame, was there a long-felt need for an extended dosing regimen for the treatment of an angiogenic eye disorder?

A. I don't think so. I think, given everything that we've looked at right now, you can see that, as early as 2007/2008, that extended dosing regimens were very commonly employed and this need had already been met.

Q. Turning to Slide 148, do you understand that Dr. Csaky also offered opinions regarding purported failure of others?

A. Yes, I do.

Q. Do you agree that there was a failure of others to achieve extended dosing regimens before 2011?

A. I do not. I think that we've detailed a number of studies that have showed success with very good visual acuity outcomes with extended dosing regimens. And certainly given the data that we've gone through in a number of studies with ranibizumab and aflibercept in DME and in AMD, I think there was a reasonable expectation of success that a POSA would have had for an extended dosing interval.

Q. And is this an accurate summary here on Slide 149 of some of the disclosures of extended dosing regimens that were known and being practiced prior to 2011?

A. That's correct.

Q. That includes those -- some of the different scenarios that were offered in the 2007 *Retinal Physician* article?

A. That is correct.

Q. And that includes the treatment of DME using ranibizumab and Lalwani 2009?

A. Yes.

Q. Does it also include the treatment of AMD using various regimens in Dixon 2009?

A. Yes.

Q. Does that include the treatment, including the disclosure of treat and extend, in Spielberg 2009?

A. Yes, it does.

Q. Treat and extend was one of the same regimens that was disclosed in the 2007 *Retinal Physician* article?

A. Yes. That was disclosed by Dr. Brown in particular, yes.

Q. And was this also confirmed by PAT Surveys in the 2010-2011 time frame?

A. It was confirmed that these were very popular treatment strategies in those years, yes.

Q. Now I'd like to shift gears and talk a little bit about unexpected results.

THE COURT: Counsel, before we do that, if we're gear-shifting again, is this a good spot for a lunch break?

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MR. McLAUGHLIN: It is.

THE COURT: Perfect.

Doctor, we're going to take a break. As I advised, I think, Dr. Trout yesterday or some others, they are permitted to feed you, but they're not permitted to talk to you. And they are hereby ordered to feed you but, otherwise, not talk to you.

But we'll take a lunch break.

No one can talk to you because you're midstream on your testimony, but you're free to step down, sir.

THE WITNESS: Fair enough. Thank you.

THE COURT: Thank you.

Counsel, let's take a break until 1:00 from our perspective, and then we'll resume with Dr. Albini's testimony. Thank you all very much.

(A recess was taken from 12:24 p.m. to 1:08 p.m.)

THE COURT: Counsel, are you ready to resume?

MR. McLAUGHLIN: We are, Your Honor.

THE COURT: You may proceed.

BY MR. McLAUGHLIN:

Q. Welcome back, Dr. Albini.

A. Thank you.

Q. So can I go to Slide 147, please.

Just want to make sure that we wrap things up here.

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Now, going back to Dr. Csaky's rebuttal opinion with respect to secondary considerations, do you agree that there was a long-felt need for an extended dosing regimen for the treatment of angiogenic eye disorders by the 2011 time frame given all the material that we reviewed in the slides prior to this?

A. I think it's been fairly well documented that that need had been answered by 2011.

Q. Thank you.

And going forward to the next slide, Slide 148.

And do you agree with Dr. Karl Csaky, Regeneron's expert, that there was a failure of others to achieve extended dosing regimens with ranibizumab by 2010-2011?

A. I think that there were a number of successes, as we've discussed throughout this testimony.

Q. And then I think we were turning to unexpected results when we broke for lunch. So let's go back to Slide 150 here in front of you.

This is showing DTX 0204, the Dixon reference. Can you describe what's shown here in this section of Dixon.

A. In this section of Dixon he's describing the CLEAR-IT 2 Phase II study, which utilized a four monthly loading doses followed by prn dosing and achieved good visual acuity outcomes.

Q. If we turn to the next slide, are these some of these outcomes that you're referring to?

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A. That's correct. In that arm with q4 loading doses and prn treatment thereafter, patients achieved mean improvement of nine ETDRS letters, which is a very good visual acuity result, with 30 percent gaining three lines or more of vision by 52 weeks. So I think these were excellent results.

Q. And is this -- can you describe what's set forth here on Slide 152 of your presentation.

A. Yeah. This details the clinical trial results that would have been available to the POSA prior to the filing patents at issue showing very good visual acuity results with a number of different regimens across diseases and across agents, again, I think really making it difficult to make an argument that good results were unexpected.

Q. What else did Dixon show about the frequency of the injections that were required for reaching those visual acuity outcomes that they saw?

A. That patients were receiving 2-milligram injections with, on average, 1.6 injections over the loading phase time. So over the 40-week prn loading protocol, patients only needed 1.6 injections on average, again showing that, even with extended treatment, good visual outcomes were obtainable.

And the median time to first reinjection in all groups was 110 days, again, further speaking to the extended dosing interval that could be used to achieve good visual acuity results.

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Q. And, again, this is coming from DTX 0204?

A. That's correct.

Q. Turning to the next slide, Slide 154. So have you reviewed the unexpected results opinions of Dr. Csaky?

A. Yes, I have.

Q. Do you agree with Dr. Csaky?

A. No, I do not. I think that the trials that we have discussed already paint a picture of a lot of industry successes, and I don't see the argument for overwhelming industry failure.

Q. And then actually I want to back up and ask you about one additional document. So if we look at Dixon. I believe you have it at DTX 0204 in your binder. If you could turn to that, please.

A. I found it.

Q. And if you turn to page 4 of that reference and look at that section on Phase II that you've been discussing.

A. I don't know if you can help me. My pages -- oh, I see it. Never mind.

Q. It's at .00 -- yeah, there you go.

A. I got it. Yep.

Go where? I'm sorry.

Q. The discussion in Section 2.6.2 about the Phase II clinical trial.

A. Yes.

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Q. Do you see there's a reference to Reference 45 there?
A. Reference 45, I see that.
Q. So if you turn to the back and take a look at what Reference 45 is. Can you do that?
A. Yes. I see that.
Q. And that Reference 45, is that a presentation entitled "VEGF Trap-Eye in Wet AMD, CLEAR-IT 2: Summary of One-Year Key Results. Paper presented at Retinal Society Annual Scientific, September 28, 2008, Scottsdale, Arizona"?
A. I see that reference.
Q. Is that another one of the references that you reviewed in connection with formulating your opinions in this case?
A. I have seen the slides from that presentation, yes.
Q. Okay.
Can we put those slides up, please. That's DTX 3173.
Is this the presentation that you've reviewed and relied upon?
A. Yes.
Q. Okay.
And if we go ahead to Slide 6, please, of the slide presentation of DTX 3173.
Is this a depiction of the study arms from that study?
A. Yes, it is.

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Q. And if we jump to Slide 9, what were some of the conclusions that were reported with respect to some of the results from the Phase II CLEAR-IT study?

A. You see them here, that there was a significant improvement in visual acuity, a significant reduction in central retinal thickness. That means decreased swelling. The groups dosed at baseline and at Week 12 showed improved visual acuity and retinal thickness, although this effect was not as robust as that seen in monthly dosing in the early phase. All the maintenance phase here was prn.

Maintained effect on visual acuity with a single dose to eight weeks and was generally well tolerated with no drug-related serious adverse events -- with no serious adverse events.

Q. If we jump to Slide 16 of this presentation, DTX 3173, can you explain what we're looking at here?

A. These are the visual acuity results from the arm that is a .5 milligrams of the low dose with monthly loading doses followed by prn dosing after Week 12 shown in the blue. And the 2-milligram dose, a higher dose, shown in the green squares, with visual acuity. This arm was also four loading doses initially and then maintained with prn injections after Week 12.

Q. Thank you. And if we could go back to the main slide deck, DDX 6.

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And if we could turn now to the issue of industry praise, that secondary consideration. We're at Slide 155, now 156. Did you review the opinions of Dr. Karl Csaky with respect to reported industry praise?

A. I did.

Q. Did you agree with Dr. Csaky's opinions?

A. I agree that there was great praise from the industry, but I don't see the connection of that praise to the dosing regimens which we are discussing in the claims today or to the isotonicity issue.

I think that there was great praise for this molecule and there was great efficacy of the molecule; but, to me as a POSA, because these dosing strategies were actually not widely adopted and retina specialists continued to use prn and treat-and-extend dosing instead of fixed eight-week dosing as described in the claims, I really don't see the connection to claim that the industry praise was due to the practices outlined in the claims in question.

MS. OBERWETTER: Your Honor, I have an objection and motion to strike in part the prior response.

Dr. Albini's report does not contain a disclosure with respect to the isotonic solution limitation as it relates to secondary indicia or industry praise in particular.

THE COURT: Understood.

Counsel?

MR. McLAUGHLIN: I think what Dr. Albini was doing was just responding to Dr. Csaky's opinions, which he noted did not address isotonicity or the aspects of Claim 6 in any way.

THE COURT: I'll overrule the objection at this point considering it's a motion to strike.

Counsel, obviously, you'll be free to address that in the posttrial briefing. And if it was not properly disclosed, the Court would disregard it, but we'll address that posttrial at this juncture. Noted, however.

You may proceed, Counsel.

BY MR. McLAUGHLIN:

Q. Let me ask it this way: In reviewing Dr. Csaky's opinions, did you see any industry praise in those opinions regarding anything having to do with an isotonic solution?

A. I did not.

Q. Did you see in Dr. Csaky's opinions any evidence for any industry praise for the use of five monthly loading doses followed by every-eight-week dosing in the treatment of DME?

A. I did not.

Q. If we could turn now to the issue of commercial success. Dr. Albini, were you asked to provide opinions regarding commercial success in this case?

A. I was.

Q. Do you understand that Dr. Csaky also provided opinions regarding commercial success?

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A. Yes.
Q. Did you review those opinions?
A. Yes.
Q. Is one of those opinions set forth here on Slide 158?
A. Yes.
Q. In reviewing his opinions, did you see where Dr. Csaky attributed any of the commercial success of Eylea to the DME-DR treatment regimens of five monthly loading doses followed by fixed every-eight-week dosing?
A. I do not see that specifically mentioned.
Q. And did you read the day two trial testimony transcript from Dr. Csaky?
A. Yes.
Q. Okay.

If we could pull that up.

This is from -- we're going to PDF page 109. There we go.

Did you see Dr. Csaky testify as follows when he was asked, "When you say you've used Eylea to treat patients with DME and DR according to the method of Claim 25, have you also done that for secondary doses step?"

And his response was, "Yes. In certain cases where there's severe DME, you need five injections, multiple injections. And, again, having, as I said before, that confidence of five injections gets us to a good place both

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anatomically and visually is a nice approach to take in some patients."

In your opinion, is a regimen that's used in some circumstances of severe DME in some patients something that sounds like being responsible for the commercial success of Eylea?

A. No.

Q. If we could go back to the slide deck, please, DDX 6. Thank you, Dr. Albini.

You also have provided opinions regarding the pharmacologic attributes of the aflibercept protein; is that correct?

A. I have.

Q. Can you explain for the Court what you've provided here on Slide 159 in this callout from DTX 2745.

A. This is an early paper from 2002 describing VEGF Trap-Eye, at that point in preclinical testing, describing that it has a higher affinity and improved pharmacokinetics relative to antibody therapeutics that were being developed at the time. Again, showing that there was reason to believe that this molecule would be a better agent based on its pharmacokinetics early on prior to any consideration of dosing regimen.

Q. And when was this disclosure published?

A. 2002.

Q. If we turn to the next slide, what else was published

regarding the pharmacologic attributes of aflibercept?

A. This is from the Dixon reference that we've referenced many times in 2009, where it also remarks on the high affinity of the molecule and the benefits of the Trap complex increasing its durability and its long duration of effect in the eye, again pointing the potential success of the molecule to its pharmacologic properties rather than to any specific dosing regimen.

Q. What you're looking at here is DTX 0204?

A. That's correct.

Q. Let's go on to the next slide, Slide 161. Can you explain to the Court what you've shown here with respect to this April 28, 2008, press release, DTX 2731.

A. Yeah. This article describes again that, due to its high affinity for all isoforms of VEGF-A as well as its long residence time in the eye, Dr. Quan Nguyen, one of the investigators in the early Regeneron trials, is claiming that that scientific -- or those pharmacologic properties of the molecule are predictive of clinical success.

Q. If we turn to the next slide, Slide 162, is this a summary of those pharmacologic attributes of aflibercept that you've just reviewed?

A. That is correct.

Q. And, in summary, starting with the assumption that Eylea has been a commercial success, in your opinion, is that

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success attributable to the properties of the molecule itself or to the features of the isotonicity or the five monthly loading dose DME aspects of the asserted claims?

A. I see not much praise or remark about isotonicity of the molecule. I think that, with regards to the dosing frequency, one of the most telling pieces of information to me was the email from Dr. Yancopoulos that we had a few slides back where he overtly declared that the success of the molecule will be based not on its dosing strategy but that it will be better than the antibody molecules available regardless of dosing strategy. And I think that's the way the success of the molecule was perceived in the community as well.

Q. So in your opinion, the commercial success of Eylea is not attributable to the five monthly loading dose dosing regimen followed by every-eight-week dosing in the treatment of DME patients?

A. Yes.

Q. So do you agree, then, with Dr. Karl Csaky's final opinion with respect to commercial success?

A. No.

Q. The next -- you were asked to provide opinions as to how certain patents assigned to Regeneron might influence whether someone could practice the subject matter claimed by the '601 and '572 patents?

A. That's correct.

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Q. Are some of those blocking patents shown here?

A. Yes. Due to the patented molecule, it would have been difficult for people other than Regeneron to have performed studies to demonstrate various dosing strategies and their success.

Q. So the '746 patent claims a method of treating retinal neovascularization; is that correct?

A. That's correct.

Q. And in your opinion, would that have prevented somebody from being able to practice the claimed methods of the '601 and '572 patents?

A. Yes.

Q. If we take a look at the '747 patent, that's -- the claim there is drawn to a therapeutic method for treating or ameliorating an eye disorder?

A. Yes. That would also preclude it.

Q. And so, in your opinion, that would preclude the ability to conduct the dosing regimens of the '601 and '572 patents?

A. Exactly right.

Q. And for the purposes of this analysis, have you been asked to assume that the sequence IDs set forth in these claims are the sequences of aflibercept?

A. Yes.

Q. If we turn to the next slide, one of these is the

'799 patent, 7,306,799, DTX 4116. Is Claim 1 there drawn to a therapeutic method for treating an eye disorder?

A. Yes.

Q. And in your opinion, would that have blocked somebody from conducting or operating the claimed dosing regimens claimed in the '601 and '572 patents?

A. Yes.

Q. And for the '758 patent, it's drawn to a method of inhibiting vascular endothelial growth factor activity in a mammal. Do you see that?

A. Yes.

Q. Would that claim have prevented somebody from operating the claimed regimens of the '601 and '572 patents?

A. Yes.

Q. I want to revisit one more aspect of your testimony earlier today.

So if we could pull up DTX 07 -- sorry -- DTX 7069, paragraph 556.

I just wanted to ask one final question on this. Did you -- you stated earlier that you did review Dr. Csaky's opinions in this regard?

A. Yes.

Q. Did Dr. Csaky offer any rebuttal regarding whether or not the language from Dixon suitable for the comfortable and nonirritating direct injection into the eye inherently

disclosed isotonicity?

A. I do not recall any rebuttal on that specific remark.

Q. Thank you.

MR. McLAUGHLIN: Nothing further from Mylan, Your Honor, with --

THE COURT: Thank you, Counsel.

MR. McLAUGHLIN: -- obviously, reservation for redirect.

THE COURT: Certainly.

Cross?

MS. OBERWETTER: Yes, Your Honor. Can I have just a minute or two to get set up at the podium?

THE COURT: You may.

Whenever you're ready, Counsel, you may proceed.

MS. OBERWETTER: Thank you, Your Honor.

CROSS-EXAMINATION

BY MS. OBERWETTER:

Q. Good afternoon, Dr. Albini.

A. Good afternoon.

Q. Dr. Albini, you've been working with Mylan's litigation counsel since 2017, correct?

A. That sounds correct, yes.

Q. Okay. So for the past five or six years?

A. Yes.

Q. That was years before this case even got filed,

correct?

A. I'm not aware of when exactly this case was filed.

Q. All right. One of Mylan's attorneys, Mr. McLaughlin, and some of these colleagues would fly down starting back in 2017 to meet with you down in Miami, correct?

A. That's correct.

Q. And you would meet in a conference room at the hospital where you worked in Miami, right?

A. That's correct.

Q. And you would sit in a room and look at Regeneron's patents, correct?

A. Among other things, yes. That's correct.

Q. And you were retained at that time to help Mylan generate ideas on how to invalidate the patents, correct?

A. I was hired for my opinions about -- mostly at that time we were discussing what the POSA or what the standard retina specialist at the time would have envisioned as reasonable dosing regimens to use. So I was not really engaged in a way to -- I think you said the words "to create strategy" or "to develop strategies."

I was more engaged in a way to guide them through the prior art and the scientific literature that was available as well as other types of literature that we've seen in my testimony such as the PAT Surveys and some of the articles from trade journals and other types of literature that may have been

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more obscure to attorneys new to this area.

Q. Dr. Albini, you've had your deposition taken in this case, correct?

A. Yes.

Q. That was a few months ago, earlier in the spring?

A. That's correct.

Q. And we did that deposition down in Miami, right?

A. That's correct.

Q. You were under oath?

A. I was.

Q. Okay.

And if we could please cue up the video clip.

Did I ask you these questions we're about to play and did you give these answers?

(Video playing.)

"Q And those are conversations that -- I guess starting in roughly the 2017 time period, what was your level of activity in working on this matter over the years through the present?

"A I think that early on every couple of months, Neil and a colleague or two would fly out to Miami, and we would sit in a conference room much like this one but usually on-site at the hospital, and go through these patents. And they -- they would ask me my opinions about the

treatment strategies and what was currently known about various treatment strategies at the time and what the prevailing practice patterns were among retina specialists at the time with regard to the treatment of angiogenic eye disorders with anti-VEGF medications.

"Q Were you retained at that time to help generate ideas on how to invalidate the patents?

"A Yes.

"MR. McLAUGHLIN: I just want to counsel you going forward, you know, to the extent that this goes to any privileged discussions or conversations, that I'll instruct you not to answer."

(Video ends.)

BY MS. OBERWETTER:

Q. Dr. Albini, you know that that role is not the same as being an independent expert, correct?

A. I think that my input into guidance of what -- as I described in that clip, guidance through what the literature was available and what the prevailing practice patterns at the time, I think that is my role as an independent expert.

I can see your concern about my answering yes to the question about developing strategies. I certainly can't tell you exactly what was going through my head as I said yes, but I

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think that my answer was that I was involved in developing strategies insofar as my independent opinions of the state of the art and what retina specialists were doing at the time is a very important component of any strategy that one would use.

But I'm not an attorney. I did not develop any of these arguments. I have no experience in patent law. I would be a very poor source to obtain information about how to invalidate a patent. I have no idea. My role --

Q. Sir, I think you've answered the question.

THE COURT: Counsel, he wasn't finished.

Go ahead.

THE WITNESS: No, I just wanted to reiterate again that my role was just to provide my experience and my opinion of what the state of the art was at the time in question.

BY MS. OBERWETTER:

Q. I'd like to pull up a slide from your opening deck, which is Demonstrative 6.152, or Slide 152. This is a slide summarizing, I think you said, the clinical trials from the relevant time period?

A. That's correct.

Q. And there are some AMD trials that are up at the top of this slide. There's three of those there, right?

A. That's correct.

Q. And only one of those, the CLEAR-IT 2 trial, relates to Eylea, correct?

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A. That's correct.
Q. Okay. And then below that you've got a couple of DME clinical trials that are listed there, right?
A. That's correct.
Q. And the visual acuity scores that you can get vary by trial; is that right?
A. That's correct.
Q. And the selection of trials on this page, you decided which trials to include on this page, correct?
A. That's correct.
Q. Everything -- and CLEAR-IT 2, I think we determined, was the Eylea Phase II trial in AMD?
A. That's true.
Q. You would agree that Lucentis, referred to on this page as ranibizumab, was further along in development than Eylea was at this point, right?
A. That's correct.
Q. You would also agree that there was much more data for Lucentis in AMD than in DME at this point, correct?
A. That's correct.
Q. And if we take a look at the two DME trials that are listed on this page, the first one is called READ 1. Do you see that one?
A. I see it.
Q. How many patients were in that trial, sir?

A. I think it was a low number of patients. I hope I'm not misspeaking. But to the best of my recollection, it was a very small study.

Q. It was ten, correct?

A. That sounds right, yes.

Q. Ten patients in the READ 1 study?

A. Yes.

Q. The DME Phase I study on that page, how many patients were in that study?

A. I believe it was a similar number, about ten patients.

Q. Was it five?

A. It could have been.

Q. You don't know?

A. I don't remember the exact number right now, but it was a very small Phase I study.

Q. These were both Phase I studies?

A. That is correct.

Q. You would agree that knowledge of how a particular drug performs expands as the number of patients increases in trials over time, correct?

A. That's correct.

Q. You would agree that, once you start treating more people, you are obtaining more information, and that can either confirm or contradict what you've seen in the preceding phase

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of your testing, right?

A. That is correct.

Q. You'd also agree that even a low rate of serious side effects can mean you would be considered not to have a safe trial, right?

A. In certain circumstances, yes.

Q. Okay. There are situations where there's even a low rate of really bad side effects, and that can make a trial deemed unsafe, correct?

A. That's correct.

Q. There are drugs that enter into Phase III that fail their Phase III clinical trial end points. Isn't that true?

A. That is true.

Q. And so a drug can get all the way to Phase III and still not make it to the market, correct?

A. Yes. And even further, a drug can pass Phase III and make it into the market and still fail in the real world.

Q. Okay. We'll come back to that.

There was recently an anti-VEGF drug with the maybe not catchy name of KSI-301 that failed its Phase III trial, correct?

A. That's correct.

Q. And you worked on a clinical trial for a different anti-VEGF drug called abicipar or abicipar?

A. That's correct.

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Q. And even during the Phase III trials for abicipar significant intraocular inflammation issues emerged, correct?

A. That's correct.

Q. That drug did not make it to the market?

A. That's correct.

Q. I think you touched on one that passes its Phase III trials and then still runs into problems. Beovu is an example of an anti-VEGF agent in that category, correct?

A. That's correct.

Q. Beovu came onto the market in early 2020. Do I have that right?

A. That sounds right.

Q. You only used it twice?

A. That's my recollection, yes.

Q. All right. And that's because, after launch, everyone learned that there is a 1-in-200 risk of severe vision loss for patients that have Beovu, right?

A. That is correct.

Q. And those safety issues for Beovu only became known to doctors after Beovu was approved?

A. That is correct.

Q. And after it passed its Phase III trials?

A. That is correct.

Q. All right. And, in fact, the experience with Beovu made doctors appreciate how lucky -- and I think you've used

the word "lucky" -- doctors have been on the safety side with the first main anti-VEGF drugs like Eylea and Lucentis and bevacizumab, correct?

A. That is correct.

Q. And it's certainly possible that more went into that than luck, right?

A. Yes.

Q. This area of medicine is so difficult that you might not even know if an approved biosimilar will perform the same as the label drug, correct?

A. I would say that's not particular to this area of medicine. There are many areas of medicine that are just as difficult or challenging, but I think that, yes, it's -- it is true that the anticipated success doesn't always materialize.

Q. When deciding on how to design the arms of a clinical trial using an agent like an anti-VEGF, you would agree there's a lot of moving pieces to that, correct?

A. Yes.

Q. All right. You need to consider the route of administration?

A. Yes.

Q. You need to consider how often a drug needs to be administered?

A. Yes.

Q. You need to consider at which visits to the doctor

the drug might be administered?

A. Correct.

Q. You need to consider the concentrations of the drug being administered?

A. Correct.

Q. You need to think about whether and how many loading doses to use?

A. That is correct.

Q. You need to consider whether to have a fixed loading dose component to the regimen?

A. That is correct.

Q. And you need to consider whether there's a fixed extended dosing component to the regimen?

A. That is correct.

Q. You'd have to consider whether to have intervening visits between periods set for fixed dosing intervals, right?

A. That is a decision that -- yes, that is a decision that needs to be made when designing protocol for sure.

Q. You would agree that in the 2010 time period there was uncertainty as to what the best dosing approaches were for anti-VEGF agents, wouldn't you?

A. I think that, as was documented in this -- in my testimony so far, there were a number of protocols that had succeeded with a number of dosing strategies that involved three to six loading doses followed by prn or fixed interval

dosing regimens, either at 4 weeks or with other 8- or even 12-week dosing regimens.

So I think there were a number of protocols to choose from, but it also wasn't an infinite field of reasonable things to try.

Q. You would agree there was uncertainty as to what the best dosing approaches were for anti-VEGF agents?

A. Yes.

Q. You know that throughout the development period for Eylea, both before 2011 and afterward, Regeneron had access to data about the performance of Eylea that the public didn't, correct?

A. I'm aware that such data existed, but I don't know much about it.

Q. Okay. They, of course, had access to such data because it was their development program, right?

A. That makes sense.

Q. I'd like to talk a little bit about some of the terminology that we've been using in this case. Let's talk first about the phrase pro re nata, or prn. Prn means as needed, correct?

A. That's correct.

Q. All right. And prn means you only treat as needed determined by the findings of an OCT scan and other components like clinical examination and visual acuity measurements,

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correct?

A. I think that's the way the POSA would have defined it.

Q. And so when you use prn dosing, the decision to redose the patient depends on the outcome of an assessment at the time you see the patient, right?

A. That is correct.

Q. And you don't know until you check the patient according to those things that I just mentioned?

A. That is correct.

Q. All right. And if instead you want to have an ex-ante decision, an ex-ante regimen where you don't have to go to the doctor between injections to get assessed, that would be an extended interval fixed dosing regimen, not a prn regimen, correct?

A. I think there's some ambiguity in the way that the term "extended interval" would be used. It was not, as I recall, a commonly used phrase among retina specialists at the time, extended interval.

So I think -- I can't think of cases in my head right now to give me guidance about how the POSA would have used the term "extended interval," whether that would necessarily mean extended injections or extended visits.

I certainly think it's reasonable to use it in either way. I just don't want to leave the impression that there was

a preferred way to use that term in the years that I'm aware of.

Q. Okay. You had your deposition taken in this case, I think we established, correct?

A. Yeah, that's correct.

Q. Okay. And if we take a look at page 241 from your deposition, I asked the following question: "If you want to have a regimen that doesn't have a required monthly visit to the doctor every month, that would be an extended-interval fixed dosing regimen, not a prn, correct"?

And your answer was, "Correct."

Did I read that correctly?

A. I don't think there's -- as I said, I don't think there's any problem in using the term that way, and I stand by what I said here in the deposition. I just don't want to leave the impression that that was a commonly used definition of the term by retina specialists back in 2010.

Q. You understood it when I asked you that question at your deposition?

A. I understood what you meant, yes.

Q. All right. You would also agree that prn and treat and extend are two different treatment strategies, correct?

A. Yes.

Q. All right. I'm going to change topics a little bit.

You talked during your testimony about a document. I

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believe it was DTX 2039 was the version used.

If we can pull that up.

That's a -- you recall generally being asked about this document during your direct examination?

A. Yes, I do.

Q. And the cover says "VEGF Trap-Eye in Wet AMD CLEAR-IT 2."

This was about a Phase II AMD trial called CLEAR-IT 2, correct?

A. That is correct.

Q. And before I ask you additional questions about this, do you have personal knowledge as to whether this was the version that was publicly presented?

A. I have no reason to think it wasn't.

Q. Do you have -- my question was a little bit different. Do you have personal knowledge as to whether this was the version that was publicly presented?

A. I don't have any independent knowledge except that it's labeled this way, and I have no reason to believe that these weren't the slides presented.

But -- you know, I was -- don't have independent documentation that these are the exact slides that were presented or that all these slides were remarked on by the investigator, but this is given as a document of that presentation and available online.

Q. I'm sorry. You did not go find this online?

A. Honestly, I don't recall -- it was so many years ago that we brought this out -- who found it. But I've seen it, and I believe I've googled for it with PDF and CLEAR-IT 2, but I don't know. So many years ago.

Q. You were not at a September 2008 Scottsdale, Arizona, presentation, correct?

A. I was not.

Q. You would agree that the CLEAR-IT 2 trial did not have an arm that tested an eight-week fixed dosing interval regimen, correct?

A. That is correct.

Q. And it also did not have an arm that had three loading doses, correct?

A. Can we go to the slide that shows the different arm treatment strategies? I just want to make sure -- I can't remember now if it was three or four.

There was an arm with monthly loading doses, but with so many of these studies I don't want to give you the wrong answer. It was either three or four that they had, one of those two.

Q. It's possible it was four, right?

A. Certainly possible, yes.

Q. Okay. We can take that slide -- we can take that presentation down.

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I'd like to talk a little bit about a study that your counsel asked you about, which was a PrONTO trial. You're familiar with the PrONTO trial?

A. I am.

Q. And I know you mentioned you had institutional pride about the PrONTO trial. That trial was before you got there, right?

A. I was there in 2006; so I think the results were -- those papers were published -- what years? I don't have it. You may have it in front of you -- 2008, 2009. So it was still certainly being talked about at the time when I was there.

Q. If we pull up the Lalwani 2009 article that is DTX 3113, this is an article that you were asked about on direct; is that right?

A. That's correct.

Q. And Dr. Lalwani is a well-regarded retina specialist?

A. That is correct.

Q. The PrONTO trial looked at three loading doses followed by prn treatment for wet AMD using ranibizumab.

Do I have that correct?

A. That's my understanding.

Q. And the PrONTO trial was generally viewed as having some positive results, I think you testified?

A. That's correct.

Q. In your opinion, the PrONTO trial initiated a major

change in the way that ophthalmologists were administering anti-VEGF agents.

Would you agree with that?

A. It was roughly at the same time. As I sort of semi-jokingly said during my direct testimony, I don't know whether it's cause and effect, how much credit you can give to this one trial. There is no doubt that prn dosing became very popular at around the same time. Maybe it would have done it without this trial; I don't know.

But I certainly remember a lot of people talking about this trial as evidence for prn dosing back at that time. So I think it very likely this trial was, at least to some small degree, responsible for the wide adoption of prn dosing back in the 2007-2008 time frame.

Q. The adoption of prn dosing itself was a major change in the way that ophthalmologists were providing these drugs, correct?

A. Yes.

Q. All right. In your opinion, the PrONTO regimen opened the door to more ophthalmologists making use of individualized prn treatment regimens for anti-VEGF agents, correct?

A. Yes.

Q. And in this publication by Dr. Lalwani, if we go down to the bottom of page 1, she says in part, "While the Phase III

trials used monthly injections, it is unclear at this time if monthly dosing is the best dosing interval. Observations made after the earlier Phase I-II studies with intravitreal ranibizumab suggested a role for OCT in determining the appropriate dosing interval for each patient."

Do you see that?

A. I do.

Q. And her reference to OCT, that's prn dosing because that's how you determine whether to re-treat, correct?

A. I think OCTs could be obtained with monthly dosing as well. So I have to be honest. Right now, I'm not exactly certain that I can pull up in my head what data she's referring to here. So I don't want to mislead and say that I know that that was prn dosing. That might have been monthly dosing and that these observations that she's talking about were made from diagnostic imaging that was obtained on patients that were dosed monthly. I don't know that.

Q. Okay. Well, Dr. Lalwani, in any event, is pointing to a lack of clarity as to whether monthly dosing is the best, correct?

A. That's correct.

Q. All right. There's another trial that was not discussed I don't think during your direct examination, which was the PIER trial.

You know the name PIER trial?

A. I'm familiar with that trial, yes.

Q. And the PIER trial was an effort to do a 12-week extended dosing interval for Lucentis, correct?

A. That is correct.

Q. And that was after three loading doses?

A. That's my recollection.

Q. And when they tried that in the PIER trial, you agree that the results were not as good as the PrONTO prn results, correct?

A. They were not as good, but they were still good.

Q. They were not as good.

A. I answered your question.

Q. Those results were viewed as somewhat discouraging with respect to attempting a 12-week dosing interval for ranibizumab, correct?

A. It depends by whom. I mean, they made it into the label for the drug. So they weren't discouraging enough not to have made it into the label.

Certainly the FDA thought that that was an appropriate dosing interval for some instances. I think you and I may have talked about this before at my deposition, but as I recall from the time, there were clinical trials that were using the PIER arm as their standard of care arm, and that was approved by the FDA.

So certainly it wasn't clear to everybody that that

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was an inappropriate dosing regimen. I think it wouldn't have made it into the label if there weren't some people who thought it was absolutely appropriate.

Q. Dr. Albini, we did talk about that at your deposition. If we can pull up page 176 of your deposition and look at lines 16 to 19.

I asked you:

"Q And the results of the PIER trial were viewed as somewhat discouraging with respect to attempting a 12-week dosing interval, correct?

"A With ranibizumab, yes."

And that's the answer you gave at your deposition, correct?

A. I think that's not in contradiction with what I just said.

Q. We can take that down.

If we take -- so the PIER results were published in an article by Dr. Regillo in 2008; is that right?

A. To the best of my recollection, yes, and I have no reason to doubt that what you're saying is true.

Q. If we pull up DTX 4099, do you recognize this as the Regillo publication about the PIER study and its one-year results?

A. Yes, I do.

Q. If we take a look in particular at DTX 4099.0009 and

go down toward the bottom conclusion paragraph at the bottom right, Dr. Regillo wrote, "In conclusion, ranibizumab administered monthly for three months and then quarterly provided VA benefit to patients with neovascular AMD and was well tolerated. However, observations from the MARINA and ANCHOR trials suggest that the PIER regimen of dosing every three months after three monthly doses provides less benefit in VA on average than continued monthly dosing. Monthly dosing may be necessary in some patients to achieve maximal treatment benefit from ranibizumab."

Do you see that?

A. I do.

Q. Dr. Regillo did not propose in this article continued efforts at extended fixed interval dosing, correct?

A. I would have to read the entire article to see what else he may or may not have proposed. I think the words speak for themselves that there was a benefit and there was demonstrated safety of this treatment regimen.

The outcomes were not as good as monthly dosing, and monthly dosing may be necessary. Again, I would highlight the word "may." He did not conclude that it definitively was. And he really doesn't make much comments on other types of dosing regimens that may be appropriate.

Q. He certainly doesn't suggest any there, correct?

A. In these couple of sentences that I'm seeing here,

no.

Q. You would agree that -- we can take that down.

You would agree that what most people were doing in the 2010 to 2011 time period were individualized assessments to determine dosing, correct?

A. I believe that's true, yes.

Q. All right. I want to talk about another document that came up during your direct examination. You talked some about a quote from a Dr. Dave Brown who practices in Houston, if we take a look at Slide 37 from the opening.

I'm sorry. It was Slide 37 from the direct examination. Thank you.

And this is the quotation I'm referring to just so you have it in mind. Do you see that?

A. I do see that.

Q. Okay. And if we take a look, actually, at the underlying exhibits, DTX 2035, and go to page 0002 where that language is found, Dr. Brown made his comments about this regimen in the context of ranibizumab, right?

A. Ranibizumab and bevacizumab probably.

Q. Not Eylea?

A. That is correct.

Q. All right. And he limits his comment about who he would go to treat-and-extend with to the population of patients with good initial visual acuity or where it's the primary eye,

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correct? That's what he says there?

A. That's correct.

Q. And he excludes individuals, if you look down at that last sentence, you have extrafoveal lesions, right?

A. Can you repeat the question? I'm sorry.

Q. He says, "I administer three doses in all cases except extrafoveal lesions," correct?

A. That's what he says, yes.

Q. That's an exclusion on what he is doing?

A. I mean, he doesn't say what he's doing in the cases of extrafoveal lesions, but, yes, he's making a differentiation in terms of his treatment strategy depending on the location of the lesion.

Q. Okay. He's also not talking here about an eight-week fixed extended dosing interval going forward, right?

A. I don't see any evidence. In fact, I think a disinterested reading of this would say that he is recommending a prn or treat-and-extend type of protocol. The assumption is that he -- after three loading doses or potentially in some cases after fewer loading doses, depending on these exclusions that he's putting in there, that he's making an assessment as he goes along about how the patient is doing. And also he comments here that he's extending the interval to ten weeks in certain situations, documenting that he's employing some extension in the technique.

I don't think that he's rigorously following any particular set-down treatment regimen that's written down somewhere, advised someplace. I think he's using his best clinical judgment in incorporating all the data, clinical data, that was available to the POSA at the time to make individualized decisions for individual patients about dosing frequency and the visit intervals.

Q. There's another part of this document I'd like to take a look at if we go forward to page 4.0004. And there's a comment partway down by Dr. Reichel right after "it is reassuring to know."

Do you see that part of the document?

A. I do.

Q. Am I saying --

A. Reichel.

Q. I hope I'm saying Dr. Reichel's name correctly. What Dr. Reichel says in response to a comment about -- in the prior paragraph where it is unlikely that treating more than often -- more often than is absolutely necessary is deleterious, Dr. Reichel says, "It may not be harmful, but we may be increasing the risk of endophthalmitis and the economic burden by treating more often than is absolutely necessary."

Do you see that, Dr. Albini?

A. I do.

Q. And Dr. Reichel is noting that you don't want to

treat more often than necessary, correct?

A. Yes, he is making that point.

Q. Okay. You would agree --

We can take that document down.

You would agree that the -- strike that. Let me start over.

In preparing your report, you did not identify any literature suggesting prior to 2011 that ranibizumab ought to be administered at an every-eight-week fixed interval, correct?

A. I think I found evidence that it was in some cases administered at an every-eight-week interval in that, for example, the dosing strategies that were employed by the prominent vitreoretinal specialists in that 2007 *Retinal Physician* roundtable shows a great deal of variability in both intervals between visits and intervals between injections, and I'm sure that there were, among those patients, certain patients that were being injected at every-eight-week interval.

So I'm sure that that did exist for some particular patients, but I think the overall concept is that the treatment regimen was being individualized to the patient and there are going to be some patients that are q8-week injection patients.

Q. I'm just going to try my question again.

You did not identify, in preparing your report, any literature suggesting that prior to 2011 ranibizumab ought to be administered at an every-week fixed interval?

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A. What I did not find is any literature that specifically said that ranibizumab ought, must, should always be injected at a q8-week interval. I did not find that documentation. That is true.

What I did find was that, from the evidence of the way in which physicians were employing injection frequency and injection intervals, there is no doubt, I think, to the POSA that there were patients who were identified as patients who needed q8-week dosing, and those patients were indeed receiving injections q8-week. But it was not given as an ultimatum that all patients need to be q8-week. It was just patient-specific.

Q. Dr. Albini, I want to take a look at another document that was addressed during your direct testimony if we look at Slide 38.

You received some questions about a couple of what are called, colloquially, PAT Survey documents; is that right?

A. That is correct.

Q. And on this page in particular, I just want to direct your attention to the top line. And this corresponds to DTX 2040, correct?

A. That is correct.

Q. All right. And if you look at the top line on the right-hand side, it says "Anti-VEGF therapy q1 month."

Do you see that?

A. I do.

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Q. And that's reflecting that 17.5 percent were using monthly dosing of -- monthly dosing of anti-VEGF agents, correct?

A. That's correct.

Q. And that is what was the first regimen recommended on the Lucentis label, right?

A. That is the first regimen recommended on the Lucentis label. Yes, it is.

Q. We can take that document down.

I'd like to look at Slide 26 from your direct examination, which references DTX 4056, I believe. And on the left-hand side you see the -- an excerpt from the ranibizumab prescribing label, correct?

A. That is correct.

Q. I think during your direct testimony you focused on the one injection every three months after the first four injections, is there in the second bullet.

Do you see that second bullet?

A. I mentioned both, I think, but yes. I see the bullet, yes.

Q. And to clarify, this is just the early Lucentis label that had wet AMD, right?

A. I think so. That's my recollection from reading it, but I'm struggling through the block label what's on there, but certainly -- it could be that, yes.

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Q. Okay. The first regimen that was recommended on the Lucentis label for wet AMD was monthly, right?

A. I believe so, yes.

Q. And the second, the one that's here in the second bullet, starts "although less effective," right?

A. That's correct.

Q. And that's what Genentech was required to say in its label when recommending less than monthly, correct?

A. I don't know for sure that they were required to say that or that they just chose to say it, but that's what's stated there, yes.

Q. We can take that document down.

I have a couple of questions for you about the isotonic solution opinions that you offered in connection with Claim 6.

In relying on Dr. Rabinow in your testimony today, did you review his deposition transcript?

A. Yes.

Q. And my other question is you have not disclosed an opinion as to what specific range outside of isotonicity you would or wouldn't use to treat the eye?

A. I have no such opinion.

Q. Okay. I'd like to turn to talking briefly about diabetic macular edema, and I'd like to talk about some of the considerations for treating patients with diabetes.

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You would agree that diabetics have a different set of comorbidities than wet AMD patients, right?

A. That is true.

Q. Diabetics have a higher rate of peripheral vascular disease than AMD patients?

A. That is true.

Q. Peripheral vascular disease can increase the risk of a stroke in a patient, correct?

A. That is true.

Q. You would also agree that during the -- what I'll call the pre-January 2011 time period there was, I think as we talked about earlier, an interest in avoiding treating patients more than was absolutely necessary, right?

A. That is true.

Q. And we've heard some about it in this case, but shots in the eye are not pleasant for anyone, right?

A. That is true.

Q. Okay. You're also not aware of any publications prior to 2011 that talked about using five loading doses for the treatment of DME, correct?

A. As we've discussed, there were a number of treatment regimens that would have resulted in five early doses, and given how the -- how it took more injections to achieve visual acuity results in DME than it did in AMD, I think that it was very likely that a lot of patients were being treated according

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to prn and did wind up getting five monthly injections or more going forward.

So I do think that five monthly doses up front were given to a lot of patients, yes.

Q. That actually was not my question.

My question is you're not aware of any publications prior to 2011 that talked about using five loading doses for the treatment of DME?

A. Not directly in those terms.

Q. Okay. You're not aware of any that talked about six loading doses for DME either?

A. I don't think so.

Q. Okay. And you're not aware of any from before July of 2013 either?

A. Not that I can tell you with confidence sitting here right now, no. I hope I'm not forgetting anything.

Q. You also didn't identify anything during your direct examination publications that talks about five loading doses specifically for diabetic retinopathy, correct?

A. That is correct.

Q. And you didn't identify any publications that talked about six loading doses for diabetic retinopathy?

A. I don't recall anything that specifically stated six loading doses. But again, the caveat is that many dosing strategies resulted in patients getting six injections off the

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top. So even though they weren't specifically labeled as six loading doses, there were many patients that were being treated in exactly that way.

Q. You have not quantified that in your report?

A. Quantified it?

Q. Right.

A. I think I've made the case that it's a permutation, I'd say even a common permutation, of some of the prn dosing regimens. I've made that case. I haven't quantified what percentage of patients got five initial doses, no.

Q. I'd like to take a look at the Diana Do 2012 article that has been discussed some in the case, including on your direct. If we can pull up DTX 3105.

This article -- and you agree Diana Do is a well-regarded retina specialist, right?

A. Yes.

Q. This article discussing the Phase II DA VINCI trial for DME, right?

A. That's correct.

Q. That's the Phase II Eylea trial for DME?

A. That's correct.

Q. And this article is what you might call the official write-up of the DA VINCI trial?

A. That's correct.

Q. At page 7 of the document, if we skip ahead into the

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document, about midway down the left-hand column, there's a discussion of safety issues regarding anti-VEGF agents in DME patients. About partway down she writes, "Most of the systemic adverse events observed were attributed to the underlying medical conditions and cardiovascular comorbidities of these diabetic patients."

Do you see that?

A. I do see that.

Q. And likewise she says, "Studies have shown that individuals with diabetes seem to have an approximately two- to fourfold greater risk for both heart disease and stroke," right?

A. That is true.

Q. And that is consistent with the understanding at the time that diabetic patients have special comorbidities that can expose them to adverse events, right?

A. That sounds fair.

Q. She also notes, if we go down a little bit further, that the DA VINCI study was not powered sufficiently to assess the relationship between VEGF inhibition and systemic adverse events or mortality, right?

A. That is correct.

Q. That is her communicating to the reader of this article a limitation on what can be concluded from this article, correct?

A. That is correct.

Q. If you take a look a little bit -- let me ask you a different question.

In this write-up Dr. Do -- you've read this article, right?

A. Yes.

Q. Dr. Do didn't propose five loading doses in this article?

A. No.

Q. And, actually, if we go down a little bit further on page 7, in the paragraph starting "because," she writes, "Because there is considerable individual variation in the progression of DME, patients could benefit from an individualized as-needed treatment regimen," correct?

A. I see that.

Q. That's what she wrote in this article?

A. That's correct.

Q. And if you go down a little bit further in that same paragraph, she wrote, "The results of this study support additional Phase III clinical studies with every-two-month dosing of VEGF Trap-Eye after an initial loading dose."

Do you see that?

A. I see that.

Q. That's what Dr. Do, the lead investigator on the study, wrote as a take-away from the study, correct?

A. I believe so, yes.
Q. We can take that document down.
You agree that DME is a slower-progressing disease than wet AMD?
A. I think that's true.
Q. And that is something that has been known for a while, correct?
A. That's correct.
Q. Lucentis was approved for DME in August of 2012. Does that sound about right?
A. That sounds about right.
Q. The dose amount in the FDA-approved label for DME was .3 milligrams, right?
A. That's correct.
Q. And that's lower than the dose amount that was approved for AMD, which is .5 milligrams, correct?
A. That's correct.
Q. You understood that the reason for the lower dose in the Lucentis label was that the FDA was concerned about possible systemic side effects from a higher dose of ranibizumab, right?
A. That in conjunction with the fact that there was no significant benefit to the higher dose, yes.
Q. All right. I'd like to change topics a little bit and start talking about the Lalwani 2009B article -- or the

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Lalwani review article from 2009, if we pull up DTX 2733.

And this is an article you addressed on your direct testimony, right?

A. That is correct.

Q. You would agree that in her 2009 review article that we're looking at here, Dr. Lalwani does not propose an ultimate solution for how to treat DME, does she?

A. I'm just thinking about that question. I think physicians very rarely propose ultimate solutions on treatment. She does not -- she's reporting data that's available and discussing some interpretation of that data that may help educate her therapeutic decisions towards her patients. There is no ultimate treatment regimen proposed or advised.

Q. If you take a look -- if we go forward a little bit to .0002 of this document, there is a paragraph partway down where she writes, in connection with the trial she's been discussing, "Both these higher-dose trials demonstrate a clinical and statistical superiority to sham treatments in terms of visual acuity and decrease in CRT. Additional trials will be necessary to determine the most effective dosing and treatment interval strategies," right?

A. I see that the article says that, yes.

Q. That's what she disclosed after going through her review of some of the current DME trials, right?

A. I think she's specifically here talking about two

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trials. I'm not exactly aware of which two trials she's talking about.

Q. All right. If we take a look at the conclusion of this article.

A. Okay.

Q. She writes in part, going down toward the bottom there, "Unlike neovascular AMD, which has in most cases responded to direct VEGF blockade, it appears likely that the treatment of DME will be more of an art form with tailoring of treatments for individual patients," correct?

A. That's what she said, yes.

Q. She's proposing an individualized treatment approach?

A. I'm just trying to understand what the context of this sentence -- do you mind repeating the question again?

Q. I'll get it as close to the same as I can.

Here in this article at her conclusion for treating DME, unlike she says AMD, it "will be more of an art form with tailoring of treatments for individual patients," and that is the approach she is proposing.

A. I think what she's trying to draw a distinction between is that in AMD -- and I hope I'm not taking this out of context, but my reading of this here is that what she means by direct VEGF blockade is that an intravitreal anti-VEGF injection is going to be the most beneficial and probably be used consistently among the entire population of exudative AMD

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patients, whereas in DME patients the treating physician may have to take into account other factors -- I'm not exactly sure what, but one could envision maybe the overall health of the patient and the risk for systemic side effects -- in choosing among the different treatment strategies across different pharmaceutical products that might be most appropriate for that patient.

I think that's what she's trying to say because I'm not sure direct VEGF blockade, how that's in contradistinction to tailoring treatment for individual patients. I don't think she's just talking about prn dosing because that's also direct VEGF blockade, right? So I think she's talking about choosing among various different types of treatment strategies that are listed in the second half of this review article.

Q. Dr. Albini, this article is what's sometimes referred to as a review article?

A. That's correct.

Q. And she does not -- you've studied this in connection with your testimony today?

A. I've read it a few times, yes.

Q. She does not identify any trials in which the investigators were experimenting with different loading doses, correct?

A. She describes a few trials, including CLEAR-IT that we've talked about and RESOLVE trial and so on, that have

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loading doses. So, no, I don't think your statement is correct. She describes quite a few trials that have -- that are experimenting with loading doses.

Q. She does not identify any trials that are experimenting with different numbers of loading doses against each other, correct?

A. I'm just trying to think. The READ and the RESOLVE. I don't think within each -- any trial there are arms pitted against each other with different loading dose strategies the way they were in CLEAR-IT. I think that's true, yes.

Q. I'd like to touch briefly on a different -- I'd like to go to one other article. One of the trials that Dr. Lalwani talks about is the RESOLVE trial. Do you recall that?

A. I do.

Q. And let's pull up DTX 4209. And this is a publication summarizing the 12-month RESOLVE Phase II study; is that right?

A. That's correct.

Q. And RESOLVE trial was experimenting with different dose amounts of ranibizumab and DME, right?

A. It had a dose-doubling component to the methodology where, if patients met certain clinical criteria, the dose, for a particular injection, could be doubled, yes.

Q. The RESOLVE trial did not have five loading doses, right?

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A. I believe it had regular loading doses. I don't want to say off the top of my head what the number is. I would guess it's three, maybe four. Maybe you can tell me. But I think that it did have then prn dosing. So, again, there were some patients that would have -- would have indeed received five regular doses at the beginning of the trial. That's, at least, my recollection of the way this study was designed.

Q. It did not involve anything called five loading doses. You know that?

A. I don't believe that the terminology that you're proposing was used, but I do want to offer to the Court that there were some patients who did in this trial, to the best of my knowledge, receive five regular doses at the beginning of the trial, yes.

Q. I'd like to go to the conclusion paragraph. This is by -- the lead author here is Pascale Massin. Is that right?

A. I'm not sure how to pronounce his name. I'm with you on this one. Massin? I don't know.

Q. That's fine.

A. He's French.

Q. That's fine, Dr. Albini. So we'll share that same perhaps botched pronunciation.

A. Okay.

Q. So if we go down to the bottom of -- I'm actually looking to go down to the bottom of .0006, or the paragraph

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that starts "given the nature of diabetes." It's actually -- yes, thank you.

And if we pull that out, what Dr. -- we'll call Massin says is "Given the nature of diabetes and variability in patients with DME with regard to disease progression and vision loss, there is a need for an individualized treatment regimen."

Do you see that?

A. I do see that.

Q. And what Dr. Massin concluded in his resolve write-up?

A. I do see that, yes.

Q. We can take that down.

As of late 2010, there were not any approved anti-VEGF treatments for DME at all, were there?

THE COURT: What year was that, Counsel, again? I'm sorry.

MS. OBERWETTER: I'm sorry. Do you want me to repeat?

THE COURT: Yes, please. Sorry.

MS. OBERWETTER: Oh, of course.

BY MS. OBERWETTER:

Q. As of late 2010 there weren't any approved anti-VEGF treatments to diabetic macular edema at all, correct?

A. I don't think that ranibizumab was approved by 2010. I recall that Macugen, I think, did get a label for DME at some

point, but I can't recall right now off the top of my head what year. But anyway, it probably doesn't matter.

But I just want to put that in there because Macugen may have been approved. I'm not 100 percent certain about that. But to the best of my recollection, ranibizumab was not.

Q. Okay. As of late 2010, Regeneron had not reported the results of its Phase II DA VINCI trial, its one-year Phase II DA VINCI trial, correct?

A. I don't think so.

Q. Okay. Do you know of a doctor named Ursula Schmidt-Erfurth?

A. Yes.

Q. She is well known to the retina community?

A. Yes.

Q. If we take a look at DTX 8151-A -- and we have appended the A to it because it was given to us as part of a broader 8151 collection -- this is a review early about the state of DME treatments.

Do you see that?

A. I do.

Q. It's the same type of article as the Lalwani 2009 review article we were just looking at a few minutes ago, right?

A. I don't remember if I've ever read this article in its entirety, but I'm assuming. It certainly looks like it on

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the surface of things, yes.

Q. The date of this article, if we look at the bottom of the first page in the right-hand corner or the left-hand -- that's fine -- is -- actually, if we go down to the publication date in the bottom right, it's December 2010.

Do you see that?

A. I do.

Q. If we take a look at page 4 of this article, there's a discussion of the DA VINCI Phase II trial on this page.

Do you see that?

A. I do now, yes.

Q. Okay. And what Dr. Schmidt-Erfurth -- first of all, she identifies the ongoing DA VINCI trial up there at the top, right?

A. I see.

Q. And then she says, "The study will follow these patients for 52 weeks, and it will be interesting to see if the results suggest that the dosing frequency with anti-VEGF compounds can be reduced from monthly injections based on these results," correct?

A. I see that.

Q. All right. She doesn't offer a prediction there based on the work in her review article, correct?

A. She doesn't here. She's saying that she's interested to see what the outcome is, but I think you cannot infer either

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a positive or a negative anticipation of success from what she's saying. Sounds like a very neutral statement.

Q. The neutral statement doesn't offer a prediction?

A. Of course not, no.

Q. If we go to the conclusion of her article that spans pages 5 and 6, she notes, first of all, that laser was still the standard of care, correct? If you look at "Thus the current standard of care is still appropriate."

A. I think one has to be careful when interpreting this comment about the standard of care. I think that, first of all, this physician doesn't practice in the United States; so she's practicing in a community that has very different regulatory bounds on it. And they're of some importance when discussing the treatment of DME in that time period prior to 2010 because in that time period bevacizumab used off-label was increasingly used and, I'm sure by 2010, was fairly routinely used in the treatment of DME.

So in European countries -- she practices in Austria -- I think there is -- there was actually a slower acceptance of bevacizumab and there was more heightened regulation of having to use the governmentally approved substance.

So in her treatment environment, she may not have had an anti-VEGF available for her to use for AMD, but that is not the case for sure in the United States after the advent of

bevacizumab in 2005.

Q. What she wrote midway through that paragraph was "This article presents an overview of the current state of knowledge regarding treatment mechanisms and modalities under investigation for DME," correct?

A. I see that she wrote that.

MS. OBERWETTER: Move to admit into evidence DTX 8151-A.

THE COURT: Any objection?

MR. McLAUGHLIN: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 8151-A was admitted.)

BY MS. OBERWETTER:

Q. Dr. Albini, you've cited this Dr. Schmidt-Erfurth article a couple of times in some of your IPR declarations; is that right?

A. I'll be honest. I don't recall the specific areas where I've cited it, but I'm not surprised to hear that.

Q. And just to refresh your recollection, if we pull up DTX 8151-B, which again we have marked individually out of a broader DTX 8151 compilation, this is your declaration from one of the IPR proceedings where you have offered written testimony?

A. Yes.

Q. And if we go down to paragraph 62 on page 34.

And you can see down toward the bottom of that excerpt that you have cited Dr. Schmidt-Erfurth's December 2010 review article previously, correct?

A. Yeah. Let me just -- I'm sorry. There's a lot of parentheses here. I'm just trying to figure out what I was trying to say.

Yeah, I have to admit I'm not 100 percent certain that that text in brackets there, "The ranibizumab PrONTO study suggested that flexible OCT-guided treatment would sustain visual acuity with fewer injections, a concept which has since become a popular model in clinical practice, particularly in Europe."

I'm assuming that's from that article, but I'm not 100 percent certain. But if you're asking me whether I had cited this article, if that's a correct reference, yeah, I did. I see that.

Q. Okay. You did not include Dr. Schmidt-Erfurth's December 2010 review article about DME on your materials considered list for this case, correct?

A. I don't recall. I don't think so, but I'm not certain.

Q. Okay. We can take that document down.

Dr. Albini, I want to go back to Slide 152 from your direct examination. And Slide 152 we looked at a little bit earlier for its listing of some of the clinical trials that

existed in the pre-2011 time period.

Do you see that?

A. That's correct.

Q. You cite a READ 1 trial, correct?

A. That's correct.

Q. There was also a READ 2 trial, wasn't there?

A. That's correct.

Q. You chose not to include READ 2 on this chart?

A. That's correct.

Q. And that was your decision?

A. That's correct.

Q. You actually cited READ 2 in your opening report in this case; is that right?

A. I believe so.

Q. Let's take a look at your -- an excerpt of your opening report. If we go to PTX 487.

And you recognize this as a copy of your opening report from this case?

A. Yes.

Q. And if we go to paragraph 327 of your report.

THE COURT: Before we do that, Counsel, again recognizing there's confidential information in this report, any concerns from defense?

Negative head shakes. Okay.

MR. McLAUGHLIN: No concerns from us, Your Honor.

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THE COURT: Understood.

Go right ahead, Counsel.

MS. OBERWETTER: Thank you, Your Honor.

BY MS. OBERWETTER:

Q. If we take a look at paragraph 327 of this report, you've got a reference to Dr. Lalwani's article and then a reference to the READ 1 article, and then at the last sentence says, "The author further notes the READ 2 program that followed READ 1 employed monthly dosing through 12 months."

Do you see that?

A. Yes.

Q. Okay. Now, you didn't put READ 2 on your list of clinical trials, right?

A. It's not on that list that we talked about, that's correct.

Q. All right. READ 2 did not actually employ monthly dosing, did it?

A. You know, I have to apologize. There's so many different trials and so many different but yet very similar dosing regimens in these trials. Obviously, when I wrote this, I thought it did. If I'm in error, I apologize.

But it looks -- as I read my text here today, it looks that I was under impression that it employed a monthly dosing regimen through 12 months.

So the way you're asking the question, I'm guessing

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that I was wrong about that. I apologize if that's true. There's a lot of different studies here. So not that I didn't take this seriously, but these reports are very, very long, as you know, and there are many, many citations here.

But please tell me if I did get that wrong.

Q. Let's take this document down.

Let's take a look at a document that we've marked as PTX 3304 that we can pass around.

MS. OBERWETTER: Approach the witness, Your Honor.

THE COURT: You may.

BY MS. OBERWETTER:

Q. Dr. Albini, what I handed you -- I've been asked to correct the record -- is actually PTX 3340, just so the number is correct.

A. I see that.

Q. Does this -- the title of the article is "One-Year Results Showing Ongoing Benefit of Ranibizumab for DME."

Does this article refresh your recollection that there was a different clinical trial regimen in READ 2?

A. As I'm skimming it here, yes. I see that this article describes "Beginning at six months re-treatment was performed on a prn basis." I'm assuming that's in all the arms. I'm not sure.

But, anyway, I see that it's certainly not 12 monthly injections, which is what I inferred from my opening report

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that you showed me.

Q. Okay. I gather you're not familiar with the READ 2 trial even though you cited it in your opening report?

A. I believe that I may be confused about the exact dosing regimen. I wouldn't say that I'm not familiar with the trial, but I would say that I can't recollect the exact dosing regimen.

Q. Is this a trial that you chose not to include on your list of trials or one that you didn't think about?

A. I think I thought about it, as evidenced by the fact that it was cited, although possibly incorrectly. So I wouldn't say that I didn't think about it.

I think that it may have not been evidence -- either because of the timing of when the results were announced or because of the data that was there, it may have not been the best trial to choose to make the point that I was trying to make.

So I don't think that the work that's been submitted is an exhaustive compendium of all the clinical trials with anti-VEGFs that were available at that time. I certainly don't think that this was left out with any sort of covert intention or for some reason.

I think there's only -- so, I mean, this took already six hours today. I don't know how many more trials we could have gone through. There's a limit to what all can be covered.

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But so my intention wasn't to have been exhaustive about everything that was there.

Q. The date of this article is February 1, 2010, correct?

A. Of this particular publication. I don't know when the formal publications came out. I'm not exactly sure what the context of this -- this is clearly an internet -- oh, looks like this is an article from *Ophthalmology Times*, and I assume that's dated February 1st.

Q. There were -- if you look at the number of patients who are described in READ 2, it's 126, correct?

A. That's correct.

Q. That's more than ten?

A. I would not disagree with that.

Q. More than ten in the READ 1 trial?

A. That's true.

Q. In the READ 2 trial you would agree that there was a six-month phase where various arms were tested, if you look down at that fifth paragraph of this document.

A. Sorry. The fifth paragraph of the document. The paragraph that starts "initially patients"?

Q. Yes.

A. Okay. I see what's described there.

Q. First of all, one of those arms had a group that received an injection of .5 milligrams at baseline in month one

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and in month three and in month five.

Do you see that?

A. I see that. So that sounds like three loading doses and then q8-week interval.

Q. Could that be two loading doses if you do two and then go further?

A. I think the supposition usually in clinical trials is that the patients are treated at month zero. So there's a first initial treatment, and then -- unless this is a very unusual trial and they didn't treat on the first visit, but typically they're treated at zero.

Q. So, Dr. Albini, I don't want to get too hung up here, but there's one at baseline and one at month one and then they skip one, correct?

A. You're right. You're right. I apologize. Yes. So two monthly loading doses followed by two q8-week loading doses. Yes, that's true.

Q. All right. And then starting in the next paragraph, it notes that "Beginning at six months, re-treatment was performed on a prn basis."

Do you see that in the next paragraph?

A. I do see that.

Q. And then it says, "Starting at six months, patients in the ranibizumab arm could be re-treated no more than once every two months and laser re-treatment no more than once every

three months."

Do you see that?

A. I see that.

Q. And that was a every-two-month prn schedule, correct?

A. That's what it sounds like from this description, yes.

Q. All right. Now, at the top of this same page that we've been on, there's a quote from Dr. Do that says, "The results from the READ 2 trial Phase II study demonstrate this anti-VEGF agent has biological activity in treating DME," and then it goes on to say that "More frequent injections may be needed to achieve enhanced visual acuity benefits."

Do you see that, sir?

A. I do. I see it.

Q. And that's a point that Dr. Do made in this article about the READ 2 one-year results in ranibizumab.

A. Is that a question or a statement?

Q. That's a question.

A. Yes, I believe so.

Q. And then if you go to page 2 of this document, it notes that by the end of 12 months the ranibizumab group had gained a mean of, I think, 6.69 letters.

Do you see that?

A. Not really.

Q. It's down under "Outcomes Comparison."

A. "Outcomes Comparison." I see that.

Q. And then if you go down a little further where Dr. Do concludes the article, she notes that "Genentech's Phase III trials for DME were testing monthly ranibizumab," correct?

A. She does say that, that's correct.

Q. And you know that those were the RISE and RIDE trials that were ongoing as of this point in time?

A. That's what she says there, yes.

Q. That's not just what she says. You know the RISE and RIDE trials were ongoing at that time?

A. That's correct.

Q. You did not mention the RISE and RIDE trials in your direct examination either, right?

A. That's correct.

Q. We can take that down.

Now, the READ 2 trial actually continued into a third year, correct?

A. I'd have to refresh my memory.

Q. You're not familiar with what happened in year three of the READ 2 trial?

A. I don't know that I can give you all the details of it. I don't -- I would have to refresh my memory. I don't think I've looked at the three-year results of the READ 2 trial in quite some time.

Q. Let's take a look at another exhibit that I will pass

around, which will be PTX 3342.

MS. OBERWETTER: And before I proceed with this one, I'd move to admit PTX 3340.

THE COURT: Any objection to 3340?

MR. McLAUGHLIN: We do object, Your Honor. So we've been scrambling over here a little bit to find out when it was produced to us. Doesn't appear on their original pretrial exchanges of their exhibits. This is the first time we're aware of this being offered to us. So we do object to it being moved into evidence.

THE COURT: Previously disclosed, Counsel?

MS. OBERWETTER: This is impeachment material, Your Honor.

THE COURT: Overruled.

BY MS. OBERWETTER:

Q. Dr. Albini, do you have PTX 3342 in front of you?

A. Yes.

Q. Okay.

THE COURT: Yes, Counsel.

MR. McLAUGHLIN: Your Honor, it's my understanding that the parties agreed that impeachment materials would not be moved into evidence.

THE COURT: We're going to have a discussion about the parties' agreement. The rules of civil procedure permit the use of impeachment material solely for that purpose. It

wasn't previously disclosed. At this point the objection is overruled.

BY MS. OBERWETTER:

Q. Dr. Albini, you have PTX 3342 in front of you, correct?

A. I do.

Q. And this relates to the three-year outcomes for the READ 2 trial; is that right?

A. That's correct.

Q. And the first author on this paper is Diana Do?

A. That's correct.

Q. And the dates listed on this paper, if you go over to the middle right of the first page, are -- there's a publication of 2013 but also published online October 8th, 2012.

Do you see that?

A. I'm sorry. Published online 2012. I'm not -- oh, over here. I see it. Yes, I see it.

Q. And if we take a look at page 142 of this article under the header "Need for Ranibizumab Injections in Year 3."

A. I see that.

Q. Do you see that page? And it says, "During year three, 14 to 28 patients, 50 percent, in the ranibizumab group met the re-treatment criteria at more than six visits and thus needed injections more frequently than every two months."

Do you see that?

A. I see that.

Q. Okay. And that is what Dr. Do is reporting happened in year three of the READ 2 trial?

A. That appears to be what she's reporting, yes.

Q. And if we take a look at the bottom of page 143 and continuing on to the top of page 144.

If we can pull that up.

And if we look down a little bit, please feel free to read that paragraph. But it says, "Despite a good visual outcome, substantial residual macular edema was noted in several patients, suggesting that receiving intraocular injections of ranibizumab only as frequently as every two months was not sufficient for many of them."

Do you see that?

A. I see that.

Q. And that is the conclusion that she reported in writing up year three of the READ 2 study, right?

A. I see that that's what she reported, yes, or concluded, yeah.

Q. And this is not a component of the READ 2 trial that you included either in your report or in your statements on direct examination, correct?

A. That's correct.

MS. OBERWETTER: Move to admit PTX 3342.

THE COURT: Any objection to 3342?

MR. McLAUGHLIN: Your Honor, at this time, yes, we do object for the same reasons as the previous one. And just to get some clarity, we're not objecting to the use of this on impeachment; our sole objection is its movement into evidence with respect to this one and the prior document.

THE COURT: Understood. For same reasons, overruled.

So the record's clear, 3340 and 3342 will be deemed admitted, recognizing it is being used as impeachment and will be afforded the weight it should be moving forward.

MR. McLAUGHLIN: Is it all right to address that in the posttrial briefing?

THE COURT: I'm sure if Madam Court Reporter has it down, of course, Counsel.

(PTX 3342 and 3340 were admitted.)

MR. McLAUGHLIN: Thank you, Your Honor.

MS. OBERWETTER: We can take that document down.

BY MS. OBERWETTER:

Q. There's a different document that was addressed in your direct examination, Dr. Albini, which was DDX 6.92, so Slide 92.

Dr. Albini, you have this slide back up in front of you?

A. I do.

Q. And it's referencing DTX 4129, correct?

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A. That's correct.

Q. And I'd like to -- first of all, this is an internal Regeneron document that you cited, right?

A. That is correct.

Q. And you cited it with reference to that "no more than three to six doses" language down in the bottom right hand of the page?

A. Right. That that would be a target product profile for aflibercept in DME.

Q. You've not found a publication that includes the language "no more than three to six doses," right?

A. I have not.

Q. Okay. It also lists -- it says monthly -- it says, "No more than three to six doses including monthly loading for first three months."

Do you see that?

A. Yes.

Q. And you are not -- first of all, that's the only number of loading doses that appears on this page, is three?

A. That's the only number of doses termed as loading doses, but the range of up to six doses given in the first six months is described there.

Q. So. You -- I apologize.

A. That would be a dose every month for six months.

Q. You have not cited or relied on any testimony

explaining the reference to induction, correct?

A. Explaining the reference for induction?

Q. Let me -- go ahead, Doctor.

A. Well, I think what I am citing here is that within Regeneron, they were discussing the need for three to six doses within the first six months in initiating treatment, which is the way that I read that -- the term "induction" there.

Q. My question is a little bit different.

You haven't relied on any fact witness testimony to explain what the reference to induction is there, correct?

A. I have not.

Q. All right. There's also nothing in that section of the document about fixed extended interval dosing, correct?

A. I do not see anything about fixed interval -- extended interval dosing.

Q. When was this document written relative to when the DA VINCI trial commenced?

A. That, I don't know.

MS. OBERWETTER: We can take that document down.

I'm going to change topics a little bit.

THE COURT: Counsel, if we're going to do that, good time to take a break?

MS. OBERWETTER: This works fine for a break, Your Honor.

THE COURT: Okay. We'll break. I don't want to

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interrupt the flow, but let's do that.

Doctor, you continue to remain midstream; so no one can converse with you. No one is being rude or discourteous. It's just the rules we abide by. You get to step down, take a personal comfort break, whatever you need, sir.

THE WITNESS: Fair enough. Thank you.

THE COURT: We'll take a break and be back in ten minutes. Thank you all.

(A recess was taken from 2:57 p.m. to 3:11 p.m.)

THE COURT: Counsel, are you ready to proceed?

MS. OBERWETTER: I'm ready to proceed, Your Honor.

THE COURT: Doctor, are you ready?

THE WITNESS: I sure am.

THE COURT: Great. Go right ahead.

BY MS. OBERWETTER:

Q. Dr. Albini, I'm going to return briefly to some of the opinions you've offered on Claim 6 and the isotonic solution limitation we were talking about earlier.

A. Okay.

Q. You would agree there could be formulations, comfortable and nonirritating, that are outside of the range of isotonic, right?

A. Not through what I've learned from Dr. Rabinow. So, no, I'm not sure that what you're saying is true.

Q. You don't know anything about that absent Dr. Rabinow, correct?

A. I am definitely relying on him because I have not offered myself as an expert in formulation. So I am using his teaching in addition to my reading of Dixon to make a conclusion about that issue.

Q. You would agree that, as of 2011, it was not known publicly what formulation Eylea was?

A. I would anticipate that that's true. I don't know for a fact what exactly about the formulation of Eylea was known in 2011. So I can't be 100 percent certain, but I would guess that the exact -- that the exact formulation was not known.

Q. You would agree that it was not public in 2011 what formulation was used in the Phase III trial described in Dixon, correct?

A. When you say what formulation, I believe that it was -- it's -- that the POSA and myself as a POSA would have interpreted that the formulation used in the clinical trials was the same as the formulation that was used in the commercially available product.

Q. The commercially available product was known later, right? Not in 2011?

A. Was known later?

Q. Right. It came onto the market after the Phase III

trials, correct?

A. Yes, but it was known well before it came out to the market.

Q. You would agree that it was not public in 2011 what formulation was used in the Phase III trial described in Dixon prior to Eylea coming onto the market?

A. As I've said, I think that the POSA would have known that the formulation that's used in the clinical trials is the same as the formulation that's brought to market.

Q. You know that once the product is brought to market, not before, correct?

A. No, I think you'd know that the product that will be brought to market is the product that's studied in the trials. I think there's an assumption that it's the same product; otherwise, we wouldn't use the clinical trials to help guide us with the use of new product.

Q. You have not identified a publication that spells out the formulation of Eylea publicly prior to it coming onto the market?

A. I have not.

Q. Okay. I'm going to change topics.

I'd like to -- you offered some opinions on your direct testimony about the '747 patent and anticipation.

Do you recall that generally?

A. I do.

Q. So let's pull up DTX 2730 and go to Example 17, which is at Column 20.

Dr. Albini, you agree that Example 17 does not itself talk about diabetic macular edema, correct?

A. I believe that this patent directs itself at angiogenic eye disorders.

Q. So my question was different. There's a title on Example 17 that says "Treatment of Age-Related Macular Degeneration," correct?

A. Yes.

Q. Example 17 does not talk about DME?

A. That is correct.

Q. Example 17 does not contain a reference to a loading phase of dosing a patient, correct?

A. It does not use that term "loading phase," that is correct.

Q. And, in fact, Example 17 discusses repeated visits back to the doctor during the first month, right?

A. It does.

Q. You have to go outside of the embodiment of Example 17 in this patent to find DME anywhere, right?

A. I believe that's true.

Q. And in forming your opinions in this case, you did not attempt to calculate the total number of regimens that are contained in Example 17, correct?

A. I did not quantify that, no.

Q. Or in the patent as a whole, correct?

A. That's correct.

Q. And I think you testified at your deposition you weren't interested in doing that because you don't like to do infinite things; is that right?

A. I don't recall if that's exactly what I said, but I think I would be very bad at doing something that's infinite.

But there's a very large number of possible regimens that are covered by this if one doesn't have a limit on the time extension that you're looking at.

But within a 6-month period or a 12-month period, there's a more limited number of regimens. But even within that period, I have to admit I have not calculated the exact number of permutations possible.

Q. Looking at Example 17 during your deposition, you referred to it as "infinite"; is that correct?

A. Honestly, I don't remember that text in the deposition, but I can't see why you would be misleading me. I'm sure that I did.

Q. I'd like to talk a little bit about the September 2009 press release that was the subject of your direct testimony, if we can pull up PTX 2617.

And this is the September 2009 Regeneron press release that you testified about.

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A. That's correct.

Q. There is a section on page 2, if we scroll forward to that, that talks about the Phase II development program in DME.

Do you see that right above "about wet AMD"?

A. I see that.

Q. Now, that discussion talks about three monthly loading doses on its face, correct?

A. Yes.

Q. And after the loading doses, any additional doses are based on prn assessment, correct?

A. That's correct.

Q. Those are not going to be fixed interval doses, right?

A. The most frequently they can occur is every month. So in that sense, they're fixed interval in that they certainly can't happen at every two weeks or every three weeks or something like that. So they are partially fixed. But they are not fixed in that patients are not going to be necessarily getting an injection every single month, although they might.

Q. In your anticipation analysis that you performed in this case, you're also assuming that these are monthly prn visits, correct?

A. That's correct.

Q. Okay. And let's take a look at Slide 52 from your direct examination. This is a slide that you used to talk

about anticipation in connection with the September 2009 press release; is that right?

A. Yes.

Q. Giving someone three loading doses and then a prn regimen does not necessarily result in that person receiving a dose at Week 12, correct?

A. The Week 12 dose is one possibility from that dosing regimen, but it is not necessarily going to occur.

Q. And if you give someone three loading doses and then you give them a prn dose at Week 12, that also does not necessarily result in that person receiving a dose at Week 16, correct?

A. It would -- correct. It would depend on the assessment of the patient at that visit.

Q. You would agree that the terminology of "loading doses" implies an early adherence to monthly treatment regardless of patient outcome for a certain number of doses, correct?

A. That sounds fair.

Q. Okay. And prn doses after loading doses would be quite different because it would include regular visits but doses only when needed, right?

A. That's correct.

Q. We can take that slide down.

I want to return briefly to we talked about the

RESOLVE trial a little bit in connection with dosing studies for ranibizumab.

Do you recall that?

A. I do.

Q. You have not undertaken an analysis of the RESOLVE trial to understand if anyone in that trial got five initial doses, whether you call them loading doses or not, right? That's not an analysis you performed?

A. You mean historically whether that actually occurred to go back and look at the trial data and find how many patients may have obtained that? I have not had access to the data to be able to do that.

Q. Okay. You haven't found out how many, if any, correct?

A. I haven't found out how many, that's true.

Q. Okay. I want to change topics a little bit. And let's look at Slide 91, which was part of your direct testimony.

There's a reference in the bottom line to the Copernicus trial. Do you see that?

A. I see that.

Q. You mentioned there the Copernicus trial you refer to always having six monthly loading doses on that page. Do you see that?

A. I do see that.

Q. Let's take a look at DTX 3198, which should be another press release.

And we're back at a September 2009 press release, and if we go again to page 2 of the press release, there's a reference in that top paragraph to the COPERNICUS trial.

Do you see that?

A. I do.

Q. There's no terminology there that refers to six loading doses, correct?

A. I don't see the term "loading doses," but again, it seems to describe six monthly intravitreal injections of VEGF Trap-Eye.

Q. Dr. Albini, it refers to six monthly injections when there is a primary end point of six months, correct?

A. That is correct.

Q. We can take that document down.

I'm going to change topics a little bit. I have a few questions for you about VEGF agents generally. You would agree that early on in the development of aflibercept, researchers recognized the promise of targeting angiogenesis as a therapeutic strategy for treating diseases characterized by increased vascularity?

A. Specifically neovascularization, but yes.

Q. You agree that angiogenic eye disorders are generally characterized by increased vascularity?

A. Specifically new vessels and also by decreased patency of less of the vessels where there's fluid that leaked into the retina. By both those characteristics, yes.

Q. Prior to the January 2011 date that we've been talking about, there was literature that, in your view, that VEGF Trap may be useful in the treatment of retinopathies given the contribution of pathological angiogenesis, correct?

A. That is correct.

Q. You also believed that the medical community believed before January 2011 that VEGF Trap-Eye could translate to good clinical efficacy outcomes, correct?

A. I think that was evidenced by a number of the publications that were reviewed towards the end of my direct testimony.

Q. Okay. And that's good clinical efficacy outcomes for angiogenic eye disorders, correct?

A. That is correct.

Q. And you believe that subsequent work by Regeneron reinforced VEGF Trap's potential as a possible angiogenic therapy for vascular eye diseases, correct?

A. That is correct.

Q. You understand that some of the claims in the patents use the word "approximately"; is that right?

A. I've seen that, yes.

Q. And the terms "approximately every four weeks" and

"approximately monthly" can be understood as meaning the same thing in the context of anti-VEGF dosing regimens, correct?

MR. McLAUGHLIN: Objection, scope. It's beyond the scope of his testimony, Your Honor.

MS. OBERWETTER: Your Honor, it's in his report, which is context for the patent claims which he is purporting to talk about in this case.

THE COURT: Is it in his report, Counsel?

MR. McLAUGHLIN: If it is, I would like to see it. I'm not sure exactly what Ms. Oberwetter is referring to.

MS. OBERWETTER: Why don't we pull up paragraphs 144 to 145.

BY MS. OBERWETTER:

Q. Dr. Albini, in your report you wrote that, in your opinion, you viewed --

THE COURT: Hold on, Ms. Oberwetter, before he gets any questions.

Counsel, does that fall within this line of questioning?

THE WITNESS: I see that.

THE COURT: One second, Doctor. Thank you.

MR. McLAUGHLIN: I see the paragraphs that counsel's referring to, but this is not something where he provided an opinion on what the word "approximately" means. What he's talking about here is the difference between every four weeks

and monthly with respects to Claim 11, I believe -- yeah, Claim 11 of the '601 patent.

But he has not offered an opinion, nor did I ask one on his direct, what his views of "approximately" are in this claim.

THE COURT: Okay.

MS. OBERWETTER: Two responses Your Honor. One is we heard three hours of testimony this morning about the claims, which he is interpreting and applying, and I think this is relevant to his understanding of them.

Point two, I would rather do this all as a whole rather than figure out do we have to recall Dr. Albini in our case? I'd rather do this today. It makes sense to do it. This is part of his opinions that were disclosed and that he has said are his views.

THE COURT: Understood. Overruled.

Ask your question again, Counsel.

BY MS. OBERWETTER:

Q. Dr. Albini, you understand the terms "approximately every four weeks" and "approximately monthly" as meaning the same thing in the context of anti-VEGF dosing regimens, correct?

A. I think that what I was trying to say here -- and it is somewhat confusing with this language and the way this claim is written, but I do think that four weeks and monthly have an

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equivalence to them. They are nearly the same thing. There may be differences in the way that "approximately" modifies the four-week period versus the monthly period.

So as to say as the time around the four-week period that's approximated, the range of time that would fall within that "approximately every four weeks" may be different than the range of time that falls in the term "approximately monthly" so that, when you say approximately monthly -- and this is just my interpretation of common usage of the English language -- I do agree that this claim is difficult to understand completely.

I would think that "approximately monthly" could mean monthly plus/minus one month, and approximately every four weeks could mean every four weeks plus/minus one week so that that interval might be difference if you really get down to it. Obviously, the terms are very, very similar.

Q. Dr. Albini, in your report you understood the phrases "approximately every four weeks" and "approximately monthly" sufficiently to equate them as meaning the same thing, right?

A. I did write that they mean the same thing. I may have not been focused as you've asked me -- or as least as I've perceived you've asked me to do here to look at the meaning of the word "approximately" within that.

And I do appreciate that "approximately" may be applied in slightly different ways to a four-week time interval versus a monthly interval, but I do think that monthly and four

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weeks are very, very similar and the same thing.

Q. We can take that slide down.

Dr. Albini, you would agree that as of 2011, the POSA would have known how to intravitreally administer an anti-VEGF agent, correct?

A. That is correct.

Q. And the POSA would have known how to do that approximately every four weeks?

A. Well, on the face of it, the obvious answer to the question is, if a POSA knows how to do it once, they know how to do it at any time interval.

The part that I'm hesitant about is I don't know that it would have been obvious necessarily what "approximately" means in and of itself. Certainly I think that, for example, if you were conducting a clinical trial and the trial said we're going to inject this drug approximately every four weeks, the trialist or the principal investigator would want to know what exactly does "approximately" mean? How big is that window? Can we be off by two days? by three days?

So I don't know that -- certainly the POSA would know how to do the injection. The question is whether the POSA would need more clarification as to that time interval.

Q. Dr. Albini, I'm going to see again if you remember your deposition in this case.

A. Sure.

Q. If we could please pull up page 230 from your deposition. And if we can put that side by side with 231.

I asked you, if you go down to line 18: "Okay. And maybe I'll get a similar answer here. But would the" --

Actually, I'm sorry. Can we pull that down and go up a little further? Apologies.

I asked at line 8:

"Q Would the POSA know how to do that approximately every four weeks?

"A He would know how to. He may not choose to, but he would know how to do that, yes."

And then I asked again at line 18:

"Q Maybe I'll get a similar answer here, but would the POSA know how to perform intravitreal injections approximately once every eight weeks?

"A I think if he can do it once, he can do it at any time interval."

Do you see that?

THE COURT: One second, Doctor.

Yes, Counsel?

MR. McLAUGHLIN: I'd like to object based on this being improper impeachment testimony. These are not the same questions that he was just asked, and he's not providing any

inconsistent testimony here.

THE COURT: I don't think that's been suggested yet. Understood. Overruled.

BY MS. OBERWETTER:

Q. Dr. Albini, these are the answers to my questions about "approximately" that you gave at your deposition, correct?

A. I think that, if you look at the context there, I was careful to say I'm still talking about the physical steps of doing it as opposed to understanding how the span of the time interval between the injections.

So if you're asking me would the POSA know how to administer the drug? Yes, they would know how to administer the drug. Would they know necessarily what "approximately every week" means? I don't think that they could know that without further clarification.

Q. That is not --

A. And I think that is consistent with the testimony that's on here.

Q. That is not clarification you sought when I asked you these questions at your deposition.

A. It's right there. I mean, I don't know. Do you not see it? I said, "And I'm still talking about the physical steps of doing it."

Q. Dr. Albini, would you agree that as of -- I'm going

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to change topics slightly.

Dr. Albini, we haven't spoken much yet about Avastin. That's bevacizumab, correct?

A. That's correct.

Q. And that was originally approved as a cancer treatment, correct?

A. That's correct.

Q. And we talked about how it's now used off-label to treat angiogenic eye disorders?

A. That's correct.

Q. I think you've testified on whatever the exact number is, it's inexpensive, and whether it's $50 or somewhere south of $200, it's in that range?

A. That's correct.

Q. In your view, any difference in efficacy -- this is your view -- any difference in efficacy between Avastin and Eylea is small, correct?

A. That's correct.

Q. You think Avastin is a good drug?

A. That's correct.

Q. And in your practice you've used a lot of Avastin, correct?

A. That's correct.

Q. Including through the present?

A. That's correct.

Q. Dr. Albini, you agree that important advancements in treating retina need to come from industry, right?

A. I know that I've said that on many occasions, and I think that given the complexity now of bringing a drug to market, I stand by that statement; they need to come from industry.

What I think might not be 100 percent true is to say that they can only come from industry. Avastin is a great example of a drug that was developed as a therapeutic agent for angiogenic eye disorders in spite of industry.

So I think there are few such examples in medicine, but I do think that Avastin is a good example where that rule that I -- or that teaching that I've given on the importance of industry and the further development of therapeutics, I think that that's an exception that proves the rule, but there are likely to be other exceptions too of important therapeutic advances that occur either without the support of industry or in spite of industry.

Q. Okay. And you have said there's an important role for industry because large organizations have more resources to bring to bear to get products to market, correct?

A. That is true.

Q. And those are things that cannot necessarily be done by physicians alone, correct?

A. Well, I wouldn't say cannot. So, again, I'll use the

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example of bevacizumab. There, Dr. Rosenfeld pretty much single-handedly brought that drug to its use. I'm sure other individuals were involved. But it was largely done by an academic institution and by a particular provider.

And so I don't know that it always has to be industry. I think in the vast majority of major progresses that are going to be made, I think it's safe to say most of them will have industry as a component of a product's success.

Q. Dr. Albini, you agree that a drug's formulation can be important to whether it is a good drug or not, correct?

A. I do agree.

Q. And, in fact, the formulation of a drug can be the key to the clinical success and efficacy of a treatment, correct?

A. I don't think the formulation can be a key to the efficacy of a treatment. I think that formulation can certainly get us into trouble with toxicity, presumably. But I think that formulation alone, aside from things like, you know, intravenous fluids, very simple things, if you're getting into more complicated molecular therapeutics, formulation alone can definitely not bring great efficacy.

Q. I'd like to take a look at page 129 of your June 22, 2022, deposition. And if we can put that side by side with 130.

And you were asked -- this is questions put to you in

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another deposition by another attorney, but you see at line 10 on 129 you were asked:

"Q Okay. And what I'm trying to understand is is it fair to say that, while the attributes of the molecule may be necessary, that they're not alone sufficient for the molecule to work on a given dosing regimen?

"A Certainly there are other attributes other than the molecule that are very important in the clinical success and efficacy of a treatment. The formulation, for example, is key."

Is that testimony you provided?

A. Yes, it is.

THE COURT: Yes, Counsel?

MR. McLAUGHLIN: Just want to object to this as being beyond the scope. This is a deposition that was taken in a different matter on a different patent and not this litigation.

THE COURT: Understood.

Counsel.

MS. OBERWETTER: Yes. It's proper impeachment evidence taken from another -- it wouldn't matter what case it was taken from.

THE COURT: What point are we impeaching the doctor on with this?

MS. OBERWETTER: Where he said he would not call formulation key.

THE COURT: Understood. Overruled.

MS. OBERWETTER: We can take that down.

BY MS. OBERWETTER:

Q. Dr. Albini, you would not prescribe a drug if it had an unsafe formulation, correct?

A. It depends on the context. I think that everything is a risk-benefit ratio. So if there was something that was, quote/unquote, unsafe about a drug but it was -- that the patient was certain to either go blind or lose their life without the drug, I think that you would administer that drug regardless of safety concerns.

So I think there's always a risk-benefit ratio. It's not -- I don't mean to make it sound as if it's always so stark between life and death, but there can be gradations within there.

Sometimes drugs with imperfect safety have such a big potential efficacy improvement that it makes sense to use them even with the safety concerns.

Certainly no drug is without safety concerns. We'd use no drugs ever if we never used any drugs with some safety issue.

Q. And you would agree that all attributes of a drug can be important to its commercial success, including things like

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its stability, its binding capacity, and its clearance, correct?

A. I believe all of the properties of a drug can be important attributes for that drug's safety and efficacy, yes.

MS. OBERWETTER: Nothing further, Your Honor. Pass the witness.

THE COURT: Understood. Thank you, Counsel.

Redirect?

MR. McLAUGHLIN: Yes, I do. Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. McLAUGHLIN:

Q. So I'd like to revisit with you, Dr. Albini, some of the questions that you heard from counsel today.

So when providing your opinions on reasonable expectation of success, you were considering the visual acuity outcomes, correct?

A. That's correct.

Q. And you understand that a reasonable expectation of success analysis, like what you've conducted in formulating your opinions in this case, requires a different standard than what is required for FDA approval; is that right?

A. That is correct.

Q. Do you also agree that drugs can fail for a number of reasons that are not related to the visual acuity outcomes, like the visual acuity that we've been discussing here today?

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A. That's correct.

Q. You were asked at one point about uncertainty as to the best dosing approaches for anti-VEGF agents.

Can I ask you, in your experience, in your practice, how were you treating patients in the clinic prior to 2010?

A. I think that much like what was described in that 2007 *Retinal Physician* report, I was using a prn and then progressing -- I don't remember exactly when I might have shifted -- to a treat-and-extend protocol.

And I don't think that I made that transition -- you know, that I decided one day I'm going to shift from one to the other. It was done on a patient-by-patient basis depending on issues. Certainly patients that had difficulty with transportation and coming in would be patients that I would shift to a treat-and-extend- protocol earlier than patients who had no problem coming in for their visits.

So I think there was a gradual transition where I shifted from prn dosing. I think I also used fewer loading doses as time went on in that time period from 2007 to 2010.

Q. But you don't dispute that there were regimens like treat and extend, as you indicated and showed in your presentation today, in use as early as 2007; is that right?

A. Absolutely. And documented in the literature, as was in my testimony.

Q. And treat and extend, is that the same type of

protocol that's currently used today?

A. I believe that that's the most commonly used treatment protocol today, yes.

Q. And does treat and extend involve individualized assessments?

A. It does. The -- one of the concepts of treat and extend is to try to determine what a dosing interval is that's required for a particular patient and then to stick to that interval. So some patients are seen as patients who require injections every four weeks, some every six weeks, some every eight weeks, and so on. And that's determined through trial and error for each individual patient.

Q. Were you using prn dosing as well in the pre-2010 time period?

A. Yes, I was.

Q. And that involved -- that was a regimen that would allow you to administer fewer injections to patients compared to a monthly dosing regimen, a fixed monthly dosing regimen, correct?

A. Yeah, that's true. And what I recall happening is that, as patients were coming in -- some patients, not all -- but as some patients came in for their, let's say, third month visit and there was no fluid seen and then they came in for their fourth month visit and there was no fluid seen, then it was a natural progression to say, "You know what? You don't

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have to come in next month. Come in in six weeks. Let's see you then." And then if there was no fluid -- so treat and extend kind of built out of prn in a very natural way for a lot of us.

Q. And treat and extend was an individualized dosing regimen that would allow not only an extension of time between injections but also an extension of time between office visits; is that right?

A. That's correct.

Q. Now, I'd like to ask you about a -- that 2008 presentation that you were shown earlier.

If I could ask to be put up on the screen, side by side, both DTX 0204 as well as that 2008 presentation. I believe it's DTX 3173.

Actually, while they're doing that, I wanted to ask you -- I'll jump ahead and ask you something else while they're finding those documents.

You were also asked about isotonicity by counsel?

A. That's correct.

Q. And your view of the injections of potentially nonisotonic formulations.

A. That's correct. I was asked about that, yes.

Q. Do you have a sense -- actually let me back up.

You were asked about the confidentiality of the Eylea formulation and what was known about it prior to 2011; is that

right?

A. That's correct.

Q. And you were asked about whether you were aware of any public disclosure of that formulation?

A. I was, yes.

Q. And you were asked about whether that formulation was confidential or not?

A. That's true. As you're asking me this question now, I'm realizing that there were certainly elements of that formulation that may not have been confidential that were known. So I maybe shouldn't have answered that as a blanket that it was not known. Some parts of the formulation I think probably were readily available and certainly could have been tested by anyone who bought the drug.

Q. Let me ask you this: Are you aware that in this litigation Regeneron is also asserting a formulation patent?

A. Yes, I'm aware of that.

Q. And I will represent to you that that formulation patent lists on its face an earliest application date of 2006, and I will also represent to you that Regeneron has represented the '865 patent covers Eylea.

Would that knowledge have been important to you in answering counsel's questions about the confidentiality and public nature of the Eylea formulation?

A. Yeah. Yes. Obviously, yes, it would have been. And

I'm sorry that I may have not answered that in the best possible way.

Q. No need to apologize, Dr. Albini.

A. I did not know that they had patented the formulation. I still don't know, sitting here now, whether the -- all the exact attributes of the formulation are available in this patent; but, again, certainly some components of the formulation would have been available, and some components of the formulation are disclosed in Dixon, as we've described earlier today.

Q. You were asked about the induction versus loading doses.

In your view, is there any real difference between induction doses and loading doses as the terms are used in practice?

A. I don't think that there was much use of the term "induction doses," and I certainly can't think of any loading doses that would not be induction doses. So I think there's a lot of overlap in those terms, and I don't know that there's any meaningful distinction in clinical practice -- or there is no meaningful distinction in clinical practice.

Q. Now that we have these documents up, let me go back to Dixon. That's 0204.

Now, you recall you were asked questions about the availability of this presentation. I believe in your earlier

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testimony, you confirmed that this presentation was cited in the references section of Dixon?

A. That's correct.

Q. And if we can go to that and take a look at that.

Let's go to the references portion of this article. Should be the second-to-last page. If we pull up Reference Number 45. If we can put it so that Dr. Albini can still see the image on the right.

It's the same title that we're looking at here?

A. Yes.

Q. Is that the same date?

A. Yes.

Q. If we go back to 0204, page 4, and if we move to page 12 of the document on the right.

So if we can look at Dixon, left-hand column towards the bottom, where it says, "Patients initially dosed on a 2-milligram schedule received an average of 1.6 more injections over the course of the treatment phase," is that consistent with the data shown to the right with respect to that dosing arm in the CLEAR-IT 2 clinical trial shown at Slide 12 where it says 1.55?

A. In here it says -- I'm sorry; I'm just confused. Here it says 1.6, and here it says 1.55. I would say those are consistent.

Q. And the 2 mg q4 regimen, do you understand that to be

the one with the every-four-month loading doses following by prn dosing?

A. That's right.

Q. Then if we flip to page 13 of this -- of the document on the right. What does it tell you about the time to reinjection in all patients in the CLEAR-IT 2 trial?

A. Somewhere it discloses the median time to reinjection. Just a minute here.

"The median time to first reinjection in all groups was 110 days," and that does look to be the exact same data that's reported in the slide on the right.

Q. Okay. Thank you.

We can take that down now.

Actually, one more thing. Can we just go back to 3173 and go to Slide 16.

Can you describe what's shown in this data here on Slide 16 of 3173?

A. This is mean change in visual acuity over time in two arms of the study, the 2-milligram dosing group that started off with the four monthly loading doses and then the .5 milligram dose with the four monthly loading doses and then prn treatment thereafter.

And do you see that there's -- in the 2-milligram group, there is a better visual acuity outcome of nine letters compared to 5.4 letters in the .5-milligram group.

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Q. Thank you. We can put that away now.

And if you recall, you were also asked about -- going back to isotonicity and your experience in injecting isotonic solutions, did the questions that were asked by counsel, did that change your opinion that a POSA clinician like yourself would accept that the aflibercept formulated for comfortable, nonirritating injection was inherently isotonic?

A. Especially after considering the teachings of a formulation expert like Dr. Rabinow, I don't think that the POSA would have -- that there's nothing in the cross-examination here today that would change anybody's mind about that.

Q. Okay. Do you recall you were also asked about the '747 patent by counsel?

A. That's correct.

Q. Specifically Example 17?

A. That's correct.

Q. That Example 17 is an example of a method of treating angiogenic eye disorder, like AMD?

A. That's correct.

Q. Is there anything that would have prevented somebody from also trying that with the diabetic retinopathy that's also disclosed in the '747 patent?

A. I think no. And, again, as an argument for the rationality of looking across diseases, we have the internal

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communications of Regeneron showing that they based some of their study design in the DME trials based on AMD trial data.

So I think people did use information from one disease space to guide their therapeutic approaches in another disease with these anti-VEGF agents.

Q. If we can pull up DTX 2198.

Just like to ask you a question that you were asked about that document with respect to RVO.

A. Sure.

Q. If we could go to page 2 of this document, top paragraph.

This is the paragraph that you were shown by counsel?

A. Yes.

Q. And this discloses that patients in both studies will receive six monthly intravitreal injections via the VEGF Trap-Eye at a dose of 2 milligrams or sham-controlled injections.

Do you see that?

A. Yes.

Q. But then this section also continues, doesn't it? At the end it says, "At the end of the initial six months, patients will be dosed on a prn, as-needed basis for another six months."

Do you see that?

A. Yeah. You know, I recalled that, but I couldn't find

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the text. I don't know what I was shown. But, yes, I see that now, yes.

Q. Does that help clarify whether or not the person of ordinary skill in the art reading this would have thought those six monthly intravitreal injections to be loading injections or not?

A. I think they would be interpreted to be those first loading injections, followed by prn dosing, just like in so many of the other trials that we've seen.

Q. You were asked questions about the formulation of Eylea and whether it can contribute to the commercial success of the product.

Ask you a question. Would you buy Eylea for your practice if it didn't have aflibercept in it?

A. No.

MR. McLAUGHLIN: Nothing further. Thank you.

THE COURT: Counsel, recross?

MS. OBERWETTER: Briefly, Your Honor.

RECROSS-EXAMINATION

BY MS. OBERWETTER:

Q. Dr. Albini, Mr. McLaughlin had questions for you about PTX 0002, the '865 patent that he directed your attention to briefly.

If we could just put that up on the screen.

I just want to be clear for the record. You have not

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undertaken any exercise to determine what this patent does or does not disclose as it relates to the Eylea formulation, correct?

A. I was not -- as we've said multiple times, I was not engaged here as an expert on formulation and my efforts were not focused on the formulation patent as a consequence of that.

MS. OBERWETTER: Nothing further.

THE COURT: Thank you.

Reredirect then, Counsel?

MR. McLAUGHLIN: Nothing further, Your Honor.

THE COURT: Doctor, I have wonderful news for you. You can step down, sir.

THE WITNESS: Fantastic.

THE COURT: Outside, you're fair game.

THE WITNESS: That was a lot of fun. Thank you.

THE COURT: I'm sure it was. Thank you very much. I appreciate it, but you're now fair game. Folks can talk to you again.

THE WITNESS: Oh, great.

THE COURT: Thank you, sir.

MR. McLAUGHLIN: Your Honor.

THE COURT: Doctor, hold on one second. Let's go ahead and --

MR. McLAUGHLIN: Read into the record the exhibits.

THE COURT: You may do so, slowly.

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MR. McLAUGHLIN: This would include DTX 204, DTX 2034, DTX 2035, DTX 3173, DTX 2040, DTX 2062, DTX 2730, DTX 2731, DTX 2733, DTX 2745, DTX 3102, DTX 3105, DTX 3115, DTX 3131, DTX 3198, DTX 3215, DTX 4008, DTX 4013, DTX 4056, DTX 4061, DTX 4113, DTX 4116, DTX 4120, DTX 4129.

THE COURT: A little bit slower, Counsel.

MR. McLAUGHLIN: Sorry. DTX 4192, DTX 4194, DTX 4900, DTX 4903, DTX 8190. And I believe we've already moved this one in, but just in case, DTX 8205.

And if I could just get clarity from my cocounsel on three remaining ones.

THE COURT: Certainly.

MR. McLAUGHLIN: There will be two more. Thank you. DTX 3144 and DTX 3316.

THE COURT: Any objection to any of those?

MS. OBERWETTER: No, Your Honor.

THE COURT: Without objection, the aforementioned list are all hereby deemed admitted.

(DTX 204, DTX 2034, DTX 2035, DTX 3173, DTX 2040, DTX 2062, DTX 2730, DTX 2731, DTX 2733, DTX 2745, DTX 3102, DTX 3105, DTX 3115, DTX 3131, DTX 3198, DTX 3215, DTX 4008, DTX 4013, DTX 4056, DTX 4061, DTX 4113 ,DTX 4116, DTX 4120, DTX 4129, DTX 4194, DTX 4900, DTX 4903, DTX 8190, DTX 8205, DTX 3144 and DTX 3316 were admitted.)

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MR. McLAUGHLIN: Thank you, Your Honor.

THE COURT: Ms. Oberwetter?

MS. OBERWETTER: I have just a few more that I did not do during the course of cross.

I think I heard DTX 3105 on Mr. McLaughlin's list. We move to admit that. DTX 4099, DTX 4209, DTX 8151-A.

THE COURT: Any objection to those?

MR. McLAUGHLIN: No objection, Your Honor.

THE COURT: Without objection, Ms. Oberwetter's list is hereby deemed admitted.

(DTX 4099, DTX 4209, and DTX 8151-A were admitted.)

THE COURT: Everyone satisfied their respective lists have all been checked off? Okay. Great.

Doctor, now you can exhale.

I do need to ask counsel about any exhibits from our video experts.

MS. MAZZOCHI: I think that --

THE COURT: Video witnesses.

MS. MAZZOCHI: Yes. My understanding is that thus far, everything has been moved in. I know our court reporter has copies, I think, of all the PTX/DTX exhibits electronically; so she should have those. And, obviously, at the end of the proceedings, I'm assuming Your Honor will want a flash drive complete with everything on it.

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THE COURT: Please.

MS. MAZZOCHI: Maybe you want to keep the paper; but as a general rule, you know, I think people might let that go by the wayside.

But I think we've been keeping track of which ones are which. Teagan had a few things he wanted to reconcile from yesterday, but otherwise, with that, I think we'll be up to date.

THE COURT: Counsel.

MR. GREGORY: Ms. Mazzochi is correct.

We have a little bit of housekeeping from the video testimony from Vanessa Smith and Parag Goyal yesterday. I believe we can read into the record and move into evidence the following, which I believe we have consent on: PTX 0353, PTX 0354, PTX 0364, PTX 0472, and PTX 0478.

MS. MAZZOCHI: And my understanding is, if that's a list that came out of meet-and-confer, then those are the ones that are agreed to.

THE COURT: Those are thereby deemed admitted.

Who does Mylan intend to call next?

MS. MAZZOCHI: So, Your Honor, we had -- again, we would like to call Karen Chu at some point as the Regeneron 30(b)(6) witness. I don't know if you want to do that now or wait till later.

Or we could -- we have roughly another 45-ish

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minutes, maybe 50 minutes of two of our last -- basically, the last two ones of ours going in by designation. Then our plan would be we would start with Dr. Rabinow tomorrow, followed by Dr. Stewart. If you'd rather kick the Chu issue till tomorrow, we could do that. The only thing is we might not have clip reports in time. That's the one concern on that.

THE COURT: Let's go ahead, and we can do the other two videos first. We'll discuss the Chu issue so we can have that ready to go going forward.

MS. MAZZOCHI: And then, Your Honor, I also wanted to make clear, our next and, I believe, last live witness as part of our case in chief will be Dr. MacMichael. Plaintiffs have been aware he is not available until Tuesday. So I don't know how long plaintiff's crosses are going to go tomorrow. So they may actually start putting on their rebuttal case. And then our last live witness will be Dr. Hofmann, but he has to come in response to their expert Dr. Manning. So I suspect that will happen next week.

THE COURT: Understood.

Any disagreement with that projected plan?

MR. BERL: Well, that's the first I've heard of it. We're fine with Dr. MacMichael, who apparently has some health issue, not coming till Tuesday. I suspect their case will take most if not all of the day tomorrow. I don't think it makes any sense for us to start our rebuttal case until they finish

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their case in chief. So we were planning to do that after Dr. MacMichael testifies on Tuesday. That's one thing.

The second thing is before the end of court today, I think it would be wise to address another issue that has arisen with respect to Dr. Rabinow. We just received their amended slides in view of Your Honor's ruling, and let's say we don't think it complies with Your Honor's ruling, to put it mildly.

THE COURT: We're going to put a pin in that.

Let's go ahead and receive the next two videos we discussed, Counsel. Then we'll take up the issue with Ms. Chu, and then we'll get to that when we get to that.

MS. MAZZOCHI: All right. Thank you, Your Honor.

Defendants next call by video deposition Ms. Abby Cahn, a Regeneron employee.

THE COURT: Thank you so much.

MS. MAZZOCHI: Your Honor, I think we may have the exhibits for Cahn. I don't know if you want a paper copy or if you would like them up on the screen and then we just submit them.

THE COURT: Are they synced on the screen?

MS. MAZZOCHI: Yes.

THE COURT: I can just watch them from there. That's fine. I'm going to work on, hopefully this evening, clearing out some space for any additional binders that might be necessary.

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VIDEO DEPOSITION OF ABBY CAHN

Q. Good morning, Ms. Cahn. If you could please state your full name and your home address for the record.

A. My name is Abby Margo Cahn. I live at 209 East 56th Street, New York, New York 10022.

Q. You understand that you're appearing here and providing testimony in your personal capacity?

A. Yes, I understand.

Q. And do you also understand that Regeneron has designated you as a witness to speak on behalf of marketing subject matter with respect to Mylan's 30(b)(6) notice?

A. Yes, I understand and am aware.

Q. This is DX 802. It is plaintiff's Regeneron, their second supplemental Rule 26(a) initial disclosures.

Have you seen this document before, Ms. Cahn?

A. Yes. I was shown this document by my lawyers during preparation.

Q. Are you aware that Regeneron identified you as a person with knowledge about the marketing and commercial success of Eylea?

A. Yes, I am aware.

Q. Okay. What is your current title at Regeneron?

A. My current title at Regeneron is executive director, marketing and customer engagement, as of January 3rd.

Q. So Regeneron, with respect to Eylea, provides both

tabletops and booths at conferences where appropriate?

A. If that is part of the tangible method of a sponsorship, then Regeneron would be able to exhibit at that medical conference.

Q. Okay. And then another thing you mentioned was providing ads at conferences. What did you mean by ads?

A. Depending upon each meeting's prospectus, which is submitted to the sponsorship portal, there are very specific -- there's a specific outline of benefits. That would include, for example, a banner, and that would be placed in either a certain location or potentially, if it's a virtual conference, on the meeting website.

Q. When Regeneron has podium time that you referred to, who speaks on behalf of Regeneron?

A. Depending upon the availability of individuals as well as the meeting, the Regeneron employees would be able to give an approved presentation at the meeting. So that, yeah.

Q. Does Regeneron ever sponsor talks given by physicians or clinicians or health care professionals?

A. So at medical conferences in general, there's a number of ways that physicians are able to appropriately educate their peers at the conference. As a marketer, I am aware of one of those -- one of those opportunities, which is referred to, essentially, as a product theater.

Q. And what is a product theater?

A. As part of the meeting prospectus, the product theater would be part of the request for support. If the sponsorship is approved, the marketing team would have the ability to work with a physician to give the on-label approved educational speaker program presentation at that meeting or convention.

Q. You used the word "thought leader liaison." What is that?

A. So at Regeneron a thought leader liaison is a field-based marketing role, and the main responsibility of that field-based marketing thought leader liaison is to gain insight into the evolving retina landscape through engagement with thought leaders in the retina community.

Q. Does Regeneron provide compensation for thought leaders?

A. Regeneron, and specific to Eylea and my role in the marketing team, we contract with advisers for -- in insight-gathering settings, such as advisory boards. We also have contracts with retina specialists who are part of the Eylea educational speaker bureau.

Q. What is Eylea educational speaker bureau?

A. The Eylea educational speaker bureau is a program that enables physicians to give approved on-label presentation of Eylea to other health care professionals.

Q. In your opinion, is it important for Regeneron to

enable physicians to give presentations concerning Eylea?

A. It is my opinion that it is important for physicians to be educated about the on-label -- the on-label information for Eylea when making treatment decisions for their patients.

Q. What are the ways that you're aware of?

A. So from the -- within the marking organization, there is a team that is responsible for scientific marketing. They are responsible for the Eylea educational speaker program, which is the presentations that physicians give to other health care professionals around the on-label use of Eylea.

The patient marketing or consumer marketing team is responsible for providing educational materials about Eylea as well as education around the diseases that Eylea is indicated for. And the promotional marketing team is responsible for developing the sales materials which our sales team uses to educate physicians and their offices about the on-label use of Eylea.

Oh, it's aligned to the regional directors. Under each regional director are medical specialists or diabetic eye medical specialists.

Q. So Eylea4U program has been active since the launch of Eylea and it continues today; is that correct?

A. So a version of Eylea4U patient assistance programs were available at launch. I would not be able to speak to the difference in the program between launch and today.

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Q. But a program Eylea4U has existed within -- the name Eylea4U has existed continuously since Eylea's launch and is ongoing today?

A. A program called Eylea4U has existed since launch and does exist today.

Q. Do you know, what insights have you gained on why physicians express an interest for a prefilled syringe?

A. So based on my conversations with physicians around the availability of treatment options for patients, there is a perception that administering intravitreal injections with a prefilled syringe may have an improved -- is an improvement on the -- sort of the safety of and decreasing the risks associated with the intravitreal injections.

Q. And based on the sales numbers, do you agree that there is a preference for the prefilled syringe over the vial of Eylea?

A. So my understanding of preference comes from insights from physicians in different settings, and based on my personal conversations with some physicians, there is a preference for a prefilled syringe.

Q. Ms. Cahn, before the lunch break I recall you mentioned a promotional marketing team for Eylea. Is my recollection correct that Regeneron has a promotional marketing team for Eylea?

A. So Regeneron has a marketing team, and there are

individuals on that marketing team who are responsible for promotion.

Q. Ms. Cahn, are you familiar with the acronym ATU?

A. I am familiar with the ATU market research surveys. I do not recall what the letters ATU stand for.

Q. DX 514 was marked as a previous deposition. The first page includes the Bates numbers RGN-EYLEA-MYLAN-701395. It's a Q3 2020 ATU combined full report.

Is this the type of document that you review in your marketing role at Regeneron?

A. So I am part of the marketing team and get invited to the market research meetings where these types of reports are shared with the marketing team.

Q. What is your understanding of the phrase "out-of-pocket costs"?

A. My understanding of "out-of-pocket costs" would be the portion of the cost that is not covered by insurance.

Q. With that understanding of out-of-pocket costs, is it your opinion that physicians might not prescribe a drug if the out-of-pocket costs for that drug are unaffordable to the patient?

A. So although I'm not a physician, it is my understanding that physicians have conversations with their patients around all of the treatment options that are available to them and make decisions together based on a number of

factors, including out-of-pocket costs based on their insurance.

Q. This is the current August 2022 label, and it's been labeled DX 520-A because it now has Bates numbers on it. The prior version used at another deposition did not have Bates numbers.

Ms. Cahn, based on your testimony, you're familiar with this package insert -- or I refer to it as a label -- this package insert for Eylea?

A. Yes, I am.

Q. You've seen this document before?

A. Yes, I have.

Q. Does the dosing and administration instructions for wet AMD provide flexibility for a clinician to dose Eylea?

A. Yes, the wet AMD dosing administration section does provide flexibility for physicians who choose to treat with Eylea.

Q. And that flexibility is with respect to the dosing schedule?

A. Yes. It would -- dosing schedule is one way to describe the time between treatments.

Q. Okay. And for wet AMD here, the label states that the physician may dose Eylea as frequently as 2 milligrams every four weeks; is that correct?

A. Yes. Some patients may need every-four-week dosing

after the first 12 weeks, which is the loading dose phase.

Q. And if we go down to the next indication, RVO, are you familiar with RVO?

A. The indication is macular edema following retinal vein occlusion, yes.

Q. MEfRVO; is that correct?

A. Yes.

Q. And the recommended dose of Eylea for MEfRVO is once every four weeks; isn't that correct?

A. Yes, that is correct.

Q. And so for DME and DR, Eylea may be dosed as frequently as 2 milligrams every four weeks; is that correct?

A. Yes. Some patients may need every-four-week monthly dosing after the first 20 weeks, which is the first five months of the loading dose in diabetic macular edema and diabetic retinopathy.

Q. So I think -- do the dosage administration instructions on the Eylea package insert require a physician dose Eylea every eight weeks?

A. No. There is the -- some patients may need every-four-week dosing as indicated in the label in each of the indications we previously reviewed.

Q. Ms. Cahn, right before the break I had you pull up DX 514. If you could turn to what is page 90 of 142. The Bates number ends in 484. And then it's pulled up on the

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screen share as well.

Okay. This slide with Bates number ending 484 is titled "Wet AMD Dosing Update." Do you see that?

A. Yes. Yes, I do.

Q. And, Ms. Cahn, do you agree that the mean dosing frequency for Eylea that's reflected on this slide is 7.5 weeks for the dosing interval?

A. So this is a -- as per the source, a Q3 2020 ATU study of 171 retinal specialists and 30 comprehensive ophthalmologists.

This -- under the sentence we just covered, projected percentage of treated eyes receiving dosing schedule with an asterisk, ongoing, following initiation of therapy.

So based on this group of physicians projecting intervals of treatment following a loading dose of Eylea for these physicians, their perception is a loading dose of what you -- mean frequency of 7.5 weeks.

Q. Okay. And if we could go to two pages down.

A. Okay.

Q. It's page ending in number 486.

A. Okay.

Q. And does this slide reflect that the mean frequency for the dosing interval for Eylea with respect to DME is 7.7 weeks?

A. So for -- again, for based on in this quarter, Q3

2020 ATU, this 164 retinal specialists and 36 comprehensive ophthalmologists, their projected percent of treated eyes receiving dosing schedule, what they project to be true, following a loading dose is the mean frequency of injections is 7.7 weeks.

Q. Okay.

Mike, if we can bring up DX 515.

DX 515 was marked at a previous deposition. First, page Bates number is RGN-EYLEA-MYLAN-700292. It is the Q4 2020 ATU combined full report.

All right. Have you seen this document before?

A. So I have reviewed a number of performance updates in my role as -- in marketing. I also reviewed a performance update with my lawyers in preposition for today. I do not recall if it was Q4 2020.

Q. If we could turn to what is page 92 of 137 in this document. The Bates number ends in 383.

A. 383. Okay. 383. Okay. It's loading.

Q. Sure. And does this slide reflect the mean dosing frequency for Eylea of 7.3 weeks?

A. So these specific physicians are recalling treatment intervals for their patients, and they are -- on average, the mean frequency of this set of physicians with this recall of their patients is 7.3 weeks.

Q. Okay. If we could go two pages down, it ends in 385

in this document.

A. Can you repeat your question.

Q. Sure. This slide is titled "DME Dosing Update."

Can you agree that the data shown here is that on average the mean frequency for Eylea dosing for DME is every 7.5 weeks?

A. So for this 2020 ATU study of 172 retina specialists and 30 comprehensive ophthalmologists who were recalling treatment intervals for a specific number of patients, the mean frequency for Eylea is 7.5 weeks.

Q. Mike, can we pull up DX 516, please.

This was previously marked at another deposition as RGN-EYLEA-MYLAN-700931 on the first page. It's on the Q4 2019 ATU report.

Okay. And if we could turn to page 98 of 153 in this document. The Bates number ends in 028.

A. Got it. I'm right there. Hold on. Yep, I do have it up.

Q. Okay. And, Ms. Cahn, do you agree that in this Q4 2019 ATU report, the data shows that the mean dosing frequency for Eylea for wet AMD is 7.0 weeks?

A. So for these 200 retina specialists surveyed for the Q4 2019 ATU study, their recollection or recall of patients on each of these agents, the mean frequency of Eylea injections is 7.0 weeks.

Q. If we can go two pages down, it ends in 030, titled "DME Dosing Update."

Ms. Cahn, do you agree that this Q4 2019 ATU report reflects a mean dosing frequency of 6.7 weeks for dosing Eylea for DME?

A. So for this -- these 200 retina specialists on Q4 2019 ATU study, they are projecting or recalling that the Eylea treatment interval for their patients, the mean frequency was 6.7 weeks.

Q. Okay.

Mike, if we could pull up DX 517.

DX 517 was marked at a prior deposition. The first page has Bates number RGN-EYLEA-MYLAN-705670. You could go to the pages ending in 689. It is page 20 of this PDF.

A. 689. Okay. Thinking. Hold on.

Q. Sure.

A. 689. Okay. I am on 689.

Q. Sure. The slide that -- the page that we're already looking at --

A. Okay.

Q. -- it reflects that the Eylea mean dosing frequency overall is 6.7 weeks; is that correct?

A. So for these physicians recalling their projected dosing intervals for a set of patients which I cannot -- which I have no understanding if they are previously treated or naive

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eyes or actually how many eyes -- there we go. Sorry -- of this set of 42,763 eyes, the overall dosing frequency and the mean in the weeks would be 6.7 weeks.

Q. DX 518.

A. DX 518. Okay. It's open.

Q. This is the Q3 2017 ATU report.

A. Okay. Its title page is up.

Q. If you can turn to page 20 of 35 of the document.

A. 20 of 35.

Q. Do you agree that this slide reflects that the overall dosing frequency for Eylea for wet AMD has a mean of 6.7 weeks?

A. So based on this slide from the -- okay -- no source on this. I do not recall which quarter and year this new document is referring to.

The physicians who completed this survey recalled that patients were dosed at different dosing frequency, although I cannot comment if these are treatment-naive eyes or those eyes that have been transitioned from another agent.

And the mean overall dosing frequency for Eylea on -- from this group of physicians recalling based on this number of patients is 6.7 weeks.

Q. So we reviewed ATU surveys -- at least one ATU survey from each of 2017, 2018, 2019, and 2020; is that correct?

A. Yes, I believe that's correct.

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Q. And we discussed a number of mean dosing frequencies for Eylea, correct?

A. We discussed the results of ATU surveys from a group of physicians who are recalling their patients' dosing intervals, yes.

Q. And do you agree that of the data we looked at, the mean dosing frequency for Eylea was always less than eight weeks?

A. So for the results of these surveys where the physicians were asked to recall that their projected dosing frequency of Eylea with the patients that they recall and are projecting according to this, in those patients the dosing frequency of Eylea is less than eight weeks.

Q. Sure. It is DX 531a.

A. DX 531a. Okay.

Q. Okay. But you, in your role, cannot speak to off-label uses of Eylea, correct?

A. That is correct. I am unable to -- unable to speak about anything other than the Eylea package insert.

Q. That's because that's what the law states, correct?

A. Yes.

Q. Do you agree that with Dr. Schleifer's comments here that here the availability of Eylea copay assistance is reversing the shift from Avastin back to Eylea?

A. My opinion of -- my opinion is that there are a

number of factors that contribute to a physician's treatment decision and that patient access and copay assistance challenges are factors that do affect physicians' abilities to choose medications.

Q. Ms. Cahn, once they load, DX 807 is going to be a brief video --

A. Okay.

Q. -- that will play, and then DX 808 is a transcript of that video.

(Video played within deposition.)

Q. Once they load, DX 807 is going to be a brief video --

A. Okay.

Q. -- that will play, and then DX 808 is a transcript of that video.

Ms. Cahn, is DX 808 an accurate transcript of the video we watched in DX 807?

A. Yes, it is.

Q. Did you discuss any trend -- a trend of Eylea was utilized more in areas where "A Beautiful Pair" was run than in areas where it was not run?

A. So I can't speak to any trends because I don't have enough information that would make -- that would lead to a trend. But I know from what Mr. Clark told me that in the markets where "A Beautiful Pair" was run compared to in markets

where "A Beautiful Pair" did not run, there was a difference of Eylea utilization in those markets.

Q. Mike, if you can mark as Tab 62 Defendant's Exhibit -- mark Tab 62 as Defendant's Exhibit 811, 811.

This is, as you can see in the top left, pulled from the hcp.eylea.us website, January 16, 2023.

A. Yes, I can see that.

Q. Are you familiar with the hcp.eylea.us website?

A. So I am not familiar specifically on the website. This is the HCP website. I am not responsible for updating or producing content for this website.

Q. The first page, DX 811, at the top it says "Wet AMD: Dosing Flexibility."

Do you see that?

A. Yes, I do.

Q. Okay. And it recites, "Flexibility to choose from three FDA-approved dosing regimens for wet AMD."

Do you see that?

A. Yes, I do.

Q. So do you agree that clinicians have flexibility to choose a dosing regimen for wet AMD, according to the current package insert for Eylea?

A. Yes. According to the package insert for Eylea, physicians may choose the dosing paradigms that are listed in the package insert.

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Q. Okay. If we can scroll down to page 4 of 12, on the top it says "DME:Dosing Flexibility."

A. In the same -- oh, I see it, yes.

Q. Okay. So you agree that physicians have flexibility with respect to DME dosing?

A. I do agree that physicians have flexibility to treat their DME patients based on the patient's need for treatment.

Q. Defendants' Exhibit 815 has the Bates number on the first page of RGN-EYLEA-MYLAN-314737.

Ms. Cahn, does this appear to be print advertisements that Regeneron ran in *Time* magazine promoting Eylea?

A. Yes, it does.

Q. And is this a different ad campaign for Eylea other than "A Beautiful Eye"?

A. Yes, this is.

Q. Mike, if you can scroll to the last page of this document ending in Bates Number 707.

Ms. Cahn, does this page of Defendant's Exhibit 817 refresh your memory that this was mailed directly to Eylea patients?

A. So this looks like a direct mail to Eylea patients once patients were enrolled in Eylea4U.

Q. And, Ms. Cahn, if you'd like to review this document, you can ask Mike to page through it at the appropriate pace.

A. Can I see the front cover, please, Mike? I can't

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really see it.

So this is another "A Beautiful Pair" print advertisement.

Q. Have you seen -- when you say another version, you mean this is a print ad that was part of the "Beautiful Pair" ad campaign?

A. Yes, that is correct.

MS. MAZZOCHI: And that's the conclusion of that video. And then for administrative purposes, I believe all of these exhibits are agreed to.

The defendants would like to rule in -- move into evidence DTX 514, 515, 516, 517, 518, 520-A, 531-A, 802, 807, 808, 811, 815, 817, and 818.

THE COURT: Any objection to any of those?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, those are hereby admitted.

(DTX 514, DTX 515, DTX 516, DTX 518, DTX 520-A, DTX 531-A, DTX 802, DTX 807, DTX 808, DTX 811, DTX 815, DTX 817, DTX 818 were admitted.)

MS. MAZZOCHI: Great. Thank you, Your Honor.

The next video deposition we have is 21 minutes. And this will be Jennifer Colyer, who is part of Regeneron's finance and marketing, and I believe she was also designated as a 30(b)(6) witness.

THE COURT: Understood.

VIDEO DEPOSITION OF JENNIFER COLYER PLAYED

Q. Mrs. Colyer, could you please state your full name and your home address for the record.

A. Sure. Jennifer Colyer, 37 Shady Lane, Dobbs Ferry, New York 10522.

Q. And the second is a document, "Jennifer Colyer 30(b)(6) Deposition Topics," which will be DX 501.

Do you have both those documents, Ms. Colyer?

A. Yes, I do.

Q. Okay. You can set that document aside.

Do you also understand that you're here testifying today as a corporate representative of Regeneron to speak on behalf of the topics listed in DX 501?

MR. GOLDSMITH: I object to the Exhibit DX 501 to the extent it's not consistent with Regeneron's December 12, 2022, letter. But the witness can answer the question.

THE WITNESS: What my lawyer just said, yes.

Q. Well, factually then, what is driving the sales of Eylea?

A. Successful scientific research.

Q. And what is that research referring to?

A. The research that was done to develop the molecule that became Eylea, aflibercept.

Q. When you say Eylea drug, you're referring to the

active ingredient aflibercept?

A. I'm referring to Eylea.

Q. When you say Eylea, what are you referring to?

A. I'm referring to Eylea, the brand name as licensed by Regeneron.

Q. What is encompassed by the brand name Eylea?

A. I'm afraid I don't fully understand. What do you mean by "encompassed"?

Q. You mentioned that when you used the word Eylea, you're referring to the brand name. And I'm trying to understand what is included, what is different between Eylea and the brand name. Is there a difference?

A. I'm afraid you're trying to make a distinction that I'm not really familiar with. To me, Eylea is a brand name that is licensed by Regeneron somewhere legally, and that is Eylea.

Q. Is the safety and efficacy of Eylea a factor that drives sales?

A. I freely admit I am no scientist. I have not been involved in clinical trial research. The safety and efficacy of Eylea would be considered a benefit absolutely in the use of Eylea.

Q. Are there any other benefits that Eylea imparts to patients?

A. As a finance person, I'm not too familiar with the

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detail behind Eylea and the clinical research and what it has proven over the past many years.

Q. Does Regeneron advertise Eylea directly to health care providers?

A. Regeneron advertises Eylea, yes, to health care providers.

Q. And does Regeneron advertise Eylea to the public?

A. Over the years Regeneron has advertised Eylea directly to the public.

Q. Does Regeneron undertake market research for Eylea?

A. Yes, it does.

Q. Are you familiar with that market research?

A. I do not work directly with that market research, no.

Q. Your current job title, is it correct that you're the executive director of commercial finance and business planning?

A. Yes.

Q. Does Regeneron have medical specialists for Eylea currently?

A. Yes, we do.

Q. And what is a medical specialist?

A. That would be a -- I guess layman term, a rep, a representative, customer representative, salesperson.

Q. Salesperson. Do those people have medical degrees? Do you know?

A. I'm not familiar with each and every one of them, but

they certainly can have a medical degree.

Q. Do you know how many medical specialists Regeneron has for Eylea, approximately?

A. I'll stick with roughly 90.

Q. And those medical specialists, do they report to the regional sales directors?

A. Yes.

Q. Does Regeneron have reimbursement and managed market specialists for Eylea?

A. Regeneron has regional business managers.

Q. Are those regional business managers, are any specifically assigned to Eylea?

A. There is a specific team of Eylea regional business managers.

Q. Do you know how many regional business managers Regeneron has for Eylea, approximately?

A. As of today, I believe there are 30.

Q. What is Eylea4U?

A. Eylea4U is the reimbursement support program utilized.

Q. What type of reimbursement support does Regeneron provide for Eylea under this Eylea4U program?

A. Copay assistance.

Q. Any other type of assistance that you're aware of?

A. The core is copay assistance.

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COURT REPORTER: Say it again?

THE WITNESS: The core is copay assistance, yes.

Q. What is a regional science manager?

A. That is typically -- how to phrase it? -- a medical science liaison. These are field-based folks that are authorized to speak about the science as opposed to -- separating them from a medical specialist, which would be a rep.

Q. Do these individuals have medical degrees?

A. I assume many of them do. I do not know the composition of the team.

Q. Do you know how many regional science managers Regeneron employs for Eylea?

A. I'm taking a second to recall that because it's not something I work with too frequently.

I want to say mid teens, mid teens meaning somewhere between 12 to 19, give or take. I'm just not recalling exact number.

Q. That's fine. That's fine.

Do you know why Regeneron provides copay assistance?

A. Similar to most other pharmaceutical companies, Regeneron provides copay assistance to help commercial patients pay the copay.

Q. Do you have an opinion whether rebates drive sales of Eylea?

A. Sales of Eylea are derived from the clinical benefit of the drug for patients.

Q. What is the clinical benefit you're referring to?

A. Why doctors prescribe it to patients.

Q. Do you know why doctors prescribe it to patients?

A. To improve their lives.

Q. Are bonuses for Eylea sales representatives related to any sales targets?

A. Field forces are paid bonuses based on achievement of targets.

Q. Do you know why Regeneron is developing a high-dose version of Eylea?

A. The benefit of a high dose would be about a longer dose -- a dosing regimen, greater weeks between injections.

Q. Is that a benefit, a longer dose duration?

A. I think personally, if I could have fewer injections directly into my eye, I would choose to do so.

Q. What has been discussed in terms of how to handle the 8-milligram high-dose version of Eylea?

A. To be fair, it hasn't gone -- it certainly hasn't left any rooms. It's not -- I freely admit, it's not necessarily something I'm comfortable discussing.

Q. Why are you not comfortable discussing it?

A. Because there is no approved plan yet. It's in active -- it's different than a lot of what we've discussed

here, which are things that have gone on in the past. It's not public knowledge. It's up for active what do we want to do? I wouldn't say we have something I could declare is a plan.

Q. What have individuals expressed they want to do with respect to a high-dose version of Eylea?

A. Make an 8-milligram version of Eylea available to the public to hopefully improve the dosing timeline so people would have to get their injections into their eye with a greater time period between them.

Q. Does Regeneron track these sales of Eylea with respect to each indication?

A. You cannot track sales based on indication.

Q. So the sales that Eylea tracks in the financial documents we looked at earlier are independent of what that Eylea is being prescribed for, what condition?

A. That is true from a sales perspective.

Q. In what context, then, have you come to learn about the indications for Eylea?

A. Sales are not tracked by indication, but certainly want -- percentage of the Eylea sales could be allocated to the indications is a separate source of analysis.

Q. Do you know who at Regeneron is responsible for approving the Eylea4U program?

A. There's a chain of approvals, authorized signature levels, and so on. If the budget exceeds a certain amount, as

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it typically does with Eylea4U, then Len Schleifer is the final approval, our CEO.

Q. What type of data does your department provide with respect to Eylea4U to this decision process?

A. If it is within the budget that was planned for the year and approved by Len for spend on Eylea, then we would confirm that this is within the approved budget.

Q. I believe you testified -- I just want to confirm -- does Regeneron have to approve all costs with respect to Eylea on an annual basis or is there an annual review?

A. Regeneron approves all budgets for all brands on an annual basis, not specific to Eylea, not specific to Eylea4U.

Q. Does Regeneron today consider Lucentis and Avastin competitors to Eylea?

A. As previously discussed, we talked about Lucentis as indeed competition and Avastin to be an off-label use in the anti-VEGF market.

Q. Have you seen -- are these the ads that ran in *People* for Eylea that you were referring to?

A. Most likely.

Q. If you could turn to the page that says Cover 1 on the bottom left. It's got 535 as the ending Bates number.

A. Yes.

Q. Do you know if this was an insert in *People* magazine?

A. I don't know. This does say at the bottom it was a

cover wrap, but I don't recall. I've read a lot of *People* magazines over the years.

Q. On this page here do you see any discussion of Eylea dosing on this advertisement page?

A. I do not see anything about dosing on this page.

Q. You can go to the next page. It's got Gate 1, lower left-hand corner.

A. Yes.

Q. Does this advertisement page state anything with respect to the dosing schedule for Eylea?

A. As I read through it, I do not see anything related to dosing.

Q. If we can go to the next page, Bates number ending in 537. Do you see the bold heading that's approximately four down in the left-hand column that says "How Is Eylea Given?"

A. Yes.

Q. And this states, "Depending on your condition, Eylea injections are given on different schedules. Consult your eye doctor to confirm which Eylea schedule is appropriate for you."

Do you see that?

A. Yes, I do.

Q. Does that statement state anything concerning an eight-week dosing schedule?

A. It does not use the number eight at all.

Q. Does it talk about how many weeks between doses of

Eylea?

A. It doesn't say anything about weeks.

Q. On the rest of this page is there any other discussion on this page concerning dosing schedules for Eylea?

A. I've not had an opportunity to read every word on the page. I'm happy to do so.

Q. Sure. Go ahead.

A. I'd like a Ctrl-F.

I do not see anything about dosing schedules on my read through this document.

Q. Okay. You can go to the next page, Cover 2.

Is there any discussion concerning Eylea dosing schedules on this page ending in Bates Number 538?

A. No, there is not.

Q. If you go to the next page, Cover 3 is in the lower left-hand corner as Bates Number 539.

If you could take a second and review the text on this page and confirm that there is no discussion of an Eylea dosing schedule on this advertisement page.

A. I do not see anything related to dosing schedules on this page.

Q. And if you could turn to the next page ending in Bates Number 540.

Can you confirm there's no discussion of an Eylea dosing schedule in this advertisement for Eylea?

A. It does not say anything about a dosing schedule on this page either.

Q. If I can have the court reporter mark as DX 529 a document that does not have any Bates numbers. It is Eylea advertisements that ran in *Good Housekeeping* in 2022.

Ms. Colyer, if you could look at pages 2 and 3 of this document. Have you ever seen these advertisements that Regeneron has run in *Good Housekeeping*?

A. I have never read *Good Housekeeping* before.

Q. Have you ever seen these advertisements before?

A. I mean, I've seen similar advertising.

Q. Where have you seen similar advertising?

A. These ads tend to be fairly consistent; so this is a fairly standard set of data.

Q. Does it appear to be the same ad that ran in all three magazines that are included here in DX 529?

A. Without comparing word for word, at a glance it does appear to be a similar ad, yes.

Q. If you could look at the ad that is the -- the first page of the advertisement that appears on page 2 of DX 529. It is entitled "Keep living life through your eyes."

Do you see that?

A. Yes.

Q. Do you see any discussion of the Eylea dosing schedule on this page of this advertisement?

A. I do not see anything on that page related to dosing regimens.

Q. If you could turn to the next page of the ad, it has a picture of a woman in a pink sweater.

A. Yes.

Q. Do you see any discussion of Eylea dosing schedule on this page of the Eylea ad?

A. I do not.

Q. If we could turn to the next page, which is the last page of this advertisement, and if you need to, take a moment to review it.

Does this page include any discussion concerning the Eylea dosing schedule?

A. It does not.

Q. Are you aware that Regeneron won awards for the "Beautiful Pair" ad campaign?

A. Yes, I am.

Q. How are you aware of that?

A. Because it was all over the place for a while. I follow LinkedIn.

Q. It was all over the place; you mean the advertising campaign was very popular?

A. No. Who I worked for, Regeneron at the time, and the team was recognized as having won awards. And I saw it posted on LinkedIn in different ways.

Q. So we looked at some print that Regeneron had for the "A Beautiful Eye" campaign that ran in *People* magazine, correct?

A. Yes, we did.

Q. Are you aware of what other media the "A Beautiful Pair" ad campaign appeared in?

A. Yes, I am.

Q. What are those sources?

A. Television.

Q. I'm going to have the court reporter mark as DX 530 a transcript of an advertisement that Regeneron ran for "A Beautiful Pair".

Do you have that transcript?

A. Yes, I do.

Q. And do you see at the top of this document it has a URL link for YouTube?

A. Yes.

Q. I'm going to play that advertisement for you that's available at that URL. If you can follow the transcript and make sure that the transcript accurately reflects what's provided in the ad.

A. Okay.

Q. Did the transcript track the video?

A. Yes, it did.

Q. And was there any discussion in this advertisement

concerning the dosing schedule for Eylea?

A. The YouTube channel did not talk about dosing schedule, no.

Q. Was the video that I played the type of ad that would have run on TV?

A. Yes, I believe it would have been similar to what would have been on TV.

MS. MAZZOCHI: And, Your Honor, that concludes the Jennifer Colyer deposition.

THE COURT: Understood. Thank you, Counsel.

MS. MAZZOCHI: In association with this, we'd like the administrative matters of entering additional exhibits into evidence. Defendants move into evidence DTX 501, 528, 529, 529-A, and 530.

THE COURT: Any objection to any of those?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, those are hereby admitted.

(DTX 501, DTX 518, DTX 529, DTX 529-A and DTX 530 were admitted.)

MS. MAZZOCHI: With that, then our next topic, I guess, Your Honor, is Ms. Chu.

THE COURT: Yeah. I'll cut to the chase on that.

After giving it some thought, as I indicated yesterday, I do think Mylan's entitled under Rule 32 to play

the portions designated as 30(b)(6) testimony.

Upon further -- I didn't say anything further past that, having wanted to research it additionally. The Court believes Mylan's likewise entitled to play other testimony from Ms. Chu outside of her 30(b)(6) role. Again, she's unavailable under Rule 32(a)(4)(B) in that she is more than 100 miles from Clarksburg, West Virginia. So there would be no limitations under the rules for using that transcript.

I'm aware the parties agreed to something to the contrary in their joint memo applying to this trial, but in all candor, we've blown through that a couple times today -- I'm sorry -- a couple times already. I know paragraph 4 indicates witnesses who are going to testify live, the parties agreed are not be permitted to play deposition testimony. I would not apply that to the 30(b)(6) designations.

But, again, the rules are what they are. The parties can agree as they like, but the rules, in all candor, trump. And from the category of what's good for the goose is likewise good for the gander, paragraph 39 dealt with the agreement that impeachment exhibits not previously disclosed would not be admitted into evidence absent good cause.

So we've already done that once today. Ms. Chu, I understand, is going to testify live as part of -- is it Regeneron's rebuttal case?

MR. GREGORY: Yes, Your Honor.

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THE COURT: Rebuttal case. But under Rule 32, I think Mylan is entitled to use that transcript regardless of which hat Ms. Chu is wearing at the time, her 30(b)(6) designee hat or her fact witness personal capacity hat. So they'll be permitted to play it as designated.

I would note, however, given this kerfuffle over it, Regeneron will have some leeway when Ms. Chu is here in person with respect to what areas they're permitted to cover.

So that's how we'll deal with Ms. Chu's testimony.

I'll direct the parties to get together this evening to review and discuss the updated slide deck of Dr. Rabinow to see what remaining issues there are.

Would that be the first witness Mylan anticipates calling in the morning?

MS. MAZZOCHI: Yes, Your Honor.

THE COURT: We'll take that up first thing, but y'all need to get together and talk about that this evening to see what, if any, disputes may remain in light of the Court's granting of Regeneron's motion to exclude those particular -- that particular opinion, I should say, of Dr. Rabinow with respect to obviousness.

Anything else we need to take up at this point of the day, then, from plaintiff's perspective?

MS. OBERWETTER: Not today, Your Honor.

MS. MAZZOCHI: Nothing from us, Your Honor.

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THE COURT: We'll see everyone in the morning. Everyone have a pleasant enough evening. Thank you all very much.

(Proceedings concluded at 5:13 p.m.)

CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 15, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 15th day of June 2023.

/s/Cindy L. Knecht
_____
Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 5

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 16, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

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Proceedings recorded utilizing realtime translation.
Transcript produced by computer-aided transcription.

Friday Morning Session,
June 16, 2023, 9:30 a.m.

- - -

THE COURT: We convene for day five then -- it's a casino in here some days -- of trial counsels presence. Had a chance to skim, but I certainly wouldn't say I've read Regeneron's second motion to exclude undisclosed expert opinion.

Would it be fair to characterize that motion as largely based on similar issues as the motion we addressed yesterday?

MR. BERL: Yes, Your Honor.

THE COURT: All right. I need to see Dr. Rabinow's report where this combination of prior art was disclosed and the explanation as to why it would be obvious, then.

MR. HUNT: Your Honor, we will have copies for you here shortly. If I may.

THE COURT: I have -- I do have his report.

MR. HUNT: Very good. Then I would like to take you to paragraph 290 of Dr. Rabinow's opening expert report. There are a number of combinations listed in paragraph 290 of both Dr. Rabinow's opening report, Your Honor. For the Court's benefit and certainly the benefit of everyone's time, we have simplified things a bit for trial today.

Dr. Rabinow, in Number 1, is testifying today

regarding the combination of Fraser with Liu. And in addition to that combination, he will separately be offering opinions today with regard to Number 4, the prior art Lucentis formulations, as evidenced by the Shams and Gaudreault articles, in combination with Fraser.

Now, I expect, Your Honor, that counsel for plaintiff is concerned that, the way that Dr. Rabinow's demonstratives have been organized, that he, they suspect, is going to offer opinions regarding the combination of Lucentis and Liu.

I have assured counsel for plaintiff that that is not Dr. Rabinow's intent, that is not a combination, as we discussed, that is disclosed in his opening report. However, it is important for the Court to keep in mind -- and I think plaintiff may have a response to this -- that prior art needs to be considered in the context of the knowledge of the person of ordinary skill in the art as a whole.

And I suspect that may be where the issue is here, Your Honor. There are certain disclosures in the Lucentis prior art, and there are certain disclosures in Fraser. And the person of ordinary skill in the art, as of June 16, 2006, would have an understanding and a body of knowledge based upon the prior art as a whole that would inform their reading of those references.

So while Dr. Rabinow is not offering opinions as to the combination of anything more than Lucentis and Fraser,

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there are certain facts that are known to the person of prior art -- I'm sorry -- the person of ordinary skill in the art that would inform their understandings of the words on the page of Gaudreault and Shams.

So I suspect that may be where the issue is. I'm happy to discuss it a bit more. But if the Court doesn't have any further questions, I'll turn it over to Mr. Berl.

THE COURT: I do not. Thank you.

Counsel?

MR. BERL: Good morning, Your Honor. I think there's some agreement that the only combinations that Mylan is permitted to rely on for motivation, for expectation of success, for meeting each limitation of the claim are the four that are written in paragraph 290 of Dr. Rabinow's report, which they've narrowed today.

The problem, however, is -- and I think this is best seen at Slide 55 of Dr. Rabinow's presentation which we have reproduced on page 6 of the motion that we filed this morning --

THE COURT: One second, please. Thank you.

MR. BERL: I've also shown it on the screen.

THE COURT: Thank you.

MR. BERL: But what this shows is -- here's the way they've organized it, Your Honor. They've organized their presentation so that first they address what they call the

obviousness of Claim 1. Then separately, much later on, they address the obviousness of the dependent claims.

Those obviously aren't two separate inquiries, because the dependent claims include all of the limitations. So when you say Claim 2 is obvious, you're saying everything from Claim 1 and Claim 2 is one claim that includes Claim 1, of course.

THE COURT: Slow down, Mr. Berl.

MR. BERL: Sorry, Ms. Knecht. I did well yesterday, but --

THE COURT: Didn't talk much yesterday. It's 9:45 and --

MR. BERL: The only reference that they cite in the presentation to fulfill the last limitation of the claim, the 98 percent native conformation limitation, is Liu. That's it. They don't have a checkmark for this by Fraser; they don't have a checkmark by Lucentis; they don't have a checkmark for anything else. That limitation is in all of the asserted claims. It's actually narrowed in some of them to get to 99 percent at 24 months. But that's it.

So then when they proceed later to the dependent claims and they say, oh, all we're really running here is Lucentis plus Fraser, pay no attention to Liu, it's already infected because they've already asserted Liu and only Liu with respect to one of the limitations of Claim 1.

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So they may make it seem like they're not running Lucentis and Liu together. They admit they're not allowed to do that. But they are. They are. And it's as clear as day. They're not allowed to do it.

So what they're doing is they're kind of merging the two arguments that they say are the two arguments they're now preserving, Fraser plus Lucentis -- sorry -- Lucentis plus Fraser and Fraser plus Liu. They're merging them. And we were concerned about it.

So what we did last time was we sent them a stipulation, a proposed stipulation that essentially says you can't merge your distinct prior art combinations because once you merge them, it's a totally separate inquiry, right? Whether there is a motivation to combine Lucentis and Liu is different than whether there's a motivation to combine Lucentis from Fraser.

Every different combination has different motivation analysis. That's why the whole case is based on what combinations they assert. So we were concerned, and we said how about this stipulation, that just makes it clear you're limited to the four combinations in Dr. Rabinow's report and you can't use art from one combination into the other.

We sent that last night. We've gotten no response. If they sign that stipulation or agree to that stipulation and Your Honor signs it, I think we're okay and they can't do that

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and it's clear. But the way they have it now and what they're clearly doing is they are, without making it clear, relying on Lucentis and Liu once you put Claim 1 together with the dependent claims as the law requires. And they're just not allowed to do that.

THE COURT: Is it this single slide?

MR. BERL: No. It's throughout. I mean, we didn't want to reproduce the whole slide deck. I have it for you if Your Honor wants me --

THE COURT: I'll get a copy soon enough.

MR. BERL: But yes. I think it starts at Slide 50 where they matriculate through the limitations of Claim 1, and then what you'll see is, when they get to this final limitation, which they address at Slide 55 which is the 98 percent, it's Liu. It's only Liu.

And then when you get to the dependent claims, which I think they start to tick them off at about Slide 79 or something like that, you'll see starting at about Slide 99 what they do is they start to address the final limitation, and there, actually, they rely on Liu for even more, 40 to 150.

They're allowed to do that for the Liu combination. They're not allowed to rely on Liu for their Lucentis plus Fraser combination. It's different. That's -- Liu's not part of that.

And then when they get to the 98 percent limitation,

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they rely for the obviousness -- if we go back to 105 or so, they're relying on Liu for that again.

So the problem is it's Lucentis plus Liu. Everyone agrees -- they just stood up and agreed -- they're not allowed to do Lucentis and Liu together.

THE COURT: Understood.

Counsel?

MR. HUNT: Thank you, Your Honor. I guess my initial point is that we've spent a lot of time looking at slides. Those are not in the record. I suspect they will not ultimately be in the record. What will be in the record is Dr. Rabinow's testimony. I've told counsel for plaintiff the combinations are Fraser and Lucentis and Fraser and Liu. Dr. Rabinow does not intend to offer opinions on the combination of Fraser and Lucentis and Liu.

I don't know how much more clear I can make it. I think maybe we just need to see if we can get the testimony in the record and Your Honor can decide the issue at that point.

With regard to the slides, I will fully admit that there may have been some checkmarks that are missed along the way. It's been -- there's been a number of iterations through the motion to exclude process.

And what will be made clear when Dr. Rabinow testifies is that the person of ordinary skill in the art -- again, through that knowledge that they have, the entire body

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of prior art as of June 16, 2006 -- would have a certain understanding when they read the Lucentis references. At that point in June 16th of 2006, the person of ordinary skill in the art would know that Lucentis is in the clinic -- it's in clinical trials -- and, therefore, they would expect and they would understand that the formulations disclosed in those Lucentis references are necessarily stable.

Now, whether that issue is -- carries enough weight at the end of the day to support the obviousness analysis, I think that's for Your Honor to decide, and I'm certain that Mr. Berl will explore on cross-examination. But to exclude prior art references on the basis of the knowledge of the person of ordinary skill in the art to not consider the body of knowledge of the person of ordinary skill in the art, the Federal Circuit has made clear would be error.

THE COURT: But I guess that gets to the point, the Federal Circuit has been abundantly clear, as this Court tried to articulate yesterday, that when we're talking about obviousness, the specific prior art needs to be identified and then an explanation needs to be identified in the expert disclosures. That's the evidentiary basis to support an obviousness defense.

If we can just say, well, a POSA knows everything that is already out there, why then does the Federal Circuit impose that requirement upon someone asserting an obviousness

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defense?

MR. HUNT: I'm not disputing, Your Honor, that there is a defined combination. But, for example, the Federal Circuit in *Arioso Diagnostics v. Verinata Health,* 805 F.3d 1359 (2005), made very clear that art can legitimately serve to document the knowledge of that skilled artisans would bring to bear in reading the prior art identified as producing obviousness.

So we can't completely cast away the knowledge of the person of ordinary skill in the art. And Dr. Rabinow, in his report, has articulated that there's -- again, the knowledge of the person of ordinary skill in the art through a reference called Avery discloses that Lucentis is in clinical trials.

So that is part of the knowledge of the person of ordinary skill in the art in this crowded field where you have really just two main players in the area of VEGF antagonists. And so that person of ordinary skill in the art at that June 16, 2006, time frame would be well aware of what's happening with Lucentis.

THE COURT: Yes, Counsel, briefly.

MR. BERL: Very briefly, Your Honor. I think that just gave the game away. I mean, what they're basically saying is we get to rely on any of the prior art that we cited. The report you have in front of you, Dr. Rabinow's report, goes through 46 different references. It starts on page 37 of his

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report, goes all the way to, like, page 146. It's, like, over 100 pages.

They can't just later say, oh, I'm going to rely on Avery. What's that? That wasn't one of their four. That's new this morning.

If they're now running a four-reference case, trying to, Shams and Gaudreault -- which is Lucentis -- plus Fraser plus Liu, out of their 46 references, do you know how many possible combinations of four references there are?

THE COURT: We've established I'm bad at math.

MR. BERL: I didn't know either. So I googled it. Google allows you to do it now. 163,185. The notion that they --

THE COURT: Thank you.

MR. BERL: -- can just come in and today say, oh, we're relying on Avery for this or Gaudreault for that, that's not how it works. The cases make that clear.

THE COURT: Understood. I'm going to hold the motion in abeyance at this point. I think counsel's articulated the dance between and among raindrops that they're going to endeavor. The Court ruled on the first motion to exclude yesterday. That holds. Those rules will apply. And we can deal with it as we go as necessary.

I don't think it's necessary at this point. We're talking about demonstrative slides. We don't need to redo

those at this point. We'll note as we go if there are issues that run afoul of the -- what I'll inartfully refer to as law of the case at this point, the Court's position on this, focusing instead on what opinions Dr. Rabinow offers.

So we'll hold that in abeyance and take it up as we go question by question, answer by answer at this point.

Anything else we need to take up before we hear from our next witness from Mylan's perspective?

MR. HUNT: No, Your Honor.

THE COURT: Plaintiff's perspective?

MR. BERL: No. Thank you, Your Honor.

THE COURT: Thank you all.

Mylan call its next witness.

MR. HUNT: Your Honor, with the Court's permission, I've brought an altitude-increasing device for the microphone for the court reporter's benefit and also a little bit for my back.

THE COURT: Understood, sir. Wellness is a focus in this courtroom. Thank you.

MR. HUNT: Your Honor, Mylan and Biocon call Dr. Barrett Rabinow to the stand.

BARRETT E. RABINOW, PhD, DEFENDANTS' WITNESS, SWORN

MR. HUNT: Your Honor, with permission, we have some copies of slides and --

THE COURT: Please.

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MR. HUNT: -- exhibits.

THE COURT: Please. Thank you.

MR. HUNT: Your Honor, may I proceed?

THE COURT: You may.

DIRECT EXAMINATION

BY MR. HUNT:

Q. Good morning, Dr. Rabinow.

A. Good morning.

Q. Could you please introduce yourself to the Court.

A. I am Barrett Rabinow.

Q. You are here testifying on behalf of defendants Mylan and Biocon?

A. I am.

Q. Did you prepare some slides to assist with your testimony today?

A. I did.

MR. HUNT: Mr. Gibson, if we could please pull up DDX 4.

BY MR. HUNT:

Q. Are these the slides that you prepared, Dr. Rabinow?

A. They are.

Q. Turning to DDX 4, Slide 2, briefly describe your academic experience, sir.

A. I earned a undergraduate degree in chemistry at Cornell University and then went to the University of Chicago,

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where I earned a master's and a PhD in physical organic chemistry.

Q. And after receiving your PhD, did you receive a fellowship?

A. Yes. I had an NIH fellowship that allowed me to learn clinical chemistry at what was then Michael Reese Medical Center in Chicago.

Q. And did your graduate studies involve a particular research or study area?

A. I studied very fast-reaction kinetics, species that lasted maybe a microsecond, studied with a flash photolysis apparatus that I built.

Q. Was your graduate research published?

A. It was published both as a thesis and in the *Journal of the American Chemical Society*.

Q. If we could go to Slide 3, Dr. Rabinow, briefly describe your industrial experience.

A. I went to Baxter Healthcare Corporation where I was there for almost 40 years, eventually earning the title of Baxter distinguished scientist, which is a title earned by less than a dozen scientists in their 50,000-person organization.

Q. If we could go to Slide 4, please, Dr. Rabinow, please tell the Court about your experience as a Baxter distinguished scientist and scientific team leader.

A. I was a -- sort of a chief problem solver for a

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number of product problems that Baxter had at the time with issues dealing with, in the case of proteins, adsorption, aggregation, issues.

A number of clients that Baxter had used Baxter products for their proteins and noticed that they were having adsorption issues. So they would contact me, and we would discuss formulation, how to prevent this.

This eventually led to getting involved with manufacturing as well as formulation, studying aggregation and adsorption issues. And I decided to study this.

So I conducted some research in the area of comparing three different proteins -- insulin, albumin, and immunoglobulin G -- and studied their adsorption on a number of different plastics to get an idea of what was the difference in terms of surface adsorption to different plastics and the rate and extent of adsorption.

We eventually published this in the *Journal of Biomaterials* and eventually got a patent on protein adsorption-resistant plastics.

We then -- Baxter had several projects of its own involving insulin. They had a project collaboration with Exubera at the time as well as a company called Epic Therapeutics making nanoparticle insulin dosage forms. So I was an active member of both of those teams.

I also worked on problems that Baxter incurred with

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their albumin in factor VIII formulation problems dealing with aggregation, stability, and inflammation issues.

I was also an expert witness involving insulin formulations after I left Baxter.

Q. Now, Dr. Rabinow, you just explained some of your experience with regard to insulin and factor VIII and albumin.

Do you consider that work to be involving the formulating and manufacturing of proteins?

A. Yes. You are essentially under the gun, under time pressures to solve problems, trying to understand what are the issues involved in a particular problem, and then try to understand not only what the scientific basis of the problem is but also develop experiments to come up with a viable solution.

Q. Did your work at Baxter result -- other than I think the publication and patent that you already mentioned -- in any other publications or patents?

A. I have something like 14 patents on various aspects of formulations, nanosuspensions, and antimeres, different sterilization processes, as well as more than 40 publications and book chapters.

Q. As part of your product development experience, do you also have regulatory experience?

A. Yes. I interacted with FDA on many occasions in somewhat rather contentious issues involving product problems and in trying to convince FDA that we understood the problem

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and were -- had a viable approach to resolving the issues.

Q. And if we could turn to Slide 5.

Do you have additional specific experience in the field of therapeutic proteins?

A. Yes. After I left Baxter, I became a consultant to pharma, both large companies and small. In this particular case I worked with Dr. Jeffrey Loeb, who is a practicing neurologist and head of the department of neurology at University of Illinois at Chicago.

His group was developing a novel and patented fusion protein involving a decoy receptor to stop disease progression in Lou Gehrig's disease, or ALS. So I prepared the formulation and grant preparation for that work involving the analytical methods, development of the administration procedures for intrathecal and intracerebral ventricular administration, and then I developed toxicity and efficacy protocols to study all of that. So that was my experience with fusion proteins using decoy receptors.

Q. And turning to Slide 6, Dr. Rabinow, how many total years of experience do you have in the field of pharmaceutical formulations?

A. Well, it's at least 25, with four years total in industry altogether.

Q. If we could go to Slide 7.

You have displayed here DTX 7091. Is DTX 7091 your

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current CV, Dr. Rabinow?

A. It is.

MR. HUNT: Your Honor, we move to admit DTX 7091 into evidence.

THE COURT: Any objection?

MR. TRASK: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 7091 was admitted.)

MR. HUNT: At this time defendants proffer Dr. Barrett Rabinow as an expert in pharmaceutical formulation science, including the development and manufacture of formulations of therapeutic proteins.

THE COURT: Any voir dire or objection?

MR. TRASK: No, sir, no objection.

THE COURT: Without objection then, motion granted. The doctor is deemed so qualified.

You may proceed, Counsel.

MR. HUNT: Thank you, Your Honor.

BY MR. HUNT:

Q. Dr. Rabinow, let's briefly summarize the opinions that you plan to provide to the Court today.

But before we do, Mr. Gibson, could we please call up PTX 2 on the screen.

Dr. Rabinow, what is the document that appears at PTX 2 on the screen?

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A. This is the '865 patent.

Q. And, Dr. Rabinow, you have your own screen, if it's easier for you to reference the screen there.

A. Yes.

Q. Okay. Very good. So this is U.S. Patent Number 11,084,865; is that right?

A. That's correct.

Q. And for purposes of our discussion today, may we refer to this patent as the '865 patent?

A. Please do.

Q. Have you been asked to render an opinion regarding the validity of certain claims of the '865 patent?

A. Yes.

Q. Okay.

Now, Mr. Gibson, if we could please have PTX 3 on the screen.

Dr. Rabinow, what is the document that appears at PTX 3 on the screen?

A. My screen has not changed.

Q. It's possible that it looks very similar. These patents, they all look the same except for that little number in the top right.

A. I'm sorry. It's like an eye chart.

It's Patent 11,253,572.

Q. And for purposes of our discussion today, may we

refer to this patent as the '572 patent?

A. Indeed.

Q. And have you been asked to render an opinion regarding certain limited terms in the '572 patent?

A. Yes.

Q. And do you intend to provide testimony today regarding the invalidity of the '865 patent?

A. Yes.

Q. And, similarly, do you intend to provide testimony today regarding certain limited elements of the '572 patent, including whether a person of ordinary skill in the art would have considered those limited elements known and/or obvious in view of the prior art?

A. Yes.

Q. Dr. Rabinow, do you also intend to provide testimony today in rebuttal to Dr. Trout's opinions regarding the '865 and '572 patents?

A. Yes.

Q. Directing your attention to Slide 8, could you briefly summarize your opinions.

A. My opinions are that one of ordinary skill in the art would have found Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent to have been anticipated by the prior art, that these same claims of the '865 would have been obvious to one of ordinary skill in the art after consideration of the prior art,

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that there is no objective evidence of nonobviousness in rebuttal to Dr. Trout and other of plaintiff's experts, and finally that the formulation elements of Claim 6 of the '572 patent were known and/or obvious to the person of ordinary skill in the art.

Q. And were you present, Doctor, in the courtroom for Dr. Trout's testimony?

A. I was.

Q. Did anything about Dr. Trout's testimony change the opinions you intend to provide today?

A. It did not.

Q. Thank you, Dr. Rabinow.

I would like to briefly discuss how you arrived at the opinions you plan to provide to the Court today.

If we could have Slide 9 called up, please.

Dr. Rabinow, do you understand that the Court has construed certain terms of the '865 patent?

A. I do.

Q. And have you set out the Court's claim constructions relevant to the '865 patent here?

A. Yes.

Q. Did you rely on the Court's claim constructions in forming your invalidity opinions?

A. I did.

Q. From whose perspective did you conduct your

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invalidity analysis with regard to the '865 patent and the '572 patent?

A. From the perspective of a person of ordinary skill in the art.

Q. And did you bring your experience and knowledge into account in rendering your opinions from the perspective of the person of ordinary skill in the art?

A. I did.

Q. Let's turn to Slide 10, please. Do you understand that defendants and Regeneron have each provided a definition of a person of ordinary skill in the art relevant to the '865 patent?

A. Yes.

Q. And I'd like to look at the top callout on this slide, Dr. Rabinow. This is paragraph 63 from your opening report, which reads, "A POSA, during the relevant time period, would have a fairly high level of education and skill. Here, a person of ordinary skill in the art would have at least a PhD in chemistry, chemical engineering, biochemistry, pharmacology, or a related field, along with one to two years of experience in the development and manufacture of formulations of therapeutic proteins or a lower degree with more practical industrial experience.

"The person of ordinary skill in the art would have access to biologists, biochemists, physicians, pharmaceutical

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formulators, and the like with knowledge and experience in the fields such as drug discovery and development and the treatment of ophthalmic conditions."

Did I read that correctly, Dr. Rabinow?

A. You did.

Q. And is this the definition of a person of ordinary skill in the art that you applied in rendering your opinions with regard to the '865 patent claims?

A. I did.

Q. Now, Dr. Trout has also provided an opinion for the person of ordinary skill in the art; is that correct?

A. Yes.

Q. And would your opinions change if the Court were to apply Dr. Trout's definition of the person of ordinary skill in the art?

A. No.

Q. Do you consider yourself at least a person of ordinary skill in the art under both definitions?

A. I do.

Q. Now I'd like to address the '572 patent, sir.

If we could go to Slide 11.

You understand that Mylan and Biocon and Regeneron -- I apologize. Just so the record's clear, defendants Mylan and Biocon collectively and Regeneron have each offered a definition of a person of ordinary skill in the art relevant to

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the '572 patent?

A. Yes.

Q. Okay.

Now, Mr. Gibson, if you could please call up DTX 7090 at page 7 to 8. This specifically is paragraph 14 of Dr. Rabinow's reply report.

Dr. Rabinow, is this DTX 7090 your reply report?

A. Yes.

Q. And is this where you discuss the person of ordinary skill in the art with regard to the '572 patent?

A. Yes.

Q. Do you recall that your report contains a number of definitions of the POSA?

A. Yes.

Q. So on the screen do you understand that Dr. Trout provided a definition of the person of ordinary skill in the art with regard to the '572 patent?

A. Yes.

Q. And that definition is "the POSA would have an advanced degree such as a master's in biopharmaceutical science or a related discipline such as chemical engineering and several years of experience in the development of biologic products. Alternatively, the POSA could have a PhD in such discipline and less experience. The POSA may collaborate with others, including a medical doctor, with experience in treating

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ophthalmic diseases."

Did I read that correctly, sir?

A. You did.

Q. And for purposes of your testimony today and given the number of definitions that have been floating around for the person of ordinary skill in the art, are you willing to accept Dr. Trout's definition of the person of ordinary skill in the art with respect to the '572 patent?

A. I am.

Q. And you consider yourself a person of ordinary skill in the art under Dr. Trout's definition as it applies to the '572 patent?

A. Yes.

Q. All right. Now, Dr. Rabinow, before we start talking about your opinions in more detail, did you review the literature relevant to the '865 patent as part of your work in this matter?

A. I did.

Q. And did you independently conduct a search for prior art or the knowledge of the person of ordinary skill in the art as of June 16th, 2006, for the '865 patent?

A. I did.

Q. And did you also consider and perform a search for potential disclosures as of January 13th, 2001, with respect to the '572 patent?

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A. I did.

Q. Did you prepare a series of slides to help illustrate your opinions regarding the knowledge of the person of skill in the art related to stable protein formulations?

A. I did.

Q. Okay.

If we could please have Slide 12 on the screen.

I apologize. My cocounsel has informed me that perhaps I misspoke. So just so that the record is clear, with regard to your analysis of the scope of prior art for the '572 patent, was that analysis performed as of January 13th, 2011?

A. Yes.

Q. Thank you.

All right. Now, turning to Slide 12, you have DTX 3492 reflected here. What is shown on Slide 12?

A. This is Andya 1 from Genentech published in 1997.

Q. And Andya 1, DTX 3492, is what's reflected on Slide 2; is that correct?

A. Yes.

Q. And did you rely on DTX 3492 in connection with your opinions?

A. I did.

Q. How does DTX 3492, Andya 1 shown here on Slide 13, inform the knowledge of the skilled person?

A. Andya presents formulations of antibodies formulated

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with trehalose and Tween 20, which is polysorbate 20, and discusses their stability at 12 months at 5 degrees and shows that there was no change in the percent intact protein for the trehalose formulation using size-exclusion chromatography.

Q. Now, on the next slide, 14, do you present another disclosure you believe is relevant to the art of stable protein formulations?

A. Yes.

Q. And what is shown on Slide 14?

A. This is Papadopoulos from Regeneron published in 2000.

Q. And DTX 3619 is the Papadopoulos reference reflected here?

A. Correct.

Q. Did you rely on DTX 3619 in connection with your opinions?

A. Yes.

Q. Turning to Slide 15, what would the person of ordinary skill in the art find significant in DTX 3619, Papadopoulos?

A. Papadopoulos is a 100-page-long patent that discusses in great detail essentially the generative history of VEGF R1R2 -- or VEGF Trap R1R2 and talks about what the various -- what were the concepts that led to the development of this product. It discusses that it was expressed in Chinese hamster

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ovary, or CHO, cells, which would have glycosylated the protein. And it discusses the asparagine sites at which glycosylation occurred as well as the entire amino acid sequence of this protein.

Q. And, Dr. Rabinow, how many glycosylation sites does the Papadopoulos reference inform the person of ordinary skill in the art exist in VEGF Trap R1R2?

A. Five.

Q. If we go to the next slide, DDX 4, Slide 16, how is DTX 3556 relevant to your analysis of the knowledge of the person of ordinary skill in the art?

A. This is Lam from Genentech, a patent published in 2001.

Q. This is DTX 3556. That's the Lam reference, right?

A. Yes.

Q. You relied on DTX 3556 in connection with your opinions?

A. I did.

Q. If we could go to Slide 17, please. What would the person of ordinary skill in the art find significant about Lam, DTX 3556?

A. Lam divulges a monoclonal antibody at a concentration of 40 mg/mL formulated with trehalose and polysorbate 20 and shows the stability in terms of percent monomer by size-exclusion chromatography at several different data points

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over a two-year period at 2 to 8 degrees centigrade and shows that it's pretty constant. So there's negligible degradation over that period.

Q. That disclosure, Dr. Rabinow, is at DTX 3556, page 27 and page 30?

A. That is correct.

Q. If we could please turn to the next slide, Slide 18.

What do you show here, Dr. Rabinow?

A. This is Andya 2 from Genentech, a patent published in 2001, DTX 3506.

Q. And did you rely on DTX 3506 in connection with your opinions?

A. I did.

Q. Now, what, if any, disclosure in DTX 3506, the Andya 2 reference, would inform the knowledge of the person of ordinary skill?

A. So Andya --

MR. HUNT: If you could go to the next slide, please, Mr. Gibson.

THE WITNESS: So Andya discloses antibody formulations involving trehalose and polysorbate 20 or Tween 20 and shows the stability at 5 degrees over a period of 12 months and states that there was no change in the percent intact protein for the trehalose formulation.

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BY MR. HUNT:

Q. And was there a particular analytical method that was used in the Andya 2 reference to present the stability results that you just discussed?

A. They use size-exclusion chromatography.

Q. And the disclosure of the stability data in Andya 2 is at DTX 3506, page 23; is that correct?

A. Yes. And 22.

Q. Thank you, Dr. Rabinow.

If we could turn, please, to Slide 20, what is DTX 728?

A. This is Wulff from Regeneron, a publication from 2002.

Q. Did you rely on DTX 728 in connection with your opinions?

A. I did.

Q. On the next slide, Dr. Rabinow, how would the disclosures of Wulff inform the person of ordinary skill?

A. Well, first of all, Wulff refers to VEGF Trap R1R2, which, by this point, the POSA would recognize as a specific entity having a known amino acid sequence glycosylation pattern, et cetera, because this was widely discussed in the literature. It would be as common, for example, as when one mentions aspirin. And a POSA would understand that that would envision the structure of acetylsalicylic acid, for example.

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He talks about VEGF Trap -- he talks about it's a recombinant chimeric protein or a fusion protein. VEGF Trap was expressed in CHO cells. And he also discusses that control animals in his animal experiments were treated with a vehicle and proceeds to give the formulation of that vehicle consisting of 5-millimolar phosphate, 5-millimolar citrate, 100-millimolar sodium chloride, .1 percent weight per volume Tween 20, and 20 percent weight per volume sucrose.

And a POSA would understand that the formulation used in the control would also be used for the -- what's known as the test arm involving that in combination with the active ingredient, the VEGF Trap R1R2.

Q. And, Dr. Rabinow, the disclosures of Wulff that you've just discussed, that's at DTX 728, page 2?

A. Yes.

Q. If we could please turn to the next slide, Slide 22. Is there an additional reference that's relative to your analysis?

A. Yes. This is Holash, also from Regeneron, a publication from 2002.

Q. And just so the record's clear, DTX 3549 is the Holash reference reflected here?

A. Yes.

Q. You relied upon the Holash reference, DTX 3549, in connection with your opinions?

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A. Yes.

Q. On the next slide, Slide 23, what would the person of ordinary skill in the art take away from DTX 3549, the Holash reference?

A. He would take away quite a lot. He would understand from the disclosure that, quote, they were able to engineer a very potent high-affinity VEGF blocker that has prolonged in vivo pharmacokinetics and pharmacodynamics. It lacks nonspecific toxicities and can effectively suppress the growth and vascularization of a number of different types of tumors in vivo.

Q. And that disclosure in Holash is at 3549, page 1; is that correct?

A. Yes.

Q. Moving to the next slide, 24, did Regeneron disclose specifics of the VEGF Trap R1R2 protein in DTX 3549, Holash?

A. Yes. They discussed that it is a fusion protein. It's purified from Chinese hamster ovary cells. And it gave a pictorial which was very illustrative in terms of showing how they combined several different receptor portions of two different receptors of VEGF to combine them to make VEGF Trap R1 and R2.

Q. So by at least 2002 would the person of ordinary skill in the art know the molecular details of VEGF Trap R1R2?

A. He would.

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Q. And is that because Regeneron itself published those molecular details and characteristics of the fusion protein?

A. That is correct.

Q. Let's discuss DDX 4, Slide 25. What is shown here, Dr. Rabinow?

A. This is Kaisheva, a patent published in 2003.

Q. And DTX 3610 is that Kaisheva '316 reference, correct?

A. Yes.

Q. Did you rely on DTX 3610 in connection with your opinions?

A. I did.

Q. What does Kaisheva '316, DTX 3610, tell the person of ordinary skill in the art about the protein formulation process?

A. Kaisheva provides a recipe for how you go about developing protein formulations. In terms of a three-step process.

I think you need to change the slide too.

Q. Oh, sorry.

If we could please go to the next slide.

A. So he talks -- the first step is you want to optimize the pH. The pH is a controlling variable, and it's rather easily determined. You would do what are known as accelerated stability tests. In other words, you conduct studies where the

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protein is formulated at different pHs and studied perhaps at 40 degrees over a period of weeks. And you select a pH that gives you the most stability. That's known as selecting the optimum solution pH.

After you've locked in the pH, you select the buffer type that will maintain that pH as well as its concentration. There's not many choices here because, for any particular pH, there's only a limited number of options for buffers.

So this is a pretty routine process, if you will. So, again, you would select -- make several different buffers at various different concentrations and study their stability over perhaps 40 degrees over a few weeks and then select the optimum buffer type and concentration which give you the most stable formulation.

So after you have locked in the pH, the buffer type, and the concentration, you're now ready to examine the effect of other excipients for either a liquid or lyophilized dosage form that you're studying. And this is all using a statistical package so everything can be understood to ensure that it has statistical significance.

Q. And these disclosures are found in DTX 3610, including at page 16?

A. Correct.

Q. If we could turn to Slide 27, please.

Is there another Kaisheva reference that's included

in your analysis, Dr. Rabinow?

A. Yes. This is Kaisheva patent published 2003.

Q. And I believe this is a patent application; is that correct?

A. That is correct.

Q. And so this is DTX 3611, the Kaisheva '417 reference, correct?

A. Yes.

Q. Did you rely on DTX 3611 in connection with your opinions?

A. Yes.

Q. Moving to Slide 28, what does DTX 3611, the Kaisheva '417 reference, tell the person of skill in the art about protein formulation stability?

A. Kaisheva discloses a rather high concentration of an antibody that is formulated with a succinate buffer as well as Tween 80, or polysorbate 80, and studies it for a percent monomer, which means he would have done size-exclusion chromatography, and finds that at 5 degrees after 12 weeks, the percent monomer is at 98.25 percent.

Q. And the disclosure of the formulation details in Kaisheva '417 is at DTX 311, page 15; is that right, Dr. Rabinow?

A. Yes.

Q. And the stability results that you have described in

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Table 5, that's at DTX 3611, page 15, as well, right?

A. That's correct.

Q. If we could please move to Slide 29.

What reference is shown here, Dr. Rabinow?

A. This is Liu from Genentech, a patent application publication published 2004.

Q. And that is DTX 730, correct, the Liu reference?

A. Yes.

Q. While I think the record may already be clear on this, did you rely on DTX 730, the Liu reference, in connection with your opinion?

A. I did.

Q. Moving to Slide 30, how is DTX 730 relevant to the knowledge of the person of ordinary skill in the art as of June 16th, 2006?

A. The Liu reference discusses high-concentration antibody formulation. So that would be of particular interest. And he discusses protein concentrations ranging from 40 to 150 mg/mL, or milligrams per milliliter. And specifically what is shown on DTX 730, page 35, is a table displaying the stability of an antibody known as E25 formulated at 80 mg/mL with a histidine buffer, a trehalose sugar stabilizer, and a polysorbate 20 component all at pH 6. And stability was monitored by size-exclusion chromatography.

A percent monomer was followed at 5 degrees for 24

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months, and the values at 6 and 14 months, for example, were 99.1 and 99.0 percent and at 24 months was at 98.8 percent.

He also discusses turbidity values as well.

Q. Now, before we move on, I want to make sure that the record is clear with regard to a few disclosures that you've referenced in the Liu publication.

Looking at DTX 730, page 35, did the Liu reference disclose a range of protein concentration?

A. Yes. He disclosed the range of 40 to 150 mg/mL; so rather high concentrations. He also discussed ranges of polysorbate of .01 percent to .1 percent and -- as well as sugar ranges, either trehalose or sucrose, ranging from 20 millimolar to 350 millimolar.

Q. And turning to the table that you have depicted on the left side of the slide, DTX 730, also on page 35, what were the concentrations of the protein formulations that Liu tested here?

A. It was 80 -- well, the bottom one that I referred to -- given the stability data for -- was 80 mg/mL in a histidine buffer and trehalose sugar formulation. Above that is an even higher concentration formulation at 150 mg/mL also using a histidine buffer.

Q. And the percent monomer data that's presented in this table, was there a particular analytical method that was used to gather that data?

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A. That was size-exclusion chromatography.
Q. And, again, that's at DTX 730, page 35, correct?
A. That is correct.
Q. And, Dr. Rabinow, I apologize if you've already mentioned this, but Liu reported the work of what company?
A. Genentech.
Q. All right.
If we could please turn to the next slide, DDX 4, Slide 31.
Does this disclose an additional relevant reference, Dr. Rabinow?
A. Yes. This is Fraser from Regeneron, an article published in 2005.
Q. And DTX 0729 is the Fraser reference reflected in your Slide 31, correct?
A. Yes.
Q. And did you rely on DTX 729 in connection with your opinions?
A. I did.
Q. Moving to Slide 32, what does DTX 729, the Fraser reference, tell the person of ordinary skill in the art regarding VEGF protein formulations?
A. Fraser discloses VEGF Trap R1R2 would automatically enable a POSA to envision the amino acid sequence of the protein, the glycosylation pattern, and other relevant

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information. It is disclosed here that the substance was provided by Regeneron and it was provided at a concentration of 24.3 mg/mL in 2-milliliter aliquots in buffer. That was composed of 5-millimolar phosphate and 5-millimolar citrate at a pH of 6, also including Tween 20 -- that's polysorbate 20 -- with 20 percent sucrose. And this is at DTX 729, page 1.

THE COURT: Sorry, Counsel, not to interrupt. We've got a new word. I don't think I've heard aliquots before or during this trial.

Can you tell me what that is, Doctor?

THE WITNESS: Yes. It's a small volume of a liquid.

THE COURT: It's a unit of measurement?

THE WITNESS: It's not quantitative, more qualitative, suggestive.

THE COURT: Oh, okay. Understood. Thank you very much.

Sorry, Counsel. Go ahead.

MR. HUNT: Problem, Your Honor. Thank you.

Mr. Gibson, could we please go to the next slide, DDX 4, Slide 33.

BY MR. HUNT:

Q. Dr. Rabinow, do you set forth here an additional reference that you believe is relevant to your analysis?

A. I do. This is Gaudreault from Genentech, a publication dating to February of 2005.

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Q. And that Gaudreault reference is DTX 2265, correct?
A. Yes.
Q. Did you rely on DTX 2265 in connection with your opinions?
A. I did.
Q. What would the person of ordinary skill in the art note in the February 2005 Gaudreault reference, DTX 2265?
A. He would note that there were preclinical pharmacokinetics -- that means animal studies -- of ranibizumab, which is a vascular endothelial growth factor fragment after a single intravitreal administration.

So he would understand that VEGF was injected intravitreally into the eye of animals and that the substance ranibizumab furthermore was formulated as 10 millimolar in a succinate buffer and 10 percent trehalose and also contained .05 percent Tween 20, or polysorbate 20.

Q. And, Dr. Rabinow, those formulation details you just discussed are found at DTX 2265, page 2; is that correct?
A. That's right.
Q. Now, the ranibizumab that is reflected on DTX 2265, page 2, would that have another name to the person of ordinary skill in the art?
A. Yes. Once it got approved, it was given the brand name of Lucentis.
Q. Turning to the next slide, DDX 4, Slide 35, what is

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shown on this slide, Dr. Rabinow?

A. This is Dix '226. Dix is from Regeneron. The date of the patent is 2019, but the priority date tracks back to the provisional application filed on March 25th of 2005.

Q. And, Dr. Rabinow, for purposes of your analysis today, have you been asked to assume that the Dix '226 patent is prior art to the '865 patent?

A. I have been so instructed, yes.

Q. And DTX 13 is that '226 patent; is that correct?

A. That's correct.

Q. And you relied on DTX 13 in connection with your opinion?

A. I did.

Q. If we could go to the next slide, what would be notable to the person of ordinary skill in the art about DTX 13, the Dix '226 patent?

A. It is stated on page 5 that it is, first of all, suitable for injection. On page 7, Example 1, it is stated that it is a liquid formulation containing 10 millimolar of phosphate, 0.1 percent polysorbate 20, 20 percent sucrose, 50 mg/mL VEGF Trap -- and then that is described further as Sequence ID Number 4 -- at a pH of 6.25; and that was stored at 5 degrees centigrade; and samples were tested at a number of time points through 24 months by size-exclusion chromatography; and that it shows that 98.6 percent of this remained intact,

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nondegraded, at 12 months; and 98.3 percent remained intact, nondegraded, at 24 months; and, furthermore, that turbidity was measured at OD405. And this was at DTX 13, page 7.

Q. Thank you, Dr. Rabinow.

And you pointed to the suitable for injection piece in DTX 13, and that's at page 5 of that exhibit, correct?

A. Correct.

Q. Is there an additional reference shown on the next slide, Slide 37?

A. Yeah. This is Rudge, also from Regeneron, a publication from 2005.

Q. And the Rudge reference that you're discussing, that's DTX 3592?

A. That is correct.

Q. Did you rely on DTX 3592 in connection with your opinions?

A. I did.

Q. If we could go to Slide 38, please.

What, if anything, would the person of ordinary skill in the art find significant about DTX 3592, Doctor?

A. It's describing the status of what they call a very potent and high-affinity VEGF blocker, termed the VEGF Trap, that may provide the opportunity to maximize the potential of VEGF blockade in cancer as well as in vascular eye diseases. And this is at page 1 of Rudge.

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It then goes on on page 4 to divulge "Initial clinical studies in human patients suffering from both AMD and diabetic edema and retinopathy appear quite promising."

Q. And, Dr. Rabinow, the disclosure of AMD at DTX 3592, page 4, would the person of ordinary skill in the art understand that to be referring to age-related macular degeneration?

A. That is correct.

Q. If he could turn, please, to Slide 39.

What is shown on this slide, Dr. Rabinow?

A. This is Ferrara from Genentech in a publication from 2005.

Q. And DTX 4041 is the Ferrara reference, correct?

A. Yes.

Q. Did you rely on DTX 4041 in connection with your opinions?

A. I did.

Q. What did Ferrara 2005 disclose regarding the possible use of anti-VEGF therapies? And if we could please go to Slide 40.

A. He disclosed that in 2004 FDA approved bevacizumab, which is a humanized anti-VEGF monoclonal antibody for the treatment of cancer in conjunction with 5FU, and he talks about very recently data of a controlled Phase III study with ranibizumab is efficacious and maintains or improves vision in

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patients with wet AMD, referring to Rosenfeld. And this is located at DTX 4041, page 6 as well as page 1.

Q. Now, the disclosure of a controlled Phase III study with ranibizumab here at DTX 4041, page 6, what, if any, significance would that have to informing the knowledge of the person of ordinary skill in the art?

A. A person of ordinary skill in the art would understand that, by the time you get to Phase III clinical trials, you're talking well into a mature development of a drug. There's a lot of money involved. There's a lot of time involved. There's a lot of additional issues. You're treating patients with your drug there. So that implies that a number of other earlier activities must necessarily have been performed, such as, for example, the development of all the analytical methods, the conduct of the stability studies, all of the preclinical studies to justify this.

THE COURT: Yes, Counsel.

MR. TRASK: Object as outside the scope of his report. There was minimal discussion of the Ferrara reference and no discussion of any stability of proteins in connection with Phase III studies in connection with Ferrara or any other reference in the report.

THE COURT: Counsel, where is it in the report?

MR. HUNT: Dr. Rabinow discusses the ranibizumab clinical trials at, I believe at least, paragraph 174 in his

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opening report and 287.

THE COURT: What was the first paragraph, Counsel? 174.

MR. HUNT: Apologies. Yes, 174, Your Honor.

THE COURT: Thank you. That's the Avery article, correct?

MR. HUNT: I believe that Avery is discussed there, yes.

THE COURT: The other paragraph is what again?

MR. HUNT: Apologies. Let me get there, Your Honor.

287, Dr. Rabinow states the published results of the Lucentis clinical trials and then references the favorable data in Shams and Gaudreault.

THE COURT: Counsel.

MR. TRASK: Yes, Your Honor. Neither of these discusses -- neither of the passages that counsel cited to involve the Ferrara reference that he's discussing now. They also don't discuss stability in particular.

THE COURT: I'm going to hold that objection in abeyance consistent with the issues raised in the second motion to exclude at this juncture, but again we want to make sure we stay within the lanes the Court's already identified.

MR. HUNT: Understand, Your Honor. Thank you.

BY MR. HUNT:

Q. If we could please turn to DTX 2264 on the next

slide.

Dr. Rabinow, is there an additional relevant formulation disclosure included here?

A. This is Avery from Genentech, an article entitled "Intravitreal Bevacizumab (Avastin) for Neovascular Age-Related Macular Degeneration," published in 2006, DTX 2264.

Q. And did you rely on DTX 2264 in connection with your opinions?

A. I did.

Q. On Slide 42, what would the person of ordinary skill find relevant about Avery in or around June -- sorry -- June 16, 2006?

A. He would understand that, number one, bevacizumab was commercially available at a concentration of 25 mg/mL, and that it was injected intravitreally into human patients with a volume -- using a volume of .05 milliliters.

Q. And that disclosure, Dr. Rabinow, is at DTX 2264, page 2?

A. That's correct.

Q. Apologies for interrupting, sir. On the second, lower half of the slide, you have included reference to another exhibit. That's DTX 3510, correct?

A. Yes, that's correct.

Q. And is DTX 3510 the Avastin prescribing information?

A. It is.

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Q. And did you rely on DTX 3510 in connection with your opinions?

A. I did.

Q. What, if anything, would the person of ordinary skill in the art find of interest with DTX 3510?

A. It states what the concentration of Avastin is, confirming what was in Avery. It states that Avastin consists of a concentration of 25 mg/mL. It further gives formulation details, noting that it is formulated with a trehalose sugar stabilizer, a phosphate buffer, and polysorbate 20.

Q. And the disclosures regarding Avastin that you've just discussed, Dr. Rabinow, are at DTX 3510, page 2; is that correct?

A. Yes.

Q. And what would the person of ordinary skill in the art understand Avastin to mean here? Does it have a different name?

A. Yes. Avastin is the brand name of bevacizumab, which is the vascular endothelial growth factor antagonist protein that was developed by Genentech.

Q. If we could turn to DTX 726 on the next slide, Slide 43, is this an additional reference that you considered, doctor?

A. This is Shams from Genentech. This is a patent publication dating from May of 2006, DTX 0726.

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Q. And did you rely on DTX 0726 in connection with your opinions?

A. I did.

Q. Moving to the next slide, what would the person of ordinary skill in the art find significant about Shams?

A. Shams is disclosed to be an example of a VEGF antagonist. Its name is ranibizumab. It referred to its brand name, Lucentis. It is described as a humanized antihuman VEGF Fab fragment for intravitreal administration.

It is supplied in a liquid-filled vial. The concentration is 10 mg/mL for the .5-milligram dose level. And if you divide those two numbers, you learn that the intended volume for intravitreal injection is .05 milliliters; and that the formulation contains a histidine buffer, a trehalose sugar stabilizer, and polysorbate 20; and that the study drug is stored at 2 to 8 degrees.

Q. And that disclosure, Dr. Rabinow, is at DTX 726, page 32; is that right?

A. That's correct.

Q. And if we look at the top of the callout that you have here, again, as of May 4th, 2006, the date of the Shams reference, would the person of ordinary skill in the art have an understanding that ranibizumab and Lucentis are synonymous?

A. Yes, they would.

Q. If you could please turn to Slide 45. What is shown

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here, Dr. Rabinow?

A. This is the Lucentis prescribing information dating from 2006 from Genentech.

Q. And DTX 3040 is the Lucentis prescribing information, correct?

A. Yes.

Q. Did you rely on DTX 3040 in connection with your opinions?

A. I did.

Q. Now, why did you include DTX 3040 in your analysis?

A. I included it to show that it essentially confirmed what we learned from Shams that was published earlier.

Q. But you're not asserting that the Lucentis prescribing information from 2006 is prior art; is that right?

A. That is correct.

Q. Looking at Slide 46, what did you find relevant about the Lucentis prescribing information?

A. So on page 4 it states that Lucentis -- ranibizumab -- injection is a monoclonal antibody fragment and that, furthermore, it is provided in a vial and that it is designed to deliver 0.05 mL of a 10-mg/mL Lucentis solution. And, furthermore, it's disclosed that the formulation comprises a histidine buffer, a trehalose sugar stabilizer, and a polysorbate 20 formulation component as well. This is at DTX 3040, page 4.

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Q. Thank you, Dr. Rabinow.

If we could turn to the next slide, Slide 47, would the person of ordinary skill in the art have had a particular understanding relating to FDA-approved protein formulations in or around June 16th, 2006?

A. He would. He would be amazed by the apparent routine nature of the ability to formulate all these different antibody formulations with surprisingly few formulation alternatives.

So as we see here, there are half a dozen different antibodies. Some of them -- many of them are fusion proteins. Some of them are not. They all involve a buffer, a surfactant, and a stabilizer for either a liquid or a lyophilized formulation. And within each category of buffer, surfactant, or stabilizer, there are, as indicated here, only two alternatives that are -- that were used.

You could -- for the buffer you can use either histidine or phosphate. For the surfactant you can choose either polysorbate 20 or polysorbate 80. For the stabilizer, you can use either trehalose or sucrose. It reads like a menu in terms of what do you want for soup, salad, appetizer in terms of limited choices here.

Q. And with apologies, Dr. Rabinow, I need to walk through a few exhibits that are referenced on your Slide 47 just for the record.

So is DTX 5036 the Remicade prescribing information

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reflected here?

A. It is.

Q. Did you rely on DTX 5036 in connection with your opinions?

A. I did.

Q. Similarly, is DTX 5037 the Xolair prescribing information reflected here?

A. It is.

Q. Did you rely on DTX 5037 in connection with your opinions?

A. I did.

Q. Is DTX 5038 the Raptiva prescribing information?

A. Yes.

Q. And did you rely on DTX 5038 in connection with your opinions?

A. I did.

Q. And, finally -- and there, I believe, is a typographical error on this slide, but DTX 5040, is that the Xolair -- I'm sorry -- is that the Herceptin prescribing information reference reflected in your Slide 47?

A. Yes.

Q. And did you rely on DTX 5040 in connection with your opinions?

A. Yes.

Q. Overall, Dr. Rabinow, what is your opinion regarding

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the general scope of prior art that would form the person of skill's understanding of the field of stable protein formulations as of June 16th, 2006?

A. It appears to be surprisingly routine in terms of including three formulation components, each with limited choices for selection and optimization.

Q. Now, Dr. Rabinow, you previously discussed your lengthy experience as a problem solver at Baxter, including on protein formulation issues.

A. Yes.

Q. In conducting your obviousness analysis, did you consider the knowledge of the person of skill in the art in or around June 16, 2006?

A. I did.

Q. Now, in the next few questions, I'd like you to put yourself into that June 16, 2006, time frame and consider the skilled person to be one of ordinary creativity. Okay?

A. Yes.

Q. In that context, let's further assume that the person of ordinary skill in the art is a problem solver developing protein formulations at a biopharmaceutical company. Okay?

A. That's fine.

Q. Now, let's also assume that senior management indicates to the person of ordinary skill in the art that the company is interested in entering the VEGF antagonist space,

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including intravitreal administration of protein formulation. Okay?

A. Fine.

Q. Based on your review of the prior art, Dr. Rabinow, what would be apparent to the person of ordinary skill in the art concerning the competitive landscape in the VEGF antagonist space, including intravitreal administration of a protein formulation, as of June 16, 2006?

A. Always of that date, a POSA would realize that there were a pretty small group of competitors. There was Genentech, which had bevacizumab that was being used off label. They had just come out with ranibizumab for the indication involving intravitreal administration. And they would realize that there was Regeneron that had the VEGF Trap R1R2.

Q. Thank you, Doctor.

MR. HUNT: Your Honor, I'm about to switch gears. I'm happy to continue, but I thought I'd offer this opportunity if Your Honor needed a personal comfort break.

THE COURT: Offer accepted, sir.

We're going to call it personal comfort and caffeine break. Let's go ahead and do that. We'll take 15 minutes at this point.

Doctor, as I know you've heard me say ad nauseam this week, you're a man without a country during the break. No one can talk to you because you're midstream.

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THE WITNESS: Understand, sir.

THE COURT: Figured you did, but for the record, no one can speak to you during the break because you're midstream on your testimony. You can step down. You can leave everything there.

Otherwise, we'll take 15 and see everyone then.

(A recess was taken from 11:00 a.m. to 11:18 a.m.)

THE COURT: Counsel, if you're ready, you may proceed.

MR. HUNT: Thank you, Your Honor.

If I could please have DDX 4, Slide 48. Thank you.

BY MR. HUNT:

Q. Dr. Rabinow, I'd like to now discuss your opinions regarding obviousness, and we're going to start with Claim 1 of the '865 patent. Okay?

A. Yes, sir.

Q. Have you prepared slides to assist with your obviousness analysis with respect to Claim 1?

A. I have.

Q. Okay.

Mr. Gibson, could we please call up DDX 4, Slide 49.

What have you included on this slide, Dr. Rabinow, to assist in your obviousness analysis?

A. So I've listed out the claimed elements of Claim 1

for the '865 on the left side of this screen; and on the right side I've indicated for Lucentis, Fraser, and Liu possibilities where we can show where these claim elements may be tracked to.

Q. Okay. Now, is Claim 1 asserted in this case?

A. No.

Q. But do you understand that your invalidity analysis must necessarily include Claim 1?

A. I do.

Q. Now, this slide references Lucentis, Dr. Rabinow. By at least June 16, 2006, were there a number of references published disclosing stable protein formulations comprising ranibizumab?

A. Yes.

Q. But for purposes of your invalidity analysis for Claim 1, are you relying on -- which references are you relying on with regard to Lucentis?

A. I'm relying on those references prior to the June 16th, 2006, priority date.

Q. Specifically, are there two references that you're relying upon?

A. Yes. I'm relying upon Shams and Gaudreault.

Q. Let's go to DDX 4, Slide 50.

What would the person of ordinary skill in the art understand regarding the product presentation of ranibizumab shown here in DTX 726, page 32, as it relates to Claim 1 of the

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'865 patent?

A. Shams discloses, first of all, a vial. He discloses intravitreal administration, which would address the ophthalmic formulation suitable for intravitreal administration. So that would all be -- so the entire claim element of a vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises would be disclosed in Shams, DTX 726, page 32.

Q. And also at DTX 726, page 32, does the Shams reference disclose formulation details?

A. It does.

Q. And what are those formulation details?

A. It discloses a histidine buffer, a trehalose sugar stabilizer, and a polysorbate 20.

Q. Apologies. Can we have Slide 50 back? Thank you.

A. And a polysorbate 20 component, which in Regeneron's infringement contention, is considered an organic cosolvent. So I'm relying upon that definition when I refer to an organic cosolvent.

Q. So just so that the record is clear, Dr. Rabinow, you've not taken any position as to whether or not polysorbate 20 is, in fact, an organic cosolvent under the Court's construction; is that correct?

A. That is correct.

Q. So for purposes of your analysis, you have assumed

that polysorbate 20 is an organic cosolvent as Regeneron suggests that it should be?

A. That is correct.

Q. Now, with regards to Shams and Gaudreault, did you have an opinion as to whether the person of ordinary skill in the art would expect the formulations disclosed there to be stable?

A. Yes. Certainly. Of course. They had to be approved by FDA.

Q. Now, if we could please turn to Slide 51.

Dr. Rabinow, can you explain how Fraser, DTX 729, relates to Claim 1?

A. Fraser discloses at DTX 729, page 2, a VEGF Trap R1R2, which the POSA would understand to be a vascular endothelial growth factor, VEGF, antagonist, which is the claim element, one of the claim elements of Claim 1; and, furthermore, by disclosing VEGF Trap R1R2, there is an inherent disclosure of the fact that this is glycosylated and comprises amino acids 27 to 457 of Sequence ID Number 4.

And additionally, there is, for confirmation, a reference made in 21 to Holash who further emphasizes that at DTX 729, pages 2 and 9.

Q. If we could turn to Slide 52.

How is the person of ordinary skill's understanding confirmed if we look at Holash?

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A. Holash, once again, refers to VEGF Trap R1R2, which, as in Fraser itself, would signify to the POSA what the amino acid sequence would be, what the glycosylation pattern would be, and explicitly also indicated from the fact that -- of the disclosure purified from Chinese hamster ovary cells at Holash DTX 3549, pages 1 and 2.

Q. Thank you, Dr. Rabinow.

Let's turn to Slide 53, please.

Can you explain how Shams, DTX 726, relates to the excipient limitations of Claim 1?

A. Shams discloses a histidine buffer, a trehalose stabilizing agent, and a polysorbate 20 organic cosolvent using Regeneron's infringement contention of the meaning of that word.

Q. Now, turning to Slide 54, what from DTX 730, the Liu reference, is shown on this slide?

A. This Liu discloses that a stable formulation is important to retain the physical and chemical stability upon storage. He furthermore states that he expects it to remain stable at 2 to 8 degrees for at least two years. And this is at DTX 730, page 15, Liu.

THE COURT: Counsel.

MR. TRASK: Objection, Your Honor. Outside the scope of the report. This is the Liu and Lucentis combination that we heard Mr. Hunt earlier this morning admit is not disclosed

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in the expert report.

On the first element of Claim 1 he used Lucentis to check the box for the vial limitation. Now here on the last limitation of Claim 1, he's using Liu to check the box for the 98 percent native conformation limitation.

The combination that's proposed for obviousness is core to the case. We had no chance to respond. Dr. Trout had no chance to respond to the Lucentis and Liu combination. This has come out of the blue. It's not disclosed under Rule 26(a)(2). And we object to testimony on this combination.

THE COURT: Counsel.

MR. HUNT: Dr. Rabinow has not offered an opinion and he will not be offering an opinion that Lucentis in combination with Liu renders Claim 1 obvious.

Dr. Rabinow is walking through disclosures of the reference. There is testimony in the record that the person of ordinary skill in the art would understand that the Lucentis formulations were being used in clinical trials. And to the extent the Court gives that weight, there's also evidence in the record that the person of ordinary skill in the art would expect that the Lucentis formulations would be stable.

We are walking through -- Dr. Rabinow is walking through the disclosures of the prior art and the person of ordinary skill's knowledge. He is not making the ultimate opinion as to obviousness yet. That will come very shortly,

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and you will not hear Lucentis in combination with Fraser. I'm sorry. Apologies. Lucentis in combination with Liu.

MR. TRASK: Your Honor, there seems to be a misunderstanding here about background art versus prior art references relied to satisfy limitations of the claims. And what's happening here is not background art. We have Lucentis checking one of the boxes as satisfying the limitation of Claim 1, which, of course, is a limitation in all of the asserted dependent claims. Liu is being used to check the box to satisfy the limitation of 98 percent, which, again, is in every asserted claim.

This is not background art. You can't simply point to general knowledge in the art to satisfy a specific claim limitations under Section 103 for obviousness purposes.

THE COURT: Understood.

Consistent with this Court's rulings of yesterday, I'll sustain the objection.

I understand, Counsel, points you make, that the doctor witness is not going to make the connection between the two; but any invitation to the Court to make that connection will not occur based on the failure to disclose, I think, consistent with the requirements the Federal Circuit has set forth.

On obviousness, the specific prior art must be referenced and reasons articulated -- or the reasons that the

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prior art makes the invention obvious is also required, neither of which have been disclosed.

So I'll sustain the objection. Again, we can proceed and leave the unconnected bodies of testimony out there. The Court will not draw that connection. And so I'll just say that now. But objection sustained.

You may proceed, Counsel.

MR. HUNT: Just to be clear, Your Honor, we're free to proceed and discuss the disclosure of the Liu reference and then we can tie it together appropriately in a few minutes, correct?

THE COURT: "Appropriately" being the key word, but otherwise, yes. But, again, I just want to make sure that I'm quite clear. The Court will not take up the invitation to put a bow on something that should have been wrapped and presented in opening disclosures.

MR. HUNT: Understood, Your Honor.

BY MR. HUNT:

Q. If we could please turn to Slide 55. And we're looking on the right-hand side at another disclosure from the Liu reference, Dr. Rabinow.

If you could please describe for the Court what is disclosed at DTX 730, page 35.

A. Liu is describing high-concentration antibody formulations. He is describing a particular formulation that

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contains a histidine buffer, a trehalose stabilizer, a polysorbate 20 component, at pH of 6. He discloses that protein concentrations of 40 to 150 mg/mL have been studied and are stable and that formulations also containing trehalose or sucrose stabilizers in a concentration range of 20 to 350 millimolar are also stable as well as a polysorbate concentration range of .01 percent to .1 percent.

In specific, he is directing attention to a table where he is describing an 80 mg/mL antibody formulation comprising histidine and trehalose and showing that, over a period of 24 months, the -- well, at three months and beyond, that -- at 5 degrees, the -- by size-exclusion chromatography, the percent monomer exceeds 98 percent to meet the claim limitation of the '865.

Q. If we could please move to Slide 56.

Dr. Rabinow, on Slide 56 have you set forth the combinations of prior art references that you contend render Claim 1 of the '865 patent obvious?

A. Yes.

Q. And is there intended to be any relation on this slide between the claims on the left and the references on the right?

A. Yes.

Q. Okay. So let's just briefly summarize your opinions.

Could you please summarize your opinion regarding the

obviousness of Claim 1 in view of Lucentis in combination with Fraser?

A. Yes. Claim 1 of the '865 would be obvious in view of Lucentis plus Fraser.

Q. And separately, can you summarize your opinion regarding obviousness of Claim 1 in view of Fraser in combination with Liu?

A. Yes. Claim 1 of the '865 would be obvious in view of Fraser plus Liu.

Q. Now, would the person of ordinary skill in the art have a reasonable expectation of success in combining the disclosures that we've discussed today of the Lucentis prior art -- that is, Shams and Gaudreault -- with the disclosures of Fraser?

A. Yes.

Q. And similarly, would the person of ordinary skill in the art have a reasonable expectation of success when combining the disclosures that we have discussed today of Fraser in combination with Liu?

A. Yes.

Q. Turning to Slide 57, do you have an opinion as to whether the person of ordinary skill in the art would have been motivated to combine her knowledge of Lucentis with Fraser?

A. Yes. It would be provided by Saishin, DTX 2751, page 1, where it is disclosed that VEGF Trap R1R2 is a fusion

protein and, further, that it -- subcutaneous or a single intravitreous injection of Vermont VEGF Trap R1R2 strongly suppressed choroidal neovascularization in mice with laser-induced rupture of Bruch's membrane.

And that, therefore, it is concluded that VEGF Trap R1R2 may provide a new agent for consideration for treatment of patients with choroidal neovascularization and diabetic macular edema. And this is back in 2003.

Q. And this disclosure from Saishin, Dr. Rabinow, is at DTX 2751, page 1?

A. Correct.

Q. And did you rely on DTX 2751, the Saishin reference, for purposes of your analysis?

A. Yes.

Q. If we could please turn to Slide 58.

Is there anything else that supports your opinion regarding the person of ordinary skill in the art's motivation to combine her knowledge of Lucentis with Fraser?

A. Saishin at DTX 2751, page 7, discloses further that VEGF Trap R1R2 deserves consideration as a potential treatment for two complications of diabetic retinopathy: retinal neovascularization and macular edema. It emphasizes again that a single intravitreous injection of VEGF Trap R1R2 markedly suppressed the development of choroidal neovascularization over the course of two weeks. And, concurrently, additional

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preclinical studies should explore modes of local delivery to the eye that can be used adjunctively or as an alternative to systemic administration. This is DTX 2751 at page 7.

Q. Thank you, Dr. Rabinow.

Now, we just discussed your opinions regarding the motivation to combine Lucentis with Fraser. Is it also your opinion that Saishin, DTX 2751, provides a motivation to combine Fraser and Liu?

A. It does.

Q. Is there any additional disclosure in Saishin besides what you've already described that is relevant to the motivation to combine Fraser with Liu?

A. Well, it's clear -- I'm sorry. Could you repeat that.

Q. Yeah.

I'm just looking for confirmation that your opinion with regard to motivation to combine Lucentis and Fraser is the same for Fraser and Liu; is that correct?

A. It is. It also provides a reasonable expectation of success to do so as well.

Q. And that's the Saishin reference, correct?

A. That is correct.

Q. Is there anything else about the knowledge of the person of ordinary skill in the art that would provide the person of ordinary skill in the art a reasonable expectation of

success in combining Lucentis and Fraser?

A. There is knowledge that Lucentis at the time that we were discussing had been used in humans. And, therefore, safety studies would have been conducted as well as stability studies.

Q. Thank you, Doctor.

I would like to now discuss your anticipation opinions with regard to the Dix '226 patent. Have you prepared some slides to assist in your presentation of anticipation to the Court?

A. Yes.

Q. Okay.

Mr. Gibson, next slide, please, Slide 60.

Dr. Rabinow, what have you included on this slide to assist in your anticipation analysis?

A. So as before, I list out the individual claim limitations of Claim 1 of the '865. And on the right side is displayed Dix '226, the cover page to page 2.

Q. This one is a little less wieldy because we're only talking about one reference, correct?

A. Yes.

Q. Shall we march through it?

A. Please do.

Q. All right.

If we could turn to Slide 61, please.

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How does Dix '226, DTX 13, disclose the initial limitations of Claim 1?

A. Dix discloses a formulation inhibiting vascular endothelial growth factor, VEGF, on page 4. And the -- it states that it is suitable for injection. He discloses a lyophilized formulation is reconstituted with sterile water suitable for injection; so that implies that there is a vial involved, which meets one of the claim limitations of Claim 1. And the POSA would understand as of the date of Dix that ophthalmic formulations as well as cancer formulations were being considered for VEGF medicaments.

Q. Would the person of ordinary skill in the art also understand from the disclosures of Dix that intravitreal administration is a possibility?

A. Yes, certainly, because that was being done already for other VEGF antagonists.

Q. If we could please move to Slide 62.

How does the Dix '226 patent relate to the VEGF antagonist limitations of Claim 1?

A. So Dix discloses a VEGF antagonist fusion protein in a Chinese hamster ovary, or CHO, cell, comprising a polynucleotide of amino acids 27 to 457 of sequence ID Number 4, wherein said fusion protein binds vascular endothelial growth factor.

So this directly discloses the claim limitation of

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essentially the essential wording of Claim 1 on the left-hand side of the screen, and it certainly discloses a vascular endothelial growth factor antagonist. And it confirms it on -- so that was -- I read that on DTX 13, page 13. And on page 6 it confirms this by stating that, again, VEGF antagonist is expressed in a CHO cell line. And it comprises, again, amino acids 27 to 457 of sequence ID Number 4 and is glycosylated at asparagine residues 62, 94, 149, 222, and 308. This is at DTX 13, page 6.

Q. If we could turn, please, to Slide 63.

Which Claim 1 elements have you highlighted from Dix '226, DTX 13, on this slide, Doctor?

A. These are formulation claim elements.

Q. And could you please describe the formulation elements that are disclosed in DTX 13 --

A. Yes.

Q. -- as they relate to Claim 1 of the '865 patent?

A. Right.

So it states at DTX 13, page 4, a polysorbate may be present. And this meets the organic cosolvent limitation using Regeneron's infringement contention definition.

It also -- on that same page of Dix, for a buffer he divulges -- discloses 1- to 10-millimolar phosphate buffer, 1- to 10-millimolar citrate buffer. And few lines down, he further discusses a 5-millimolar phosphate buffer and

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5-millimolar citrate buffer. And, furthermore, on DTX 13, page 7, he also discloses 10-millimolar phosphate.

And a stabilizing agent as a claim element of Claim 1 is disclosed by 20 percent by sucrose on page 7 of Dix. It's mentioned multiple times on pages 4 and 7, sucrose.

Q. If we could turn to Slide 64.

Dr. Rabinow, how does DTX 13, the Dix '226 patent, relate to the stability elements of Claim 1?

A. So DTX 13 at page 7 displays Table 1, which shows the percent VEGF Trap native conformation values of a 50 mg/mL protein formulation stored at 5 degrees at three months where the value is 98.8 percent, which exceeds the claim limitation of at least 98 percent VEGF in native conformation following storage at 5 degrees for two months as measured by size-exclusion chromatography.

Q. I just want to make sure that I'm clear. The Table 1 in DTX 13, page 7, that you display here, Doctor, indicates that the data is reflecting percent VEGF Trap native configuration.

Do you see that?

A. I do.

Q. Would a person of ordinary skill in the art have an understanding of whether there's a difference between native configuration and native conformation as reflected in Claim 1?

A. They're essentially equivalent.

Q. And does DTX 13, the Dix '226 patent, also disclose that the stability data reflected in Table 1 was measured by a particular analytical method?

A. It was size-exclusion chromatography.

Q. Turning to Slide 65, can you summarize your opinion regarding the Dix '226 reference as it relates to your anticipation analysis of Claim 1 of the '865 patent?

A. Yes. Dix '226 anticipates all of the claim limitations of Claim 1 of the '865 and therefore anticipates Claim 1.

Q. And your testimony, just so that it's clear, is that the Dix '226 patent discloses each and every limitation of Claim 1, correct?

A. That's correct.

Q. Now I'd like to move to your anticipation opinions with regard to the dependent claims.

If we could go to Slide 66, please.

Do you have opinions regarding the dependent claims as it relates to the Dix '226 patent --

A. Yes.

Q. -- DTX 13?

A. Yes. The Dix '226 anticipates Claims 4, 7, 9, 11, and 14 through 17.

Q. Let's go to Slide 67 and first look at Claim 2 of the '865 patent.

What have you highlighted on Slide 67 relating to the concentration limitations of Claim 2 of the '865 patent?

A. Dix --

THE COURT: One second, Doctor.

Yes, Counsel?

MR. TRASK: Your Honor, I object to the passage at the bottom of this slide. It's outside the scope of his expert reports. The 40 mg/mL prelyophilized solution is discussed nowhere in either of the doctor's reports.

THE COURT: Understood.

Counsel?

MR. HUNT: Your Honor, I'd need a minute to take a look through the report, but the Dix '226 patent is very clear from day one that there has been anticipation argument that Dix '226 patent, DTX 13, is prior art for all that it discloses. And there is and can be no argument that plaintiff has not been put on notice of this anticipation theory that the Dix '226 patent anticipates the claims of the '865 patent.

So, with that, Your Honor, if you'll permit me a moment, I'll take a look through the expert report.

THE COURT: Understood. Okay, Counsel.

MR. TRASK: If I may while he's looking.

So to be clear, the top box discloses a range of 10 to 50 mg/mL of fusion protein. That's disclosed in the doctor's report, and we don't object to that.

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There's several paragraphs in the report which I can point counsel to -- paragraph 124 of the opening report, paragraph 8 of the reply report -- where that passage is disclosed, the 10 to 50 range. We disagree that's a disclosure of 40, but it's disclosed and they can rely on it. The 40 mg/mL prelyophilized solution is nowhere in the report. Counsel is free to look, of course.

THE COURT: But that's from the Dix reference, correct?

MR. TRASK: It's in the Dix reference, but it was never discussed. And there are sections in the report purporting to state where Dix discloses 40 mg/mL. That passage is discussed nowhere in the report.

THE COURT: Understood.

At this point, objection will be overruled. Counsel of course will be free to probe that particular issue on cross and likewise address it in posttrial submissions.

But for now, objection overruled.

MR. HUNT: Thank you, Your Honor.

BY MR. HUNT:

Q. If we could go to Slide 68, please. How does DTX 13, the Dix '226 patent, disclose the polysorbate limitations of Claims 2, 4, and 5 of the '865 patent, Dr. Rabinow?

A. On page 4 it discloses polysorbate may be present. That addresses that claim element of Claim 2 where it

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discloses -- comprises polysorbate. The range in Dix is .05 to .15 percent polysorbate 20, which overlaps the claim limitation of .03 percent to .1 percent polysorbate 20 of Claim 4 as well as the limitation of Claim 5 of .1, .01, to 3 percent polysorbate 20.

So Dix discloses the presence of polysorbate 20 as well as its ranges, which address Claims 2, 4, and 5.

Q. If we could turn to Slide 69.

How does DTX 13, the Dix '226 patent, relate to the buffer limitation of dependent Claim 7?

A. The buffer limitation is 5- to 25-millimolar buffer. Dix discloses 1- to 10-millimolar phosphate buffer, 1- to 10-millimolar citrate; and a few lines down, 5-millimolar phosphate buffer, 5-millimolar citrate buffer on page 4 of DTX 13.

Q. And with respect to the added limitation of Claim 9 of the '865 patent, Dr. Rabinow, on the next slide, what is expressly disclosed in Dix '226, DTX 13?

A. On pages 4 and -- well, on page 4 it discloses pH 6.25, which lies in the interval of the Claim 9 limitation of pH about 6.2 to 6.3. And, furthermore, on page 7 of Dix it discloses pH of about 6 to 6.5, which similarly overlaps the range of 6.2 to 6.3, the claim limitation of Claim 9.

Q. If we could go to DDX 4, Slide 71, what does Dix '226, DTX 13, disclose regarding the additional stabilizing

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agent limitations of Claims 10 and 11?

A. On page 4 of Dix, it is stated that the formulation contains sucrose, which addresses the claim element of -- the stabilizing agent comprises a sugar of Claim 10.

Claim 11 goes beyond that and specifies that the sugar is selected from the group consisting of sucrose, et cetera. And sucrose is specifically disclosed on page 4. So that addresses claim -- the Claim 11 limitation as well.

Q. And, Dr. Rabinow, are these the same two passages of Dix that we looked at on the prior slide?

A. Yes.

Q. And I just -- I want to make the record clear. You referred to page -- DTX 13, page 4. And I think that that same page number was reflected here, but on the prior slide the second callout was referred to as DTX 13, page 7. Do you understand that the second callout on this page is also at DTX 13, page 7?

A. Yes.

Q. If we could please move to Slide 72.

Now, Dr. Rabinow, you may have mentioned this earlier in connection with the VEGF antagonist elements of Claim 1, but what does Dix '226, DTX 13, disclose regarding the glycosylation characteristics of Claim 14 of the '865 patent?

A. Dix discloses the fusion protein comprises amino acids 27 to 457 of sequence ID Number 4 and is glycosylated at

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asparagine residues at 62, 94, 149, 222, and 308. So it fully discloses the claim element of Claim 14.

Q. And that is at DTX 13, page 6, correct, Doctor?

A. That is correct.

Q. Finally, let's discuss the stability limitations in the dependent claims of the '865 patent. On DDX 4, Slide 73, what have you highlighted here from DTX 13, the Dix '226 patent?

A. Dix discloses in Example 1 on page 7 that turbidity was measured at OD405 and furthermore provides data at three months of a formulation stored at 5 degrees. And the turbidity value is zero, thus meeting the claim limitation of a turbidity of .01 or lower at OD405 after two months storage at 5 degrees.

Q. Now, turning to Slide 74, what does DTX 13, the Dix '226 patent, disclose regarding formulation stability over time?

A. In Table 9 on page 9 is listed the percent native configuration, equivalent as we said before to conformation, at two months' storage of 5 degrees, a value of 99.6 percent, thus meeting the claim limitation of at least 99 percent after two months at 5 degrees.

Q. And, Dr. Rabinow, does Dix tell us what analytical method is used to generate the data reflected in Table 9?

A. Yes. Size-exclusion chromatography.

Q. And Table 9 is at DTX 13, page 9, correct?

A. Yes.

Q. Turning to Slide 75, what does Dix '226, DTX 13, disclose regarding the further stability limitations of Claim 17?

A. Dix on page 7, Table 1, provides a value for percent VEGF Trap native configuration -- equivalent, as we said, to conformation -- at 24 months, 5 degrees storage, of 98.3 percent, which meets therefore the limitation of at least 98 percent of VEGF antagonist following storage at 5 degrees for 24 months as measured by size-exclusion chromatography. The same technique was used in Dix.

Q. Now, looking at Table 1 of the Dix '226 patent at DTX 13, page 7, there's a reference here to VEGF Trap.

Do you see that?

A. Yes.

Q. And would the person of ordinary skill in the art understand, or does the Dix '226 patent tell them, that VEGF Trap is in fact a VEGF antagonist fusion protein?

A. Yes.

Q. Dr. Rabinow, if we look at DDX 4, Slide 75, is it your opinion that Dix '226, DTX 13, discloses each and every limitation of the asserted claims of the '865 patent?

A. They are. It is.

Q. And, therefore, is it your opinion that the Dix '225 [sic] patent, DTX 13, anticipates the asserted claims of the

'865 patent?

A. That is correct. I agree with that.

Q. Dr. Rabinow, I'd like to now return to your obviousness analysis and specifically focus on the asserted dependent claims.

Could we please display Slide 77, Mr. Gibson.

Now, Dr. Rabinow, have you prepared a summary chart to assist you in comparing the prior art disclosures, and specifically your asserted combination of Lucentis and Fraser, and separately Fraser and Liu, to Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent?

A. Yes.

Q. Is it your opinion that Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent would have been obvious to one of ordinary skill in the art after consideration of Fraser in combination with Liu?

A. Yes.

Q. Is it also your opinion that Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent would have been obvious to one of ordinary skill in the art after consideration of the Lucentis disclosures in Shams and Gaudreault in combination with Fraser?

A. Yes.

Q. With that in mind, Doctor, I would like to proceed to discuss some of the disclosures in the prior art. And then

after that discussion, we can further revisit your obviousness combinations. Okay?

A. Fine.

Q. Turning to the next slide, Slide 78, how does Fraser, DTX 729, apply to the dependent claims of the '865 patent?

A. Fraser discloses 2-mL aliquots that were used to dose the monkeys in his study. And it is clear that, individually, solutions had to be withdrawn from 2 mL because, in certain cases, multiple vials were drawn. So that addresses the claim limitation of the vial of Claim 1 in Claim 2.

Furthermore, Fraser discloses VEGF Trap R1R2 as provided by Regeneron Pharmaceuticals, Inc., Tarrytown, New York, which addresses the claim element of Claim 2, said VEGF antagonist fusion protein.

40 mg/mL is the claim element. Fraser has 24.3 mg/mL, which, by routine experimentation in light of what the prior art was that is known by the POSA, could have been so optimized. Fraser also discloses a buffer -- I'm sorry. Let me back up.

The final claim element of Claim 2 is polysorbate, which is addressed in -- on page 2 of Fraser by the term "Tween 20." So that addresses fully Claim 2.

The disclosure of .1 percent weight-per-volume Tween 20 similarly addresses Claims 4 and Claims 5 because the .1 percent weight per volume clearly addresses Claim 4 as

well as Claim 5. It's in the interval denoted by the extremes of values. So that addresses Claims 4 and 5.

The claim element of 5- to 25-millimolar buffer of Claim 7 is disclosed by Fraser's use of the term "5-millimolar phosphate, 5-millimolar citrate." So that addresses Claim 7.

Claim 9 has a limitation of pH about 6.2 to 6.3. And Fraser discloses pH 6.0, which is about 6.2 to 6.3.

Claim 10 has a limitation of comprising a sugar, and the term "20 percent sucrose" is expressly disclosed in Fraser. So that addresses Claim 10 as well as Claim 11, which specifies the group consisting of sucrose, et cetera.

Finally, Claim 14, the claim limitation of said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residue 62, 94, 149, 222, and 308 of sequence ID Number 4 is addressed by the term that Fraser uses, "VEGF Trap R1R2 (Regeneron Pharmaceuticals)," which a POSA would know by that point referred unambiguously to a protein molecule fusion protein glycosylation pattern, amino acid sequence of that descriptor in the claim limitations of Claim 14.

Q. Thank you, Dr. Rabinow.

And if I may, especially when you're reading from a technical document, if you could please make a point to try and talk just a bit slower for the court reporter's benefit. I think everyone would appreciate it.

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A. I apologize.

Q. Thank you.

Now, I want to revisit your discussion of the 24.3 mg/mL concentration that's disclosed in the Fraser reference DTX 729, page 2, that we've been discussing.

How does the 24.3 mg/mL dose in Fraser compare to the 40 mg/mL limitation in Claim 2 in light of what is disclosed in Fraser?

A. Fraser discloses a 24.3 mg/mL formulation. He uses that to dose monkeys of various sizes, and he has various doses that are given to each monkey.

The smallest dose that was administered is .1 milliliters. That was administered to his animals.

.1 mL times 24.3 mg/mL would give a dose of 2.43 milligrams to the monkeys, which is the -- conservatively the lowest dose of the series. Okay?

The POSA would know as well, for intravitreal administration for humans, that values of .05 milliliters were administered from both bevacizumab as well as ranibizumab.

So 2.43 milligrams divided by .05 mL, or say -- just because we want to be generous here, .06 mL, because we're expecting some wastage, would give you a value of 40 mg/mL.

Q. And when you indicated a moment ago, Dr. Rabinow, that I believe the person of ordinary skill in the art would want to be generous, that's with regard to the injection

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volume; is that right?

A. That's correct.

Q. And why is it your testimony that the person of ordinary skill in the art might consider adding a small volume to the injection liquid?

A. There would be hang-up perhaps in the syringe.

Q. What do you mean by hang-up?

A. When you inject a volume from a syringe into the eye or anywhere else, there is residual that is left in the needle and the bore of the syringe.

Q. So looking at the disclosures of DTX 729, the Fraser reference, it's your opinion that the 24.3 mg/mL dose that is described there could actually, if used for intravitreal administration in humans, end up somewhere between 40 and 50 mg/mL?

A. Correct.

Q. Now, Dr. Rabinow, I'd like to next briefly revisit the Dix '226 patent. If we go to Slide 79.

Is it your opinion that Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent would also have been obvious to one of ordinary skill in the art after consideration of the Dix '226 patent, either alone or in combination with Liu -- I'm sorry. I apologize. Strike that. Strike that on this paper here, Your Honor. Many apologies. Let me start over.

Dr. Rabinow, next I'd like to briefly revisit the

Dix '226 patent, DTX 13. Is it your opinion that Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent would have been obvious to one of ordinary skill in the art after consideration of the disclosures of the Dix '226 patent alone in view of the knowledge of the person of ordinary skill in the art?

A. Yes.

Q. Is it for the same reasons that we discussed a few minutes ago with respect to the anticipation analysis of DTX 13, the Dix '226 patent?

A. Yes.

Q. I'd like to briefly walk through these again. If we could turn to the next slide, Slide 80.

I believe you've testified already that DTX 13, pages 4 and pages 5, explicitly or inherently disclose certain limitations of Claims 2, 4, 5, 7, 9, 10, and 11. Is that right?

A. Yes.

Q. And those relevant disclosures are at DTX 13, page 4, and DTX 13, page 5; is that correct?

A. Yes.

Q. Turning to the next slide.

THE COURT: Yes, Counsel.

MR. TRASK: Your Honor, I just wanted to note for the record Regeneron, of course, is advancing the position that the Dix '226 patent is not properly prior art under the 103(c) safe

harbor. Just for purposes of preservation, I wanted to note that we're maintaining that objection during this part of the testimony.

THE COURT: No. Understood.

You may proceed, Counsel.

MR. HUNT: Thank you, Your Honor.

BY MR. HUNT:

Q. Now, could we please pull up Slide 85.

Dr. Rabinow, could you please briefly summarize your opinion regarding the stabilizing agent limitations of Claims 10 and 11 of the Dix '226 patent, DTX 13.

A. Dixon on page 7 calls out sucrose. That's disclosed, and that meets the claim limitation of a sugar in Claim 10, and also in Claim 11 the limitation, the group consisting of sucrose, et al. So that addresses the claim limitations of 10 and 11.

Q. If we could turn to Slide 86.

I believe it's your testimony, Doctor, that the Dix '226 patent discloses the VEGF antagonist fusion protein element of Claim 14.

Could you confirm your opinion as to where that is disclosed in the Dix '226 patent, DTX 13?

A. That is disclosed on page 6.

Q. If we could next turn to Slide 86.

To briefly recap, what does Dix 226, DTX 13, disclose

regarding the stability elements of Claims 16 and 17?

A. On page 9 Dix discloses the percent native configuration at two months and by size-exclusion chromatography. That value is 99.6 percent, which meets the Claim 16 claim limitation of at least 99 percent is present in native conformation after two months at 5 degrees as measured by size-exclusion chromatography.

Dix also indicates that after 24 months at 5 degrees, there is a value of 99.3 percent native configuration. And that meets the Claim 17 limitation of at least 98 percent of said VEGF antagonist fusion protein is present in native conformation following storage at 5 degrees for 24 months as measured by size-exclusion chromatography.

Q. And if we could -- I think we need to revisit Claim 15, which oddly is on the next slide. So if we go to the next slide.

Could you please briefly describe the disclosures of Dix '226, DTX 13, with regard to the turbidity limitations of Claim 15.

A. Dixon page 7 discloses a value of zero for the three-month, 5-degree OD405 turbidity measurement, which meets the Claim 15 claim limitation of a turbidity of .01 or lower at OD405 after two months storage at 5 degrees.

Q. And if we could turn quickly to Slide 90, just to confirm -- and, again, this is only with respect to the

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Dix '226 patent -- what is your opinion as to whether the Dix '226 patent discloses all of the elements of the dependent claims of the '865 patent?

A. The dependent claims are all disclosed by Dix and, therefore, are obvious.

Q. All right. Now, I'd like to turn to your opinions regarding the prior art disclosures of Lucentis.

Which two references do you rely on, Dr. Rabinow, for prior art disclosures relevant to Lucentis?

A. Shams and Gaudreault.

Q. Turning to Slide 92, please, can you explain what disclosure from Shams is shown on this slide?

A. Shams discloses a vial, which is a claim limitation of Claim 2, and --

Q. That is at DTX-- sorry. Go ahead.

A. That is at DTX 726 at page 32.

He discloses a ranibizumab, which is a known VEGF antagonist fusion protein. And he discloses polysorbate 20 as well. And while the concentration of ranibizumab is 10 mg/mL, Gaudreault discloses 40 mg/mL. So that addresses all of the claim elements of Claim 2.

Q. All right. And I want to go to Slide 93 quickly.

And this -- Dr. Rabinow, you testified a moment ago that the Gaudreault reference assisted with the 40 mg/mL concentration; is that correct?

A. That's correct.

Q. And this relevant disclosure, in your view, is at DTX 2265, page 2; is that right?

A. Correct.

Q. All right. And if we could turn to Slide 94, please.

This is the polysorbate limitation you discussed a moment ago, right?

A. Yes.

Q. And that's at DTX 726, page 32?

A. Correct.

Q. Now, turning to Slide 95, does the Lucentis prior art disclose anything about buffer amounts in the formulation?

A. Yes. Shams, on page 32, discloses a histidine buffer, 10 millimolar. So that meets the claim limitation of 5- to 25-millimolar buffer of Claim 7.

Q. And turning to Slide 96, Doctor, can you explain what the person of ordinary skill in the art would know regarding Lucentis and the stabilizing agent element of Claims 10 and 11?

A. Right. Shams discloses on page 32 trehalose, which is a sugar. So that meets the claim limitation of Claim 10 as well as Claim 11, which specifies that such sugar is selected from the group consisting of, among other things, trehalose.

Q. And now, Dr. Rabinow, I'd like to ask you about the stability elements of Claims 15, 16, and 17.

Is it your opinion that the person of ordinary skill

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in the art as of June 16, 2006, would have understood the formulation disclosed in Shams or Gaudreault was stable?

A. Yes.

Q. Finally, turning to the next slide, Slide 97, Dr. Rabinow, please summarize your opinion with respect to the Lucentis prior art disclosures and the asserted claims of the '865 patent.

A. All of the asserted dependent claims are obvious.

Q. Now, I'd like to turn next to your opinions regarding the disclosures of Liu, Dr. Rabinow.

Could I please have Slide 99 on the screen, Mr. Gibson.

Dr. Rabinow, what do you show on Slide 99 with regard to the disclosure of Liu, DTX 730?

A. Liu discloses on page 9 an antibody with a specified concentration -- a disclosed concentration range of 40 to 150 mg/mL, which meets the claim limitation of 2, VEGF antagonist fusion protein is 40 mg/mL.

THE COURT: Yes, counsel.

MR. TRASK: Your Honor, I'd just like to restate our objection and renew our objection that Your Honor sustained several moments ago.

Here, of course, we have the application of Liu to Claim 2, which expressly refers to the vial of Claim 1. And we saw earlier in Claim 1 that Lucentis was being applied for a

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particular limitation to check the box. So in Regeneron's view, this is an improper combination, not disclosed in the doctor's report.

THE COURT: Understood.

Any response to that, Counsel?

MR. HUNT: I believe, Your Honor, again, we're walking through the disclosures of the prior art. Dr. Rabinow has offered opinions as to why Claim 1 of the '865 patent is invalid as obvious over the combination of Fraser and Liu and, separately, Fraser and Lucentis.

The disclosure that Dr. Rabinow is discussing now, I believe Your Honor will find out in a few minutes when he summarizes his obviousness combinations, that the disclosure of Liu for Claim 2 is intended solely for discussion of the combination of Fraser and Liu. It will not be combined with Lucentis.

THE COURT: Understood.

Same ruling applies. And I'll reiterate the Court will not accept any invitation to tie the two together for the reasons already articulated. But objection sustained, for lack of a better term, I guess.

But you may proceed, Counsel.

MR. HUNT: Thank you, Your Honor.

BY MR. HUNT:

Q. Now, if we could turn next to Slide 100.

Dr. Rabinow, what from DTX 730, the Liu reference, is relevant to the elements of Claims 2, 4, and 5 concerning polysorbate 20?

A. Polysorbate is disclosed on DTX 730, page 9. That meets the claim limitation comprises polysorbate of Claim 2. The polysorbate range of .01 percent to .1 percent is disclosed also on page 9 of Liu, and that meets the claim limitation of Claim 4 of .03 to about .1 percent polysorbate 20.

And the same range disclosed by Liu of polysorbate .01 percent to .1 percent also meets the claim limitation of Claim 5 of .01 percent to 3 percent polysorbate 20.

Q. And on the next slide, 101, Dr. Rabinow, what does DTX 730, the Liu reference, disclose concerning formulation buffer concentration?

A. Liu on page 9 discloses a 10- to 100-millimolar histidine buffer, which meet claim limitation range of 5- to 25-millimolar buffer of Claim 7.

Q. And on Slide 102, Dr. Rabinow, what would the person of ordinary skill in the art know from the disclosure of DTX 730, the Liu reference, as it relates to the stabilizing agent elements of Claims 10 and 11?

A. Page 9 specifies a sugar, for example, trehalose or sucrose. And that expressly meets the claim limitation of Claim 10, sugar, as well as Claim 11, the group consisting of

sucrose, sorbitol, glycerol, trehalose of Claim 11.

Q. And finally, on Slide 103, Dr. Rabinow, what does DTX 730, the Liu reference, contain that is relevant to the stability elements of Claims 15 through 17 of the '865 patent?

A. On page 9 Liu lists the stability of a formulation, an 80 mg/mL formulation, comprising histidine and trehalose, listing out, first of all, turbidity values and using Dr. Trout's proposed deduction of what the -- the change in the value of turbidity is, subtracting the initial value from the subsequent values at different time points.

So here we would be subtracting turbidity values at time zero, storage at 5 degrees, the turbidity value of 0.20; and that subtracted from the three-month value would leave a value of zero turbidity, which would meet the claim limitation of turbidity of .01 or lower at OD405 after two months' storage at 5 degrees for Claim 15.

Q. And is it also your opinion, Dr. Rabinow, that DTX 730 of the Liu reference discloses the stability elements of Claims 16 and 17?

A. Yes.

Q. And where is that disclosure found?

A. That is also on DTX 730, page 35, of Liu in the table showing stability data for the 80 mg/mL antibody formulation. And he indicates a value of 96.8 percent size-exclusion chromatography percent monomer, which therefore would meet

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the -- I'm sorry.

He -- okay. He shows a value of 99.1 percent size-exclusion chromatography percent monomer at six months and 99.0 percent after 14 months, which meets the claim limitation of at least 99 percent of said VEGF antagonist fusion protein is present in native conformation after two months storage at 5 degrees as measured by size-exclusion chromatography.

Q. And, Dr. Rabinow, just so that I'm sure the record is clear, it's your opinion that the after two-month storage at 5 degrees C limitation in Claim 16 of the '865 patent refers to any time point after two months, correct?

A. Correct. Furthermore, a value is provided of SEC data at 24 months' storage at 5 degrees, and that value is 98.8 percent. That meets the claim limitation of at least 98 percent of said VEGF antagonist fusion protein present in native conformation following storage at 5 degrees for 24 months as measured by size-exclusion chromatography for Claim 17.

Q. If we could turn to Slide 106, please.

Dr. Rabinow, is it your opinion that the dependent claims of the '865 patent are obvious in view of the combination of Fraser and Lucentis as understood in connection with the knowledge of the person of ordinary skill in the art?

A. Yes.

Q. And, separately, is it your opinion that the prior

art disclosures of Fraser in combination with Liu render the dependent claims of the '865 patent obvious?

A. Yes.

Q. If we could turn to Slide 107, please.

Would the person of ordinary skill in the art have been motivated to combine Fraser and Liu, or separately Fraser and Lucentis, to make an ophthalmic formulation suitable for intravitreal administration?

A. Yes. Saishin -- we covered this before, but Saishin at DTX 2751 at page 1 states -- discloses, "VEGF Trap R1R2 strongly suppressed choroidal neovascularization" and further down that page, "may provide a new agent for consideration for treatment of patients with choroidal neovascularization and diabetic macular edema."

Q. And so it's your testimony, Doctor, that the person of ordinary skill in the art would be motivated to combine Fraser and Liu on the basis of the disclosure of the Saishin reference, DTX 2751?

A. That is correct. And, furthermore, would have a reasonable expectation of success in doing so.

Q. And, separately, it's your opinion that the person of ordinary skill in the art would have been motivated to combine Fraser and Lucentis to make an ophthalmic formulation suitable for intravitreal administration on the basis of the disclosures of Saishin?

A. That is correct, for the same reasons.

Q. And just in case I didn't cover it before, did you rely on Saishin, DTX 2751, in support of your opinions?

A. Yes.

Q. If we can go to the next slide, please.

What specifically in Saishin is it, your opinion, provides the person of ordinary skill in the art with a motivation to combine Fraser and Liu or, separately, Fraser and Lucentis?

A. Saishin at DTX 2751, page 7, discloses, "VEGF Trap R1R2 deserves consideration as a potential treatment for two complications of diabetic retinopathy, retinal neovascularization and macular edema. A single intravitreous injection of VEGF Trap R1R2 markedly suppressed the development of choroidal neovascularization over the course two of weeks. Concurrently, additional preclinical studies should explore modes of local delivery to the eye that can be used adjunctively or as an alternative to systemic administration."

Q. And so just to summarize, Dr. Rabinow, what is your opinion with regard to the combination of the -- strike that. Let me start over.

Dr. Rabinow, what is your opinion with regard to the combination of the disclosures of Fraser and Liu with respect to the obviousness of the dependent claims of the '865 patent?

A. The dependent claims would be obvious.

Q. And, again, just to confirm separately, what is your opinion as to the disclosures of Fraser combined with Lucentis as it relates to the dependent claims of the '865 patent?

A. The dependent claims would be obvious.

Q. Thank you.

MR. HUNT: Your Honor, I have just a little bit left. This is a breaking point. I thought I'd give you the option. I can continue for -- I don't know -- maybe 15 minutes or --

THE COURT: Why don't we go ahead and take a break at this point if it's going to be that long before you transition or wrap on direct. So we'll go ahead and take our lunch break at this point.

Doctor, I've got good news for you. You get to have a quiet, secluded lunch.

THE WITNESS: Thank you, Your Honor.

THE COURT: And consistent with this Court's prior orders, they're ordered to feed you, but they can't talk to you. But during the lunch break, you're on your own, of course, because you're midstream. Nobody can converse with you about your testimony so far or the remainder of it.

But you can step down, sir. You can leave all your materials there. Have a great lunch.

Why do not we take 30 for lunch. Let's resume at 1:00 and pick up with the doctor's direct examination at that point. Thank you all very much.

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(A recess was taken from 12:33 p.m. to 1:15 p.m.)

THE COURT: Counsel, are you ready to resume?

MR. HUNT: I am, Your Honor.

THE COURT: The floor is yours.

MR. HUNT: Thank you, Your Honor.

BY MR. HUNT:

Q. Dr. Rabinow, if you'll bear with me for a few minutes. As tends to happen when you give a lawyer time to think, I need to circle back on a few things. Okay?

If I could please bring up Slide 61.

Now, Dr. Rabinow, you testified earlier today regarding certain disclosures of the Dix '226 patent, correct?

A. Yes.

Q. And on the bottom of your Slide 61 is reflected DTX 13, page 5. And I believe it was your testimony that page 5 of DTX 13 discloses that the formulations are suitable for injection; is that right?

A. Yes.

Q. Is it your opinion that the Dix '226 patent inherently discloses the intravitreal administration -- I'm sorry -- the ophthalmic formulation suitable for intravitreal administration element of Claim 1?

A. Yes.

Q. If we could turn now to Slide 80, please.

And, again, I want to be clear. First, Dr. Rabinow, I'm asking only about the disclosure of DTX 13 on page 4 at the top of the slide. And I just wanted to make sure that the record is clear.

What does DTX 13, page 4, disclose regarding the concentration of the fusion protein described there?

A. From Dix?

Q. That's correct. Dix '226, DTX 13, page 4. What is the concentration disclosed on page 4 of the fusion protein?

A. 25 mg/mL.

Q. I'm sorry, sir. I'm asking you about the yellow highlight on DTX --

A. Oh, I'm sorry.

10 to 50 mg/mL.

Q. Okay. So the Dix '226 patent, DTX 13 at page 4, discloses a range of 10 to 50 mg/mL of the fusion protein; is that right?

A. Yes, that is correct.

Q. Thank you.

Now, Dr. Rabinow, do you recall earlier today we discussed the Andya reference, DTX 3492?

A. Yes.

Q. And you also testified that it's your opinion that the person of ordinary skill in the art has a reasonable expectation of success in combining Fraser and Liu; is that

right?

A. Yes.

Q. What, if anything, about DTX 3492, the Andya reference, would give the person of ordinary skill in the art a reasonable expectation of success in combining the disclosures of Fraser and Liu?

A. If I -- all right. So there were two Andya references. One dealt with a road map for formulating proteins; another one dealt with stability, I believe, of a high-concentration protein. Which Andya reference are you referring to?

Q. Yes. Doctor, I'm sorry that I was not clear. I'm deferring to DTX 3492 which is Andya 1.

A. Okay. So I believe that that refers to the road map for how you would formulate; is that right?

MR. HUNT: Mr. Gibson, could we please get Slide 13 up on the screen.

BY MR. HUNT:

Q. Is this DTX 3492 the Andya 1 reference?

A. Yes. I'm sorry. Yes, correct, it is.

Q. And so just to quickly revisit my question, what, if anything, about DTX 3492 would provide the person of ordinary skill in the art a reasonable expectation of success in combining the disclosures of Fraser and Liu?

A. There is an indication here that one can achieve

long-term stability for 12 months at 5 degrees in terms of there being no change in the percent intact protein for antibody formulations that contain -- that are formulated with trehalose and Tween 20.

Q. And is it likewise your opinion that the disclosures of DTX 3492, the Andya reference, would provide the person of ordinary skill in the art a reasonable expectation of success in combining the disclosures of the Lucentis references and Fraser?

A. Yes.

Q. Is it for the same reason as the other combination, Fraser and Liu?

A. Yes.

Q. All right.

If we could now go to -- apologies -- Slide 111, Mr. Gibson.

Dr. Rabinow, I would like to discuss certain objective evidence of nonobviousness. Do you understand that Dr. Trout has offered certain opinions in this case that there exists objective evidence of nonobviousness of the asserted claims of the '865 patent?

A. Yes.

Q. And have you formed an opinion in response to Dr. Trout?

A. Yes.

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Q. And generally speaking, what is that opinion?

A. That it's a red herring, that it was already known at the time that Dr. Ferrara published this document that there was successful use of bevacizumab intravitreally so it would obviate any theoretical issue concerning the ability or nonability of large molecules like VEGF Trap to penetrate the retina.

Q. Okay. Let's go to Slide 112. And we're looking at PTX 701. Is that the Ferrara reference you were speaking of a moment ago?

A. Yes.

Q. And do you understand Dr. Trout to rely on the Ferrara reference, PTX 701, in support of his opinion on purported industry skepticism?

A. Yes.

Q. Do you agree with Dr. Trout's opinion that there would be skepticism in the industry?

A. No.

Q. Why not?

A. For a number of reasons.

Well, for one thing, Dr. Ferrara was employed by Genentech. So as an employee of Genentech, one would naturally expect that his opinions might be tainted in favor of supporting the competitive advantage of the molecules advanced by Genentech versus those of Regeneron.

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Q. Let's take a quick look at PTX 701 on the next slide. Is this the portion of PTX 701 that Dr. Trout relies upon?

A. Yes.

Q. And, Dr. Rabinow, were you present for Dr. Trout's testimony earlier this week?

A. I was.

Q. Do you recall Dr. Trout's testimony wherein he compared the size of aflibercept, ranibizumab, and aspirin?

A. Yes.

Q. Do you agree with Dr. Trout and Ferrara 2006 that VEGF Trap R1R2 would have been too large to penetrate the retina?

A. No.

Q. Why not?

A. Because it had already been demonstrated prior to that in 2005 that bevacizumab, which was an even larger antibody at, I believe, 149 kilodaltons compared to the 113 kilodaltons for VEGF Trap R1R2, that bevacizumab had been employed successfully in mid-2005 intravitreal injections and had demonstrated a remarkable improvement ophthalmologically of patients who were afflicted with overzealous vascular endothelial growth factor.

Q. Now, in your opinion, would the person of ordinary skill in the art be discouraged from developing a stable

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protein formulation comprising VEGF Trap R1R2 based on its size?

A. Hardly. In fact, he would be incentivized to do so.

Q. Let's take a look a little bit closer at the Ferrara paper on the screen.

In the -- on page 4 how would the industry have viewed the Ferrara 2006 review paper and specifically the disclosure that you've called out here?

A. They would have looked at the data. They would have compared the data with the dosing pattern for the two branches of the animals, which, in this case, involved a systemic administration as well as an intravitreal administration.

And it appears that there were five separate systemic administrations of VEGF Trap and there was one intravitreal administration. The five systemic inoculations inhibited neovascularization by 75 percent, which is large -- a large effect.

The one intravitreal administration of the same agent resulted in a 25 percent inhibition, which, on the surface, is, in absolute terms, a smaller number than a 75 percent inhibition, but that must be taken into consideration with the number of doses that were administered. So one might argue that, on a relative basis, the intravitreal administration demonstrated higher efficacy than the systemic.

Q. Thank you, Dr. Rabinow. I want to break that down

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just a little bit.

Looking at PTX 701, page 4, the 25 percent limit -- inhibition mention that you have covered, is there a citation after that?

A. Yes.

Q. And I apologize.

A. I'm sorry. Yes. A citation to Footnote 80 to Saishin.

Q. And just after that Footnote 80 -- we'll get to that in just a minute -- the Ferrara reference suggests that there's limited efficacy. Do you see that?

A. Yes.

Q. Do you agree that the -- that there was limited efficacy of VEGF Trap R1R2 at this time frame?

A. No.

Q. So let's go to Slide 114 and take a closer look at the Saishin reference.

Apologize. If we could go ahead one more.

So have you prepared a demonstrative, Dr. Rabinow, to help compare the disclosure of Saishin with the disclosure of Ferrara?

A. I have.

Q. And on the slide, do we have the disclosure of Ferrara, PTX 701 at page 4, with the language called out to the right of it?

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A. Right.

Q. Okay. And now you've added DTX 2751 at page 4. Is that the Saishin reference?

A. It is.

Q. Taking a closer look at Saishin, what is disclosed here at DTX 2751, page 4?

A. There is a plot of the choroidal neovascularization area that was measured following administration of five doses -- of subcutaneous doses of VEGF Trap R1R2 in comparison with a FC control. And there is a 75 percent reduction in the -- in the area of -- from the subcutaneous administration following five subcutaneous doses.

Q. Where do you find your support for there being five subcutaneous doses?

A. Well, it states in the yellow there "Prior to laser" -- a laser was used to cause rupture of Bruch's membrane, which is an anatomical feature of the eye.

"Prior to laser and on days" -- so that's prior; so that's day zero. And on days two, five, eight, and eleven. So that's a total of five dose administrations.

Q. And that's set forth on DTX 2751, page 4, correct?

A. Yes.

Q. Okay.

If we could advance the slides to 116, please. Oh, apologies. You can stay right there.

Now, on the right-hand side you have included DTX 2751, the Saishin reference on page 5. What is shown here?

A. So what is shown here is the result of the reduction of choroidal neovascularization in comparison with an FC control from a single intravitreous injection of VEGF Trap R1R2. There is something like a 25 percent reduction. And the statistical significance is at the same level of confidence, .0001, as that of the subcutaneous doses.

Q. So looking at DTX 2751, page 5, how many doses of intravenous VEGF Trap R1R2 were administered?

A. One.

Q. And how do you interpret the results of the graph at DTX 2751, page 5?

A. It was pretty darn effective because a single intravitreous dose suppressed choroidal neovascularization.

Q. I apologize.

I apparently may have said "intravenous" instead of "intravitreous," sir. So if you'll permit me, I'd like to restate my question.

DTX 2751, page 5, what is disclosed on that page regarding the single intravitreous injection of VEGF Trap R1R2 and its related response?

A. There was a statistically significant decrease in choroidal neovascularization of perhaps 25 percent, and that was at a very high degree of statistical confidence of P value

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less than .0001, which means it was as statistically significant as the figure shown for subcutaneous administration on page 4.

Q. And if we could go to the next slide.

Have you prepared a demonstrative to show what Saishin actually disclosed?

A. Yes.

Q. If the dose frequency from Saishin, DTX 2751, pages 4 through 5, is properly reflected in Ferrara, what would the person of skill in the art understand about the number of doses of intravitreal injection?

A. That the single intravitreous injection was able to exert a, relatively speaking, much larger effect than the subcutaneous dosing because only a single intravitreous injection resulted in a 25 percent decrease, whereas it took five subcutaneous injections to achieve a 75 percent reduction.

Q. Now, Dr. Rabinow, do you agree with Dr. Trout's opinion regarding skepticism?

A. No.

Q. If we could turn to Slide 119, please.

Dr. Rabinow, do you understand that Dr. Trout has argued that the person of skill in the art would find unexpected safety and efficacy through the use of Eylea?

A. No.

Q. And why do you disagree?

A. Eylea was intentionally designed to be a superior molecule from both a safety perspective largely because its affinity for VEGF was so great. So it had -- Eylea had a 20-fold greater affinity for VEGF than did ranibizumab.

What that means is that it binds it so tightly that it prevents attachment of Eylea to the extracellular matrix around the eye; that is to say, it would result in less toxicity.

This is pointed out by Holash as early as -- I'm not sure -- 2003, I think, where he says that the development of Eylea was designed to have very high affinity so that two things were achieved. Not only did it bind extraordinarily tightly to the target VEGF, but it prevented off-target binding to anatomy -- anatomical parts of the eye that it was not intended to bind to.

And as a result of that, it would not mediate toxicity to the same level as ranibizumab. So that's the affinity/toxicity analysis.

Additionally to that, Eylea was designed intentionally to be large. It was a full antibody. It was glycosylated at five positions and at a very large molecular weight. And as a result, its pharmacokinetics were prolonged. And this is shown as early as 2000 in Papadopoulos, where he showed the PK, pharmacokinetic, curves after administration of Eylea to animals.

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Q. Now, Dr. Rabinow, do the '865 patent asserted claims require that the claimed protein formulation demonstrate safety or efficacy?

A. No.

Q. Now I want to turn to Slide 119 that's on the screen. And you understand that Dr. Trout relies on the Thomas reference, PTX-1155 --

A. Yes.

Q. -- in support of his opinion that the efficacy unexpected?

A. Correct.

Q. And you disagree with this, correct?

A. Yes.

Q. Please describe your disagreement with the Thomas reference, PTX 1155.

A. Well, I see that Dr. Trout states that this unexpected safety and efficacy holds both in comparison to the closest prior art relating to Lucentis and in a comparison to any of the other prior art, whereas, in point of fact, there was enormous discussion and strategizing on the part of Regeneron to intentionally design their molecule with prolonged pharmacokinetics precisely because they could decrease the frequency of intravitreal injection, would -- which would be a tremendous improvement over the monthly administration requirements of Lucentis to give a q2 months, or every two

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months, injection. It would be a phenomenal competitive advantage.

Q. I want to focus on the formulation components. Okay?

So if we could turn to Slide 120.

If we compare the formulation components between Lucentis and Eylea, what, if any, conclusion would the person of ordinary skill in the art draw regarding the contribution of formulation components to safety and efficacy?

A. He would look and -- he/she would look and observe that these were all known in the prior art. There was nothing special so that there would be no substantial impact to safety or efficacy.

Q. And if we could turn to Slide 123.

Dr. Rabinow, do you disagree with Dr. Trout's opinion regarding copying?

A. Yes.

Q. Why?

A. The formulation components for Eylea are displayed in the far right column in the lower table compared to Yesafili in the middle column. And you see that the buffer differs. There's histidine used for Yesafili versus sodium phosphate for Eylea. The surfactant, polysorbate 20, is the same. The stabilizer is different. There's trehalose used for Yesafili versus sucrose for Eylea. And Eylea in addition contains sodium chloride, which is lacking in Yesafili.

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Furthermore, as we've considered the state of the art of half a dozen antibody proteins, fusion and otherwise, polysorbates were essential to include in the formulations to anticipate the common failure mode of denaturation and adsorption which occurs for all proteins. Everybody was putting polysorbate 20 or 80, preferably polysorbate 20, into their protein formulations.

Q. Dr. Rabinow, do you agree with any of Dr. Trout's supposed evidence of nonobviousness?

A. No.

Q. I'd like to now turn briefly to the next slide, 125, and discuss the '572 patent and the limited claim term of formulated as an isotonic solution in Claim 6.

A. Fine.

Q. Now, Dr. Rabinow, did you review the term "isotonic solution" as it appears in Claim 6 of the '572 patent and compare it to the disclosures of the prior art to determine whether the person of ordinary skill in the art of the '572 patent would have considered these claim elements known and/or obvious as of January 13, 2011?

A. I did.

Q. If we could turn to Slide 126.

Dr. Rabinow, did you review the Hecht reference?

A. Yes.

Q. And that's DTX 3588, correct?

A. Yes.

Q. And you relied on the Hecht reference in connection with your opinions?

A. Yes.

Q. And when was the Hecht reference published?

A. 1995.

Q. And we see that at DTX 3588 on page 3, correct?

A. Yes.

Q. Now, if we turn to Slide 127, what is the title of Chapter 89 in DTX 3588?

A. "Ophthalmic Preparations."

Q. And do you consider an intravitreal injection to be an ophthalmic preparation, Doctor?

A. Yes.

Q. If we could turn to the next slide, Slide 128.

What does Hecht teach the person of ordinary skill in the art regarding formulations of ophthalmic solutions?

A. On page 11 Hecht states that ophthalmic solutions are formulated to be sterile, isotonic, and buffered for stability and comfort. On page 13 he further discloses, given a choice, isotonicity always is desirable and particularly is important in intraocular solutions.

Further, on page 11 under "General Considerations," it is disclosed a number of requirements must be considered in the preparation of ophthalmic solutions. These include, among

other things, tonicity.

Q. Apologies, Doctor. Please continue.

A. And he states what he means by tonicity in the box at the bottom on page 13.

Q. So we've discussed a number of disclosures in Hecht. And I just want to make sure that the record is clear. That's DTX 3588 at page 11 and 13, correct?

A. Yes.

Q. If we could turn to Slide 129, please.

Dr. Rabinow, what reference is depicted here?

A. This is a 2009 reference by Dixon, "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration."

Q. And this is DTX 204, correct?

A. Yes.

Q. And you relied on DTX --

A. Yes.

Q. -- in forming your opinions?

A. Yes.

Q. If we could look at the first page of DTX 204, when was this reference published?

A. 2009.

Q. If we could turn to Slide 130, please.

What does Dixon teach the person of ordinary skill in the art regarding intravitreal injections containing aflibercept?

A. On page 3 it is disclosed VEGF Trap-Eye, which is aflibercept, is also formulated with different buffers and at different concentrations for buffers in common suitable for the comfortable, nonirritating direct injection into the eye.

Q. What would the person of ordinary skill in the art understand in or around January 13, 2011, reading the disclosure of Dixon, suitable for the comfortable, nonirritating direct injection into the eye?

A. He would understand, among other things, that it should be isotonic.

Q. Now, Dr. Rabinow, if a formulation is not isotonic, would it cause irritation in the patient when injected into the eye?

A. It could.

Q. And based on this, is it your opinion that the person of ordinary skill in the art as of January 13, 2011, would know that the formulation used in Dixon was isotonic?

A. Yes.

Q. In fact, isn't it your opinion that the person of ordinary skill in the art would expect that the aflibercept formulation used in Dixon was isotonic?

A. Yes.

Q. And would the person of ordinary skill in the art have been motivated to formulate aflibercept as an isotonic solution so that it would be nonirritating when administered to

a patient's eye?

A. Yes.

Q. And, finally, would the person of ordinary skill in the art have had a reasonable expectation of success in formulating aflibercept as an isotonic solution so that it would be nonirritating when administered to a patient's eye?

A. Yes.

Q. Now, I briefly want to touch on your deposition. Do you recall at your deposition that counsel for plaintiff asked you some questions about isotonicity?

A. Very well.

Q. Okay. And did we see that during the opening statement? Were you present for that, the opening statements here in this court?

A. Oh, yes. Yes, indeed.

Q. Did we see some of your testimony regarding isotonic solution during the opening statement?

A. I believe we did.

Q. Do you recall that questioning?

A. Yes, I did.

Q. From your deposition?

A. Oh, yes.

Q. And in what context were the questions being asked in connection with the testimony that plaintiff's counsel displayed during the opening statement?

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A. I was shown a document displaying a very high hypertonic solution which was purported to be a -- for intravitreal use. And I was asked did I believe that that would have been acceptable or not.

Q. And do you consider that testimony to have been taken out of context?

A. Yes.

MR. HUNT: Your Honor, at this time I pass the witness.

THE COURT: Thank you, Counsel.

MR. TRASK: Thank you, Your Honor. May I have a moment?

THE COURT: You may. Permission granted to approach to distribute any materials.

MR. TRASK: Thank you, Your Honor.

THE COURT: Whenever you're ready, Counsel, you may proceed.

MR. TRASK: Thank you, very much, Your Honor. Andrew Trask on behalf of Regeneron.

CROSS-EXAMINATION

BY MR. TRASK:

Q. Good afternoon, Doctor. Good to see you again.

A. Good afternoon. You too, sir.

Q. Doctor, you rely on the formulation disclosed in the Fraser reference for obviousness, correct?

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A. Yes.
Q. You didn't testify that Fraser anticipates the '865 patent, did you?
A. No.
Q. The study reported in Fraser involved monkeys, not humans, correct?
A. Yes.
Q. And the researchers in Fraser were studying the effects on female monkeys' ovaries, right?
A. Yes.
Q. They weren't studying the monkeys' eyes at all, right, Doctor?
A. Correct.
Q. Fraser didn't involve any ophthalmic disorder at all, did it?
A. Correct.
Q. The only method of administration disclosed by Fraser is intravenous injection, right?
A. Yes.
Q. Intravenous injection is a totally different method of administration compared to intravitreal injection, right?
A. Yes.
Q. Intravitreal injection involves injection into the eye, not the vein. You agree with that?
A. Yes.

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Q. Fraser says not one word about injecting its formulation into the eye, correct?

A. Yes.

Q. Fraser also says nothing about the particular amino acid sequence of the molecule that was injected into the monkeys in that study, correct?

A. There's an inherent disclosure.

Q. The amino acid sequence is not recited in Fraser, correct, Doctor?

A. He mentions VEGF Trap R1R2.

Q. That's not a disclosure of the amino acid sequence as stated in Fraser, correct?

A. A POSA would understand what the amino acid sequence was by the term VEGF Trap R1R2.

Q. And that's based on information outside of Fraser, correct?

A. That's based upon common knowledge that a person of ordinary skill in the art would know by virtue of working in this very restricted field with very few participants, and it would be expected that he would be mindful of all of the relevant literature in this tiny area in which he was working.

Q. Doctor, every asserted claim of the '865 patent requires an organic cosolvent. You understand that?

A. Yes.

Q. You're familiar with the Court's construction of the

term "organic cosolvent" in the claims of the '865 patent, right?

A. Yes.

Q. The Court construed "organic cosolvent" to mean an organic substance added to the primary solvent to increase the solubility of the VEGF antagonist, right?

A. Yes.

Q. Now, the Fraser formulation includes polysorbate, right?

A. Yes.

Q. And that's the substance in Fraser's formulation that you believe meets the organic cosolvent limitation of the asserted claims, right?

A. Yes.

Q. Now, at your deposition in this case you took the position that, in order to answer the question of whether a substance meets the Court's construction of organic cosolvent, you've got to do an experiment in order to determine if the substance is to be considered a cosolvent or not, right?

A. Yes.

MR. HUNT: Objection, Your Honor. To the extent that counsel is intending to elicit testimony regarding infringement of the '865 patent, it's been made clear that Dr. Rabinow is not offering any opinions regarding infringement.

THE COURT: Understood. Overruled at this point.

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You may proceed, Counsel.

MR. TRASK: Thank you, Your Honor.

BY MR. TRASK:

Q. Now, you're not taking that position here at trial, right?

A. Correct.

Q. But your position at deposition was that experimental data is required to prove whether or not an organic cosolvent is present, right?

A. That's what I said at the time.

Q. Now, you can't point to any data from such an experiment on the formulation disclosed in Fraser, right?

A. Correct.

Q. And you yourself didn't do any experiments on the Fraser formulation to show that its polysorbate 20 meets the Court's construction for organic cosolvent?

A. Correct.

Q. And there's no data in your report demonstrating that the polysorbate 20 in the Fraser formulation is an organic cosolvent under the Court's claim construction, right?

A. I believe I prefaced my comments here by saying "assuming Regeneron's infringement contention of the definition of polysorbate as a cosolvent," and then I proceeded to give my opinion.

So I was not -- I was not asked to consider

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infringement; so I didn't have to worry about that. I'm merely assuming Regeneron's infringement contention, and then I proceeded on to do what I was being asked to do, which was to discuss invalidity and obviousness.

Q. I'll ask the question again, Doctor.

There's nothing in your report demonstrating that the polysorbate 20 in the Fraser formulation is an organic cosolvent under the Court's claim construction, right?

A. I don't know. I didn't consider that question.

Q. Fraser itself does not disclose any experimental data showing that its polysorbate 20 meets the Court's construction of organic cosolvent, right?

A. I believe that's correct.

Q. Now, when the Court issued its construction of the claim term "organic cosolvent," it adopted Mylan's proposed construction for that term, right?

A. Yes.

Q. You served your opening and reply reports in this case on the Court's schedule prior to the Court issuing its claim construction order, right?

A. Yes.

Q. And so you served two opening reports, one under Regeneron's construction, the other under Mylan's construction, right?

A. Yes.

Q. And you didn't include any data in your report under Mylan's construction showing that polysorbate 20 functions as an organic cosolvent. We just agreed to that, right?

A. Yes.

Q. And the reason that that's not in your report under Mylan's construction is that you understood from Mylan's lawyers that the construction of organic cosolvent that they urged the Court to adopt would not be accepted by the Court, right?

A. There was discussion about two differing opinions as to the claim construction, and so we wrote two reports.

Q. I'll ask the question again, Doctor.

The reason that data is not in your report under Mylan's construction is that you understood from Mylan's lawyers that the construction of organic cosolvent that they urged the Court to adopt would not be accepted by the Court, right?

A. I think I said something to that effect at the time.

Q. At the time being your deposition, correct?

A. Yes.

Q. Was that a truthful statement at your deposition, Doctor?

A. Yeah. I mean, I wouldn't lie in my deposition.

Q. You got the impression from Mylan's lawyers that Regeneron's construction was going to be accepted by the Court,

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right?

A. That's what I said at the time, yes.

Q. Was that a truthful statement at the time, doctor?

A. Yes.

Q. You were so certain that Mylan's construction wasn't going to be accepted by the Court that you didn't really pay much attention to it, right?

A. Well, we paid sufficient attention to write two reports. That part is true.

Q. Doctor, you were so certain that Mylan's construction wasn't going to be accepted that you didn't really pay much attention to it. Is that true?

A. I think -- I think that's taken out of context. I think what I said was there was so much information, so much documents, patents, articles, I found it difficult, frankly, to keep up with it all; and I had all I could do to simply deal with the documents that I was given and I was being asked to study and to understand without going off on my own and doing, frankly, what Regeneron's job would have been, which is to prove their infringement contention, if that's what you're asking.

Q. Doctor, we established that you were deposed in this case, right?

A. Yes.

Q. That was back in March of this year?

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A. Correct.

Q. Can we look at transcript page 241, line 7 through 22, please.

I want you to confirm, Doctor, that I'm reading this correctly from your transcript.

"Q Well, I don't know what data you're talking about, Doctor, and I don't think it's referenced in your report. Your opinion on this is at paragraph 210 of your report. So I need to know whether there's actual data you're relying on or not.

"A Let me say this. I know I have seen data where Regeneron studied citrate, phosphate, buffered, otherwise optimized R1R2 formulations both with and without polysorbate 20. Can I show that to you right now? No.

"Q It's not in your report, right?

"A No. And the reason why it's not in my report is that we didn't think, frankly, that the Mylan claim construction was going to be accepted. We didn't really pay that much attention to it."

Did I read that correctly?

A. Yes.

Q. For purposes of preparing your report, Doctor,

Mylan's lawyers instructed you to assume that Regeneron's claim construction was going to be adopted by the Court, right?

A. Yes.

Q. You were led to believe by Mylan's attorneys that the Court would adopt Regeneron's claim construction of the organic cosolvent term, right?

A. I don't know to what extent I can share what Mylan's attorneys discussed with me, but they indicated that there was a high degree of uncertainty as to which claim construction was going to be accepted. And they -- and in view of that, they asked me to write two reports and to assume two different kinds of things. So I'm not sure how else I can answer your question.

Q. I'll ask the question again, Doctor.

You were led to believe by Mylan's attorneys that the Court would adopt Regeneron's claim construction of the organic cosolvent term, correct?

A. The probability of that was -- was significant, I would say that, yeah.

Q. Can we look at the doctor's transcript at page 250, lines 8 to 14, please.

I'm going to read the question and answer, Doctor, and I'd like you to confirm whether I read it correctly.

"Q Why did you assume that the Court would adopt Regeneron's claim construction of the

organic cosolvent term?"

There was an objection. And then you answered:

"A I was led to believe that by my attorneys."

Did I read that correctly?

A. Yes.

Q. And because you were instructed by Mylan's attorneys to assume that the Court would adopt Regeneron's construction, you provided no data supporting the notion that Fraser's polysorbate is an organic cosolvent under the construction that was ultimately adopted by the Court, correct?

A. Yes.

Q. When it came to proving invalidity under Mylan's constructions, the constructions that we're here today to address, you were pulling your punches, weren't you?

A. I'm sorry?

Q. When it came to proving invalidity under Mylan's constructions, the construction at issue in this trial today, you were pulling your punches, weren't you?

A. I'm not sure what you mean by that.

Q. Let's look at the doctor's transcript at page 249, line 11 through 250, line 7.

"Q Well, in the report under Mylan's construction, you provided no data supporting the notion that Fraser's polysorbate is an organic

cosolvent under Mylan's construction, right?"

Objection.

"A I guess I was pulling my punches, wasn't I? I was assuming, really, that we were going with Regeneron's claim construction and that polysorbate was going to be declared a solvent."

Did I read that right, Doctor?

A. Yes, you did.

Q. As we just discussed a moment ago, you served two opening expert reports, one under Mylan's construction and another under Regeneron's construction, right?

A. Yes.

Q. Then Dr. Trout served an expert report responding to your opinions on validity, right?

A. Yes.

Q. In response to Dr. Trout, you only served one reply report, right?

A. Yes.

Q. And that reply report was premised on Regeneron's claim construction, right?

A. It was premised on the assumption that we were assuming Regeneron's infringement claim contention of what a polysorbate was, and I think I may have specified that.

Q. Your reply report, the only reply report you served

in this case, assumes Regeneron's claim construction proposals for the claim terms "organic cosolvent" and "native conformation" in the '865 patent, right?

A. I think I felt that, unless I phrased it that way there, we wouldn't be at trial because Regeneron wouldn't have any patent at all. They wouldn't be enabled. It means that there would not have been enablement of any cosolvent. So I naturally assumed that, all right, there's going to be a trial; let's discuss this.

Q. Let's take a look at PTX 63, please.

THE COURT: Is that PTX, Counsel?

MR. TRASK: PTX, Your Honor. Thank you.

THE COURT: Thank you.

BY MR. TRASK:

Q. This is your reply report in this case, is it not?

A. Yes.

Q. If you look at page 1 of the document.

You see in the highlighting in the middle of paragraph 3, you say that "This report discloses my opinions assuming Regeneron Pharmaceutical, Inc.'s claim construction proposal for the claim terms 'organic cosolvent' and 'native conformation.'"

Do you see that?

A. Yes.

Q. Now, further down in Footnote 3, also on page 1 of

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your reply report, you said, "To the extent the Court does not adopt Regeneron's claim construction proposal or submit its own construction for either term, I reserve the right to amend and/or supplement this report accordingly."

Did I get that right?

A. Yes.

Q. You never amended or supplemented your report from that point until this time today, did you?

A. No.

Q. You don't have any opinions under Mylan's claim construction in this reply report, do you?

A. No.

Q. You understand, Doctor, that this whole trial on the '865 patent is about the asserted claims of the '865 patent as interpreted by the Court under the Court's claim construction order, right?

A. Yes.

Q. But you never submitted a reply report assuming that construction, did you?

A. I wasn't asked to opine on infringement. I accepted Regeneron's infringement contention for the definition of polysorbate 20.

Q. Doctor, you have no disclosed response to Dr. Trout's opinions that the asserted claims of the '865 patent are valid under the construction ordered by the Court, correct?

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A. Correct.

Q. Turning back to Fraser, let's look at DTX 729. This is the Fraser publication.

Now, Fraser explains that the aim of the study was to evaluate the effects of transient inhibition of VEGF on pituitary-ovarian function in the macaque.

Does that sound right?

A. Yes.

Q. The macaque is a monkey, correct?

A. Yes.

Q. And as we discussed a moment ago, Fraser used an intravenous injection, right?

A. Yes.

Q. When you inject intravenously, the injected dose circulates throughout the bloodstream, right?

A. Correct.

Q. Now, you testified on direct that the POSA would have taken Fraser's dose used to evaluate the effects of transient inhibition on ovarian function in monkeys and used that as an intravitreal dose to treat ophthalmic indications, right?

A. Yes.

Q. You don't cite any evidence teaching to use an intravitreal dose based on a dose designed to inhibit VEGF in a monkey's ovaries, right?

A. No.

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Q. Now, in order to do the calculations you performed to get from the information disclosed in Fraser to the claimed 40 mg/mL dose, you had to rely on a value for the dose volume administered intravitreally, right?

A. Yes.

Q. And your testimony was that, for purposes of converting Fraser's dose in a monkey for inhibiting ovarian function into an intravitreal dose for treating an ophthalmic indication, the person of ordinary skill would use a .06-milliliter intravitreal injection volume, right?

A. Yes.

Q. And you testified that you use a .06-milliliter volume to be generous, right?

A. Yes.

Q. Because that's not exactly what's disclosed in the literature, is it?

A. No.

Q. You pointed to the Gaudreault and Shams references.

A. Well, wait. Let me revise that.

It is common for manufacturers of sterile fluids, of which an intravitreal injection is an example, to have an overage in the drug container to accommodate insufficient delivery of the drug solution to the site of administration. That part is well known.

Q. You cite no literature for that proposition, right,

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Doctor?

A. I mean, this is what a POSA knows, right? I mean, Baxter put in -- I can't disclose exactly what they put in, but they put in an overage. In every one of their 10,000 different codes of intravenous solution, there's an overage in there to accommodate the fact that you can't get everything out of the container.

So you want to be sure that you deliver the labeled amount of solution and you're accommodating hang-up -- hang-up in the container, in the IV tubing, in the sets, in the pumps, in the butterfly injection site, in the patient. So that part's known.

Q. The references you combined with Fraser were Gaudreault and Shams, right?

A. Yes.

Q. And those disclose a .05-milliliter injection volume, not a .06-milliliter injection volume, right?

A. Yes.

Q. If you had used that .05 injection volume disclosed in the prior art in your calculations, it wouldn't have worked out to 40 mg/mL, would it?

A. Right.

Q. And each asserted claim of the '865 patent requires 40 mg/mL, right, Doctor?

A. Right. Well, let me -- let me clarify that. We're

not talking about anticipation; we're talking about obviousness. For obviousness, a POSA is allowed reasonable experimental optimization. So a POSA would know that you don't have to get exactly 40 mg/mL or you could get there to optimize it further.

Q. Doctor, the requirement of 40 mg/mL in each asserted claim of the '865 patent means that, if the prior art references don't disclose 40 mg/mL, either expressly or inherently, then the reference can't anticipate the claims, right?

A. You're right. But we weren't talking about anticipation here. You were talking about obviousness.

Q. If we look at DDX 4.79, please. This is one of the doctor's slides.

Doctor, you presented this slide as part of your direct testimony?

A. Yes.

Q. You see for the first limitation in -- shown in the slide, Claim 2, that requires 40 mg/mL, right?

A. Yes.

Q. And you checked the box under Fraser for that limitation, right?

A. Yes.

Q. What's the concentration of aflibercept -- of VEGF Trap disclosed in the Fraser reference?

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A. 24.3 mg/mL, I believe.

Q. We can take that down.

You understand, Doctor, that each of the asserted claims of the '865 patent also requires a vial for holding the formulation, right?

A. Yes.

Q. Fraser doesn't expressly disclose that its formulation is contained in a vial?

A. He's talking about an aliquot, 2-milliliter aliquots in Fraser, which means it has to be contained in something, containing a small volume of liquid. A POSA reading that would read my chapter in Remington's on packaging systems and know that a vial is the most likely candidate for such a container.

Q. You believe that the disclosure of a vial is inherent, correct?

A. Yes.

Q. You think it's probable that Fraser used a vial, right?

A. Yes. Well, a POSA reading Fraser would know that the most likely container for delivery of a liquid medication would be a vial, yes.

Q. You agree that the Fraser paper itself doesn't say that, right?

A. Yes.

Q. You're familiar with the Court's construction of the

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term "native conformation" in the claims of the '865 patent?

A. Yes.

Q. In your opinion, determining whether a protein is in its native conformation under the Court's construction is based upon simply running size-exclusion chromatography, right?

A. Repeat that.

Q. In your opinion, determining whether a protein is in native conformation under the Court's construction is based upon simply running size-exclusion chromatography, right?

A. I believe the Court left that open, if I recall properly. It wasn't clear what -- if that would be sufficient or not, and so I went with the size-exclusion chromatography.

Q. I'm asking, in your opinion, Doctor, determining whether a protein is in native conformation under the Court's construction is based upon simply running size-exclusion chromatography?

A. I interpreted that that was suitable for what I had to do, yes.

Q. I'm going to ask the question one more time, Doctor.

In your opinion, determining whether a protein is in native conformation under the Court's construction is based upon simply running size-exclusion chromatography; is that right?

A. I looked at the art in which that terminology was used, and there was sufficient prior art that, in fact,

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conflated native conformation with size-exclusion chromatography.

So there was certainly a case to be made that size-exclusion chromatography would have been adequate to declare that to be suitable for what we were doing.

Q. Now, Fraser doesn't disclose the at least 98 percent native conformation limitation, right?

A. Right.

Q. Claim 15 of the '865 patent requires a limitation involving turbidity, right?

A. Yes.

Q. And the requirement is that the turbidity be .01 or lower at OD405 following storage, right?

A. Yes.

Q. Fraser doesn't disclose that turbidity limitation either, right?

A. Well, I think we discussed this, that there was a declaration made by Regeneron stating that the -- a Dix formulation had, in fact -- was, in fact, the one that had been used by Fraser. And in the Dix document there was the requisite stability information for both turbidity as well as native conformation over the requisite period of time at the requisite temperature of 5 degrees.

So it was inherent in what Fraser used that we learned that that had been inherently disclosed.

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Q. Doctor, if the Court rules that Dix cannot be considered for anticipation or obviousness, then you have no aflibercept data to rely on to argue that Fraser inherently discloses the 98 percent native conformation limitation, right?

A. I'm not an attorney. I can't comment on that.

Q. And if the Court rules that Dix cannot be considered for anticipation or obviousness, then you also have no aflibercept data to rely on to argue that the Fraser publication discloses the turbidity limitations of Claim 15, right?

A. Again, I'm not an attorney. I can't comment on that.

Q. All of the asserted claims of the '865 patent require that the VEGF antagonist fusion protein comprised amino acids 27 to 457 of SEQ ID4, correct?

A. Yes.

Q. You don't argue that Fraser expressly discloses that amino acid sequence. We established that a moment ago, right?

A. Yes.

Q. Your position on the Fraser patent is based in part upon the disclosure of the Dix patent, right?

A. Yes.

Q. The Dix patent is only 11 pages long, right, Doctor?

A. I don't recall.

Q. You haven't read the entire Dix patent, have you, Doctor?

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A. I've read it some time ago.

Q. You didn't read it before your deposition, did you, Doctor?

A. I certainly don't recall that, no.

Q. You don't recall reading it before your deposition in full, correct?

A. I don't recall reading it or not reading it.

Q. Before alleging that an inventor's patent is invalid in light of a given document's disclosure, do you think it's important to read the whole document to fully understand its disclosure?

A. Yes.

Q. Let's look at the doctor's transcript at page 177, line 19, through 178, line 1.

Doctor, referring to the Dix patent, I asked you:

"Q There are other SEQ IDs disclosed in this patent, right?"

And you answered, "I would have to read this document in order to figure out if it were logical that it would refer to it," correct?

A. That's what's written here, yes.

Q. Now, you agree that the Dix '546 and Dix '226 patents have the same disclosures, right?

A. Yes.

Q. The Dix patent states that, "VEGF expression is

nearly ubiquitous in human cancer." Does that sound right?

A. Yes.

Q. And it explains that blocking VEGF "inhibits growth of implanted tumor cells."

Does that sound right?

A. Yes.

Q. Dix is referring to cancer in those passages, right?

A. Yes.

Q. Dix never refers to any ophthalmic indication, does it?

A. I don't believe so.

Q. It never refers to age-related macular degeneration, right?

A. I think we're talking about how a POSA would read Dix. A POSA would read Dix in light of what he knew was relevant. The history of what was going on at the time, that it was known that VEGF was useful, it may have been discovered originally in cancer, but it quickly was discussed in light of neovascularization in the retina. And people were, in fact, studying it for that purpose and injecting humans intravitreally for that.

So a person tasked with developing a -- an ocular dosage form would certainly be mindful of his surroundings.

Q. I'll ask the question again, Doctor.

Dix never refers to age-related macular degeneration,

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right?

A. I don't believe so.

Q. Dix never refers to diabetic macular edema, right?

A. I believe that that's correct.

Q. Dix never refers to diabetic retinopathy, right?

A. I believe that that's correct.

Q. Dix refers to administering formulations subcutaneously and intravenously, true?

A. I believe that's correct.

Q. Dix never refers to intravitreal administration, does it?

A. I don't believe so.

Q. And as we established a moment ago, intravitreal injection is a totally different method of administration from intravenous and subcutaneous administrations, right?

A. Yes.

Q. Now, Doctor, were you in the courtroom on Monday when Mr. Berl explained that Dix can't be relied on for obviousness if Dix and the '865 patent were co-owned by Regeneron or subject to an obligation of assignment to Regeneron at the time of the '865 patent's invention?

A. I believe I heard that.

Q. You don't have any opinions on the ownership of the Dix '226 or Dix '546 patents, right?

A. That's beyond my pay grade.

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Q. You don't dispute that the Dix '226 and Dix '546 patents are owned by Regeneron today, do you?

A. I'm not an attorney. I originally tried to delve into this area, and I realized that I was quickly becoming mired with all kinds of complexities. And I realized I had better stay out of this, and I would leave that to my attorneys to discuss.

So I can't really comment on, you know, specific aspects of ownership, because I realize that it's a very complex web in terms of who owns what, what was the law at which time. The law was changing. So I am aware -- I know enough to realize that I could get into real trouble if I tried to opine in that area; so I left this to my attorneys.

Q. Doctor, you don't dispute that, from September 2005 onward, the Dix '226 and Dix '546 patents were owned by Regeneron, right?

A. I believe that there are connotations about ownership that I may or may not be aware of; so I feel that I probably should not comment on that.

Q. You don't dispute that, as of September 2005 onward, all four inventors named on the Dix '226 and Dix '546 patents had an obligation to assign their inventions to Regeneron, right?

A. I understand that, but I'm not sure what that means in the context of the larger question you are asking. I'm not

an attorney.

Q. You don't have any opinions on the ownership of Regeneron's '865 patent, true?

A. There are implications of what you're asking that I believe go beyond the question that you're asking me.

Q. You don't dispute that, from September 2005 onward, the inventions in the '865 patent were owned by Regeneron, do you?

A. I don't have any comment.

Q. And you don't dispute that, from September 2005 onward, all four inventors named on the '865 patent had an obligation to assign their inventions to Regeneron, right?

A. Again, I'm not an attorney; so I can't really comment.

Q. Now, the two Dix references you're relying on are patents, right?

A. Yes.

Q. Now, are you aware that a reference patent can be considered prior art as of its provisional filing date only if the provisional application provides written description support for the claims in that reference patent?

A. I have seen that point argued and discussed. Again, I'm not an attorney, and I feel that I can't really comment on that.

Q. Okay.

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Can we put up Slide 3, please.

Doctor, do you see on the screen here is a quote from the Federal Circuit's *Dynamic Drinkware* case?

A. I see this.

Q. Do you see that it says a reference patent is only entitled to claim the benefit of the filing date of its provisional application if the disclosure of the provisional application provides support for the claims in the reference patent in compliance with 112, paragraph 1?

A. Yes.

THE COURT: Yes, Counsel?

MR. HUNT: I'm sorry, Your Honor.

Objection. This entire line of questioning is outside the scope of the direct. We did not in any way open the door to a discussion of whether the Dix '226 patent was commonly owned and/or has priority. The doctor assumed for purposes of his analysis that it would be prior art, and that's the end of it.

THE COURT: Counsel?

MR. TRASK: Thank you, Your Honor.

So Mylan and Biocon are relying on the March 25, 2005, date of the Dix patent. That is the provisional date. There's an obligation under the law that, if they're going to rely on that date, they need to show written description support in the provisional application. I'm trying to

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establish that the doctor didn't make that showing in relying upon that date.

MR. HUNT: Just additionally, Your Honor, to the extent that this line of questioning is attempting to elicit patent law expertise from a pharmaceutical formulator, we would object on that additional basis.

THE COURT: Understood.

I won't speak for any other courts or judges. But I, with all due respect, Doctor, wouldn't think that was binding on anyone.

Objection otherwise overruled, though with the assumption with respect to these materials are a basis of the doctor's opinions which were put at issue once disclosed and called at a witness.

You may proceed, Counsel.

MR. TRASK: Thank you, Your Honor. I'll move through this rather quickly.

BY MR. TRASK:

Q. Now, of course, you're relying on the Dix '226 and '546 patents as prior art, right, Doctor?

A. Yes.

Q. And you're relying on the March 25, 2005, filing date of the Dix patents as their prior art date, right?

A. Yes.

Q. Okay.

Let's look at the slide from the doctor's presentation, DDX 4.36.

You presented this slide during your direct examination, Doctor?

A. Yes.

Q. This is the Dix '226 patent, right?

A. Yes.

Q. And these -- the text from the Dix patents is from the issued patent, right?

A. Yes.

Q. But up at the top of the slide you have a March 25, 2005, date, correct?

A. Yes.

Q. That's the provisional filing date for the Dix application, right?

A. Yes.

Q. Do you know, Doctor, whether Example 1 shown on the slide right there is present at all in the provisional application of Dix?

A. No. I don't know.

Q. You didn't do that analysis, right?

A. I did not.

MR. TRASK: You can take that down.

BY MR. TRASK:

Q. You didn't evaluate whether the claims of the

Dix '226 patent have written description support in the disclosure of Dix's 2005 provisional application?

A. No.

Q. You didn't evaluate whether the claims of the Dix '546 patent have written description support in the disclosure of Dix's 2005 provisional application?

A. No.

Q. You don't have an opinion that the Dix '226 patent is entitled to claim the benefit of its 2005 priority date, do you?

A. I'm not an attorney. I can't comment.

Q. And you don't have an opinion that the Dix '546 patent is entitled to claim the benefit of its 2005 priority date, right?

A. Again, I'm not an attorney. I can't comment.

Q. Let's turn to Dix itself and the 40 mg/mL concentration.

In your opinion, Dix discloses 40 mg/mL, right?

A. Yes.

Q. Now, Dix has a number of formulations in its working examples towards the end of the document, right?

A. Yes.

Q. None of those formulations disclose 40 mg/mL of aflibercept, right?

A. I'd have to see it again. I don't recall.

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Q. Well, I believe you have the Dix document in your binder, Doctor, if you'd like to take a look and confirm.

THE COURT: Do you know which number that is, Counsel?

MR. TRASK: Yes, Your Honor. I'm sorry. It's D, as in defendant, TX 0013.

THE COURT: Thank you.

BY MR. TRASK:

Q. The examples start at Column 7 of that patent, Doctor.

A. I don't think I have it.

THE COURT: Did you say Column 7, Counsel?

THE WITNESS: I'm sorry. Where do I --

MR. TRASK: Column 7.

THE COURT: Thank you.

BY MR. TRASK:

Q. Are you there, Doctor?

A. Yes. I'm looking over it.

I see that they're talking about a 50 mg/mL. They're talking about a 75 mg/mL. They're talking about 100 mg/mL, and they're talking about a 50 to 100 mg/mL.

These concentrations are all higher than 40 mg/mL. And in the context of what is noteworthy about stability of proteins, if you have stability at a higher concentration, that is a very good basis for assuming you're going to have

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stability at a lower concentration. And 40 is not all that different from 50.

So it's hard for me to -- and I'm reciting this, I believe, in an obviousness arena, in which case there is reasonable routine experimentation that is permitted to get from 50 down to 40.

Q. The question I had asked, Doctor, was none of the working formulation in Dix's examples have 40 mg/mL of a VEGF antagonist fusion protein; is that right?

A. Right. But it states very clearly that formulations of 40 up to some very large number are envisioned in this patent.

Q. Doctor, I'm only asking you about the examples starting at Column 7.

A. I believe that's correct.

Q. Just for the record, Doctor, you agree that the working examples in the Dix patent starting at Column 7, none of those disclose 40 mg/mL of a VEGF antagonist fusion protein, right?

A. Correct.

Q. Now, you testified earlier today that Dix discloses 40 mg/mL because it discloses a range of 10 to 50 mg/mL of a VEGF-specific fusion protein antagonist, right?

A. Yes.

Q. You agree that a concentration of specifically

40 mg/mL is not expressly disclosed by that 10 to 50 mg/mL range, right?

A. Correct. But it is disclosed in the paragraph lower down where it specifically mentions 40 mg/mL in connection with a lyophilized dosage form.

Q. I didn't ask you about that, Doctor. And that's not disclosed in your report, is it?

A. I can't remember. It may have been.

Q. In your opinion, Doctor, Dix's disclosure of the 10 to 50 mg/mL concentration range is a disclosure of every possible value falling within that range, right?

A. Yes.

Q. And so the 10 to 50 mg/mL range of a VEGF antagonist is a disclosure to the POSA of 28 mg/mL, right?

A. Yes.

Q. 37.2 mg/mL?

A. Yes.

Q. 49.35 mg/mL?

A. Yes.

Q. Now, the formulations claimed in the '865 patent don't allow for 40 mg/mL of any VEGF-specific fusion protein; they require 40 mg/mL of the VEGF antagonist fusion protein comprising amino acids 27 to 457 of SEQ ID Number 4, right?

A. That's what's stated in the claims.

Q. Okay.

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Can we look at P2.12.1, please.

Do you know what's shown here, Doctor?

A. It's the amino acid sequence of SEQ ID4, I believe.

Q. And in order for a VEGF antagonist to meet the limitations of the claims in the patent, it needs to meet every single amino acid in this -- shown in this diagram, right?

A. Yes.

Q. Every one of these three -- every one of these three-letter sequences is a specific amino acid residue, right?

A. Yes.

Q. And if even one of those amino acids is different, it doesn't fall within the scope of the '865 patent claims, right?

A. Yes.

Q. You can take that down.

Now, if we look at Dix '226, again, DTX 013, at Column 2, lines 20 to 24.

A. I'm sorry. Say that again.

Q. Yes. We're going to look at the Dix '226 patent at Column 2, lines 20 to 24. It's also shown on the screen.

THE COURT: That's, again, DTX 13, Counsel?

MR. TRASK: That's right, Your Honor.

THE COURT: Thank you.

THE WITNESS: Okay.

BY MR. TRASK:

Q. This is the disclosure of 10 to 50 mg/mL that you're

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relying on, right?

A. Yes.

Q. This doesn't say 10 to 50 mg/mL of the long amino acid sequence that we just looked at on the screen, right?

A. I think a POSA reading this would assume we're talking about a VEGF-specific fusion protein antagonist where the SEQ ID is given.

Q. You think that a POSA would read VEGF-specific fusion protein antagonist in the Dix patent and assume that it means only the SEQ ID4 sequence that we just saw on the screen?

A. Well, it could comprise a very limited class of such compounds and denote that 10 to 50 mg/mL is a suitable concentration of them.

Q. Let's look at the same document, Column 2, lines 3 through 15. This is the immediately prior paragraph to the one we were just looking at.

And it says -- starting at the top, line 4 of the patent, it refers to a "VEGF-specific fusion protein antagonist comprising a fusion protein comprising a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and an Ig domain 3 of a second VEGF receptor and a multimerizing component."

Do you see that?

A. Yes.

Q. That's not the specific amino acid sequence of

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SEQ ID4, right?

A. Right.

Q. It also says that the "VEGF-specific fusion protein antagonist, the first VEGF receptor can be FLT1 and the second VEGF receptor can be FLK1 or FLT1."

Do you see that?

A. Yes.

Q. That's not the specific amino acid sequence of SEQ ID4 that we just looked at on the screen, right?

A. Correct.

Q. And even more particularly it says the fusion protein has the amino acid sequence of SEQ ID2 or SEQ ID4.

Do you see that?

A. Yes.

Q. That's not limited to only SEQ ID4, is it?

A. Right.

Q. Okay.

You can take that down.

Dix's SEQ ID2 and SEQ ID4 are different fusion proteins. Do you agree with that?

A. They're modifications, yes.

Q. They're different fusion proteins from one another, right, Doctor?

A. There are slight differences in their sequence, yes.

Q. One of them meets the limitations of the '865 patent,

but one of them does not, right?

A. Yes.

Q. It's nevertheless your opinion that when Dix discloses 10 to 50 milligrams per milliliter of the fusion protein, that that discloses 40 mg/mL of a VEGF antagonist fusion protein having amino acids 27 through 457 of SEQ ID4, right?

A. I think it discloses both. I think that disclosure applies to both sequences.

Q. I'm going to turn now to the '865 patent. This is PTX 2, P as in plaintiff.

THE COURT: Thank you, Counsel.

Do you have that, Doctor?

THE WITNESS: I'm sorry. What was that?

BY MR. TRASK:

Q. It's PTX 2, the '865 patent.

THE COURT: It's in the defendants' binder. I think -- yeah, I think you're on the right one, Doctor.

BY MR. TRASK:

Q. Whenever you're ready, Doctor.

A. What is the DTX number?

Q. It's P as in plaintiff, Number 2.

THE COURT: About halfway through, sir.

THE WITNESS: Thank you.

Okay. I have it.

BY MR. TRASK:

Q. You're obviously familiar with this patent, right, Doctor?

A. Yes.

Q. You understand that the '865 patent claims priority to a provisional application filed on June 16, 2006, right?

A. Yes.

Q. And that June 2006 provisional application is listed right on the face of the '865 patent, right?

A. Yes.

Q. If we go to P223, please. Do you see that on the screen, Doctor?

A. Yes.

Q. This is the face of the '865 patent indicating that it claims priority to a provisional application number 60,814,484 filed on June 16, 2006, right?

A. Yes.

Q. Okay.

Can we have P243, please.

Let's look now at Column 1 of the same patent, the asserted '865 patent. This is the cross-reference to related applications section of the '865 patent, Doctor, Column 1 of PTX 2.

A. Okay.

Q. Do you see this document states that the application

is a continued application -- I'll restate that.

This states that the application is a continuation application of a number of applications, including claiming the benefit under 35 USC Section 119(e) of US Provisional Application Number 60,814,484 filed June 16, 2006?

A. Where is that particular sentence?

Q. It's in the left -- it's in Column 1 towards the bottom of PTX 2.

A. Okay. And the '484, is that what you're referring to?

Q. It's the highlighted passage on the screen.

Maybe we can blow that up for the doctor.

Do you see here in Column 1 of the '865 patent it states that it's claiming priority to the provisional application number 60,814,484 filed on June 16, 2006?

A. Yes.

Q. Okay.

We can take that down.

Now, you understand from Mylan's counsel that the earliest priority date to which the '865 patent is entitled is June 16, 2006?

A. Yes.

Q. You didn't separately analyze whether the '865 patent is entitled to its June 16, 2006, priority date, did you?

A. No.

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Q. You just took the word of Mylan's counsel on that, right?

A. Yes, because I'm not an attorney.

Q. And that's the date you applied in determining what teachings made up prior art to the asserted '865 patent, right?

A. Correct.

Q. Let's turn now to the Rudge reference. This is D, as in defendants', TX 3592.

A. Okay.

Q. You relied on this reference in your direct testimony, right, Doctor?

A. Yes.

Q. And in your opinion, Rudge is prior art to the '865 patent?

A. Yes.

Q. And that's because, in your view, Rudge was published in 2005, right?

A. Yes.

Q. Okay.

Can we have DDX 4.37, please.

Let's look at this slide from your direct testimony, Doctor.

Do you see Slide 37 with the Rudge reference on it?

A. Yes.

Q. And you're citing it as a 2005 reference, both with

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the copyright date at the bottom and the 2005 year at the top, right?

A. Yes.

Q. Now, Rudge -- you've read the Rudge reference, right?

A. Yes.

Q. Do you know that it cites a number of references from 2006?

A. Such as? I see one relating to Heier as an abstract. Is that what you're referring to?

Q. Are you aware that there's a number of references cited in the Rudge paper dated from 2006, Doctor?

A. I see two abstracts which could very well have been announcements of a symposium, looks like ARVO or IOVS, where very often they have -- abstracts are published in advance of the symposium.

Is that what you are referring to?

Q. Let me look at the next slide in your presentation, Slide 38. This is the passage from Rudge that you were relying upon in your direct testimony, right?

A. Yes.

Q. It says, "Initial clinical studies in human patients suffering from both AMD and diabetic macular edema and retinopathy appear quite promising," right?

A. Yes.

Q. Do you know what Rudge cites in support for this

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statement?

A. I forgot.

Q. Let's take a look.

Can we have DTX 3592 at the pages 4 and 5, the paragraph spanning those two pages, pages 4 and 5 of the PDF.

This is the passage you were quoting on your slide, correct, Doctor?

A. Yes.

Q. What's cited as support for that statement?

A. 2006 references.

Q. Those weren't available in 2005, were they?

A. Nguyen was available as an abstract in 2006. Shah was also available as an abstract. As I indicated, very often abstracts are published in advance. And so I'm not sure that that's -- what you're saying is correct.

Q. Your view is that these abstracts were published online a year earlier than the date reported in the Rudge paper?

A. We're not talking a year online. It could be a few months. It could be a few months that -- you know, Rudge was published late in 2005 and he had availability to abstracts that were going to appear and had a 2006 publication date. I don't know.

Q. So you believe, Doctor, that these references dated in 2006 were, in fact, available online in 2005?

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A. I'm not sure what the situation is. Okay? I'm trying to make sense of what you're presenting me with given the fact that Rudge, obviously, has a publication date of 2005, and I'm trying to make sense of what you're asking me, and I'm trying to come up with a generous -- I'm going out of my way to try to anticipate why there's a 2006 reference in these things. And I'm thinking that the most likely thing is that it refers to an abstract that may have been available online.

Q. May have been online in 2005? Is that your position?

A. Yeah.

Q. And you think that's true of all of the references cited from 2006 in that paper?

A. Well, I haven't read all of the references. I've seen about three of them that all specify abstract. So it makes me wonder if there's something peculiar going on related to abstracts for conferences that were published ahead of a conference. Very often abstracts have to be published ahead of a conference so that the participants will know if there is something of interest to them there.

Q. Let me go back to the doctor's Slide 38, please.

Doctor, you prepared this slide?

A. Yes. It was prepared for me.

Q. Did you review the slide before it was presented to the Court?

A. Yes.

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Q. Did you notice that this passage was based upon citations from 2006?

A. No.

Q. You never looked to see what the source of this statement was, right?

A. Right.

MR. TRASK: Can we look at D3592.7.1, please?

THE COURT: Can you give us that number one more time.

MR. TRASK: This is just a callout for the screen.

THE COURT: No, understood, but for our record if you wouldn't mind repeating that.

MR. TRASK: Oh, sure, yes. It's D3592.7.1.

THE COURT: Thank you.

BY MR. TRASK:

Q. Here are two more references cited in the Rudge paper, right, Doctor?

A. Yes.

Q. These are the Mulay and Rixe -- if I'm pronouncing those correctly -- publications. And both of these are cited among the references in the Rudge paper, right?

A. Right. Those are both abstracts, yes.

Q. When you say these are abstracts, it's your view that, even though they say 2006, they were published online in 2005; is that right?

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A. I am familiar with -- when I see something that says "Proceedings of the American Society of Clinical Oncology, Abstract" that those look like -- I don't know -- poster presentations that are going to be presented at a conference in 2006, and for that reason they may very well have a 2000 date of publication. But they would be printed well ahead of the conference time so that participants could decide whether or not there was information relevant to their interests ahead of time.

Q. Have you reviewed either the Mulay or the Rixe publication cited in the Rudge paper that you rely on?

A. No.

MR. TRASK: I'm going to pass up a couple of exhibits, Your Honor.

May I pass up the exhibits, Your Honor?

THE COURT: You may.

BY MR. TRASK:

Q. Do you have those exhibits in front of you, Doctor?

A. Yes.

MR. TRASK: For the record, I've handed up to the witness and to the Court the Mulay paper, spelled M-U-L-A-Y. This is PTX 3344. And the Rixe paper -- R-I-X-E -- PTX 3346.

BY MR. TRASK:

Q. Do you have those in front of you, Doctor?

A. Yes.

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Q. Can I have PTX 3344, please.

Doctor, you see that in the Mulay paper -- this is a printout of that paper from the internet. It says it was published online on June 20, 2006.

Do you see that?

A. Yes.

Q. Can we also look at the Rixe paper, please.

You see that the Rixe paper as well was published online June 20, 2006?

A. Yes.

Q. Both of those papers were published after the June 16, 2006, priority date of the '865 patent, right?

A. Yes.

THE COURT: I'm sorry. Was that yes, Doctor?

THE WITNESS: Yes.

THE COURT: Thank you.

BY MR. TRASK:

Q. If Rudge was citing papers published after June 16, 2006, then it can't be prior art relative to the '865 patent's provisional application filing date, right?

A. Well, I guess I'm confused. I don't understand why there's a 2005 date ascribed to Rudge.

Q. It's confusing, right?

A. It is confusing.

Q. You don't cite any evidence demonstrating that Rudge

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was published prior to June 16, 2006, right?

A. I just have that 2005 date that's on the -- that appears on the face of the article.

Q. If Rudge was, in fact, published after June 16, 2006, then your reliance on it for invalidity of the '865 patent wouldn't be proper, right?

A. I don't know. It depends on the reasons, you know, why that was the case. I mean, as far as this goes -- I mean, it was common knowledge of a POSA that, as early as 2005, around June 2005, intravitreal bevacizumab was administered to patients, and they got that -- this is in Avery.

So it was entirely -- made perfect sense to me that an article around 2005 would contain information that would be demonstrating positive results from VEGF Trap or VEGF antagonists that were administered intravitreally.

Q. Like to turn now to the Liu reference.

THE COURT: Is that a good transition point?

MR. TRASK: Perfect, Your Honor.

THE COURT: Why don't we go ahead and take our afternoon break, then, at this point if we're getting into a different topic.

Again, Doctor, because you're midstream, you can't speak with anyone about your testimony. I just don't want you to think anyone is being rude or discourteous to you if they flee from you during the courtroom or in the hallway.

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But we'll take 15 minutes and then resume with cross of Dr. Rabinow. Thank you all.

(A recess was taken from 3:00 p.m. to 3:17 p.m.)

THE COURT: Counsel, if you're ready, you may proceed.

MR. TRASK: Thank you, Your Honor.

BY MR. TRASK:

Q. Let's turn to the Liu reference, Doctor. This is D, as in defendants', TX730. Here's the front cover of the Liu reference, Doctor. Let me know when you're there.

THE COURT: Is that in your binder, Counsel, or is that it --

MR. TRASK: It should be in the binder I handed up. I believe it's in theirs as well.

THE COURT: You said D730?

MR. TRASK: Correct. You know what? I'm wrong. It's not in the binder I handed up because it's in the binder that the doctor had on direct.

THE COURT: It is.

MR. TRASK: Apologies for that.

THE COURT: It will be in the white binder, doctor.

THE WITNESS: Okay.

BY MR. TRASK:

Q. This is one of the references that you mentioned

during your direct testimony?

A. Yes.

Q. Liu doesn't disclose intravitreal administration, does it, Doctor?

A. Liu is silent as to the method of administration, I believe. He's discussing antibody formulations.

Q. Did you say --

A. It's not an efficacy or toxicity paper; it's a formulation paper.

Q. I don't know if I heard that. Did you say Liu is silent as to the route of administration?

A. Yes.

Q. Can we have paragraph 221 from Liu, please.

Doctor, I'm at paragraph 221 of the Liu reference.

THE COURT: What page is that on, Counsel?

MR. TRASK: 29.

THE COURT: Exhibit page 29, correct?

MR. TRASK: Correct. It says .0029 at the bottom.

THE COURT: Understood. Thank you.

BY MR. TRASK:

Q. Doctor, do you see paragraph 221 of the Liu reference?

A. Yes.

Q. Liu is not silent as to the method of administration, is it?

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A. Liu mentions a number of methods of administration. Looks like he's trying to cover quite a bit of real estate in terms of administration.

Q. He is covering a lot of real estate, isn't he?

A. Yes, he is.

Q. He mentions -- he or she -- mentions subcutaneous, intravenous -- this is going to test my pronunciation skills -- intraperitoneal, intramuscular, intra-arterial, intralesional, and intraarticular routes.

Do you see that?

A. Yes, I do.

Q. It also mentions topical administration and inhalation or by sustained-release or extended-release means.

Do you see all of that?

A. Yeah, I see all of that.

Q. It's almost everything but the kitchen sink, right, Doctor?

A. Pretty much.

Q. But intravitreal is not listed there, is it, Doctor?

A. No. Nor is the method of administration listed in the claims.

Q. Liu doesn't disclose aflibercept either, does it, Doctor?

A. No, certainly not.

Q. If we look at Slide 55 from your demonstrative deck

this morning, you presented this slide this morning during your direct testimony regarding the disclosure of Liu?

A. Yes.

Q. And you relied on the formulation and data shown in these passages from Liu to check the box for the claim requirement wherein at least 98 percent of the VEGF antagonist is present in native conformation following storage at 5 degrees Celsius for two months as measured by size-exclusion chromatography, right?

A. Yes.

Q. And you reviewed this slide before you presented it to the Court?

A. Yes.

Q. This slide is showing a protein formulation from Example 2 of Liu, right?

A. Yes.

Q. Did you choose whether or not to highlight particular information on this slide?

A. Yes.

Q. You didn't highlight the protein itself in this formulation, right?

A. I highlighted the parts that would enable a viewer in this court to track to what were the claim limitations of the Claim 1 of the patent.

Q. This formulation contains 80 mg/mL of E25.

Do you see that?

A. Yes.

Q. On the top right?

A. Yes.

Q. Do you see that under the word "Formulations"?

A. Yes.

Q. E25 is an antibody, right?

A. Correct.

Q. Antibody is different from a fusion protein, right?

A. No. An antibody comprises roughly 40 percent of aflibercept.

Q. You think this antibody is the same as aflibercept, Doctor?

A. This antibody has an Fc fragment that comprises 40 percent of the molecular weight of aflibercept. From that perspective, antibodies are similar in terms of molecular weights. And as we've seen from the display of half a dozen of antibodies that have been approved, both fusion proteins and non, their stabilization packages, as embodied in their formulations, are remarkably uniform.

Q. Let's look at Liu at PDF page 34. You can zoom in on the text under Example 1.

Do you see this passage from Liu explains what E25 is under the words "Example 1"?

A. Yes.

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Q. Do you see E25 is an anti-IgE rhuMAB-E25?
A. Yes.
Q. That's not a VEGF antagonist, is it?
A. No.
Q. And it's not a fusion protein, right?
A. It's an antibody.
Q. Which is not a fusion protein, right?
A. 40 percent of the weight of aflibercept is an antibody. That's why we used antibodies as models for formulations. They're very similar.
Q. E25 is not aflibercept, right?
A. No, but there is a lot of overlap between the Fc fragment contained in E25 and the aflibercept molecule.
Q. If we go back to the doctor's slide, please.
Now, you highlighted stability data for the E25 antibody, right?
A. Yes.
Q. There's no stability data on this slide for aflibercept?
A. Correct.
Q. And there's no stability data on this slide for a VEGF antagonist, right?
A. Correct.
Q. You nevertheless checked the box for at least 98 percent of the VEGF antagonist being present in native

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conformation, right?

A. As I explained in my expert reports, both of them, we used antibodies as models for aflibercept because 40 percent of the weight of aflibercept is comprised of the Fc fraction of a typical antibody.

So it's a good model, and as if that weren't enough, we see from half a dozen of the approved antibodies, whether fusion proteins or not, that they all involve buffers, surfactants, and stabilizing sugars. And within each of those categories, only two different choices are necessary to stabilize them. And as a result, these are all approved, which means that they all have SEC information that shows that they're stable as well as turbidity.

So this is common, common, to all proteins, certainly to all antibodies, including the antibody representation in aflibercept.

Q. Doctor, I'll ask the question again.

There's no stability data here for aflibercept, right?

A. No.

Q. You agree that different proteins have different propensities for aggregation, right?

A. That statement covers a lot of real estate in terms of the propensity for degradation.

Q. Do you agree, Doctor, that different proteins have

different propensities for aggregation?

A. Yes.

MR. HUNT: Your Honor, this is outside the scope of the direct. We didn't have any discussion of protein aggregation.

THE COURT: Where are we in the scheme of things, Counsel, in terms of being related to the direct?

MR. TRASK: Sure. This was a slide shown on direct. The doctor checked the box for the claim limitation about native conformation, which is a measure of aggregation. And so I'm trying to establish that the data that the doctor pointed to here is not aggregation data for the VEGF antagonist in the claims.

THE COURT: Understood. Overruled.

BY MR. TRASK:

Q. I'm not sure if I got an answer to that question, Doctor. You agree that different proteins have different propensities for aggregation, right?

A. Yes.

Q. Just because one protein has a given native conformation at a specific condition, the person of ordinary skill wouldn't expect that a different protein will have the same native conformation at that condition, right?

A. Correct.

Q. I'd like now to turn to the Lam reference. This is

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D -- defendants' -- TX 3556. This one too is in defendants' binder, the direct binder.

Doctor, do you see the Lam application shown on the screen?

A. I do.

Q. You discussed this paper in your direct testimony?

A. Yes.

Q. You're relying on this publication for purposes of your opinions?

A. Yes.

Q. This is a patent about antibody formulations, right?

A. Yes.

Q. I think we've established this, but aflibercept is not an antibody, correct?

A. No. What I said was that 40 percent of the weight of aflibercept matched the Fc part of an antibody, that there is a very high degree of identicality of an antibody with aflibercept.

It is for that reason that we consulted the antibody formulation literature, particularly that of Genentech, which develops and approves these molecules as models for what to expect from aflibercept.

Q. It's a simple question, Doctor. Is aflibercept an antibody?

A. It has a very high resemblance to an antibody. It

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looks like an antibody. If you look at the diagram of what aflibercept was that Dr. Yancopoulos presented, it showed a wide receiver with two arms and a rather solid trunk standing up there and taking up a large amount of real estate inside of an airplane and being able to hold a football on two sides. It's a Y shape. That is what an antibody is.

Q. I'll ask the question again, Doctor. It's a simple one, I think.

Is aflibercept an antibody?

A. Yes. Absolutely.

Q. Do you know if Lam describes routes of administration?

A. I don't know.

Q. Take a look at D3556.39.1, please.

I'm on page 39 of the Lam reference, looking at the screen here. Do you see the section called administration of the formulation?

A. Yes.

Q. Were you aware that this passage existed in the Lam reference?

A. I think I read over it, and I saw that he was trying to cover a lot of administration real estate, in fact, all of the known methods of administration.

Turns out that intravitreal was rather recent compared to when this patent came out, and for that reason it

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didn't make it into his list.

Q. Pretty long list here, right, Doctor?

A. It's a pretty long list, but he did not anticipate intravitreal because it is, in fact, prior art.

Q. Prior art wouldn't have anticipated intravitreal administration, right?

A. I think very few people at that time would have.

Q. If we turn to the doctor's slide Number 17, please.

Doctor, you helped prepare this slide?

A. Yes.

Q. This is a slide showing disclosure from the Lam reference we just looked at, right?

A. Yes.

Q. And you reproduced some information here from the Lam reference about the rhuMAB-CD20 antibody, right?

A. Yes.

Q. That's not aflibercept, right?

A. Correct.

Q. Now, you highlighted some of the ingredients of this formulation in the text on the right of your slide, correct?

A. Yes.

Q. You did that highlighting?

A. I worked with the presentation people who highlighted that to indicate what are the areas that would enable us to compare to the claim elements of the '865.

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Q. I noticed you didn't highlight 0.9 percent benzyl alcohol. That's listed as one of the ingredients in this formulation you're relying on, right?

A. Correct.

Q. Do you think it's a good idea to inject 0.9 percent benzyl alcohol into the eye, Doctor?

A. This Lam is not -- I didn't choose this reference as a model for what to administer to the eye. I chose this reference as what kind of an antibody and associated formulation elements would provide knowledge to the POSA about stability. So there's a linkage between formulation antibody on the one hand and stability on the other.

The formulation element -- benzyl alcohol is an antimicrobial agent, and we would not -- I'm not looking to this as a model, for example, for what to administer to the eye. I'm looking at it as a model for what to expect for stability from this kind of a API.

Q. You agree that this formulation is not a good idea to administer to the eye intravitreally, right?

A. I wasn't proposing it for that.

Q. Do you agree with me?

A. I don't understand the question. I was using this as an indicator of what to expect for stability from an antibody. It had nothing to do with administration to the eye; so I'm not sure why you're bringing that up.

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Q. Doctor, do you have an opinion on whether the formulation shown here in Lam is a good idea to administer to the eye intravitreally?

A. I'm not sure about benzyl alcohol. I'd probably have a question about that, but that's not why I brought this data up, and it does not affect the conclusions that I drew.

Q. You'd defer to an ophthalmologist about whether or not to inject a given substance into the eye?

A. Yes.

Q. And you'd consult with an ophthalmologist about whether it's a good idea to inject benzyl alcohol into the vitreous, right?

A. I would defer to an ophthalmologist's opinion.

Q. You haven't spoken with an ophthalmologist to inform your opinions in this case, right?

A. I didn't have to because that's not what I'm using this information for. I'm not suggesting that this be injected in someone's eye.

Q. Doctor, you haven't spoken with an ophthalmologist to inform your opinions in this case, right?

A. That is correct.

Q. Okay.

I'd like to turn now to the doctor's Slide 47, please.

Doctor, you prepared this slide -- or -- with the

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assistance of counsel?

A. Yes.

Q. When you presented this slide to the Court, I heard you say many of these are fusion proteins. Do you stand by that testimony?

A. There's a number of them that are fusion proteins, yes.

Q. Which ones of these are fusion proteins?

A. Lucentis, Avastin. I can't remember. I looked them up, and I saw that there was at least one other one. There's a number of these that are humanized mouse antibodies. So in that sense, they're fusion proteins that are man-made.

Q. Doctor, Lucentis is described on this slide as being an antibody. Do you see that under "Active Ingredient"?

A. Yes.

Q. Avastin is described on this slide as being an antibody. Do you see that?

A. Yes.

Q. Every single one of the drugs on this slide is described as being an antibody, right?

A. Yes.

Q. They're not described in this slide as being a fusion protein, are they?

A. An antibody is what the -- is how they are described in the prescribing information.

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Q. Okay.

You can take that down.

Let's turn to Avery. This is Defendants' Exhibit 2264.

Can we put this up, please. Thank you.

Do you see the Avery reference, Doctor?

A. Yes.

Q. I want to ask you about the date of this reference. You see it's dated March 2006?

A. Yes.

Q. The paper doesn't indicate when in 2006 -- when in March of 2006 this reference was publicly available, right?

A. Not on this.

Q. You understand that Regeneron's position in this case is that the inventors of the '865 patent conceived of their invention no later than March 21, 2006?

A. I think I read that in Dr. Trout's report.

Q. If the Court accepts that March 21, 2006, date as the invention date for the '865 patent, then references can qualify as prior art only if they predate March 21, 2006, right?

A. There's no information in the evidence that was purported to demonstrate that Regeneron could swear behind the June 16th, 2006, date to get that earlier date. There was no information. There were empty protocols, and there was no data there. So that was a -- that was a red herring.

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Q. Doctor, let me ask the question again.

If the Court accepts a March 21, 2006, invention date for the '865 patent, then references qualify as prior art to the '865 patent only if they were publicly available prior to March 21, 2006, right?

A. I'm not a patent attorney; so I can't answer that.

Q. You haven't seen any evidence in this case about when this Avery reference was published in March, right?

A. I looked up the -- I googled "ophthalmology journal" and looked and convinced myself that it was -- that Avery was listed in March of 2006, and that was adequate for me to feel comfortable with the publication date for this.

Q. You don't know when in March 2006 Avery was published, right, Doctor?

A. That is correct.

Q. Doctor, in your opinion, the ability to optimize a protein formulation was a skill possessed by the person of ordinary skill as of 2006, right?

A. Yes.

Q. And as of 2006, in your opinion, optimizing the stability of a protein formulation was routine for the POSA?

A. Yes.

Q. If a POSA were designing a suitable intravitreal formulation of a protein drug, it would be helpful to know a suitable concentration at which the protein has a low

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aggregation tendency?

A. A POSA would determine that by routine experimentation. You can't know this ahead of time.

Q. If the POSA were informed of the concentration at which the protein had a low propensity for aggregation, then less experimentation would be required of the POSA, right?

A. Perhaps.

Q. You agree that pH has a strong influence on a protein's aggregation rate?

A. It could.

Q. It would be helpful for the POSA to know the pH range at which the protein drug has a low tendency to aggregate, right?

A. It would be nice but not essential because those experiments are relatively easy to run and would require on the order of several weeks. So I wouldn't say it's a major benefit to have that information because this is routinely done by the protein development chemist.

Q. By 2006, many analytical assays were known to the POSA for assessing the physical stability of protein formulations?

A. Yes.

Q. Size-exclusion chromatography was known to the POSA before 2006?

A. Yes.

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Q. It was a routine technique at that time?
A. Yes.
Q. The POSA could develop a size-exclusion chromatography method without undue experimentation?
A. Yes.
Q. And size-exclusion chromatography was commonly used by the POSA to analyze the physical stability of protein formulations?
A. Yes.
Q. I want to run through several analytical techniques, and I'll try not to belabor this.

Reverse-phase liquid chromatography was a routine technique as of 2006?
A. Yes.
Q. The POSA could have developed one of those methods readily?
A. Yes.
Q. Hydrophobic interaction chromatography was a routine technique as of 2006?
A. Yes.

MR. HUNT: Your Honor, my apologies. Size-exclusion chromatography is set forth in the '865 patent. We're getting outside the scope of the direct here. We didn't have any direct testimony regarding the various analytical methods beyond what's disclosed and required by the claims of the '865

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patent.

THE COURT: Understood.

Counsel?

MR. TRASK: If I may, Your Honor, there's one more that's directly discussed in the patent and certainly relevant to the data we've seen, and then I'll move on.

THE COURT: All right. Understood.

BY MR. TRASK:

Q. Laser light scattering analysis was a routine technique as of 2006?

A. Yes.

Q. And the POSA would have developed one of those techniques as of 2006 without undue experimentation?

A. Yes.

Q. Now, do you recall if any of the publications that we've discussed today set forth the order of addition of the formulation ingredients for making the formulation?

A. I don't recall that.

Q. Could the POSA have determined an appropriate order of addition to make the formulations falling within the scope of the '865 patent?

A. Yes.

Q. The work required to determine an appropriate order of addition would have been routine experimentation?

A. Yes.

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Q. And it wouldn't require undue experimentation to make formulations falling within the scope of the asserted claims, right?

A. Correct.

Q. If a prior art reference disclosed the ingredients of a formulation but didn't provide the mixing rate to use when mixing those ingredients together to make a formulation, the POSA could have optimized the mixing rate?

A. Yes.

Q. And that work would not have involved undue experimentation?

A. No.

Q. Let's move to the topic of tonicity, Doctor.

The term "hypertonic" means that the formulation has a greater concentration of dissolved molecules than would be in equilibrium with living cells?

A. Yes.

Q. And the term "isotonic" means that the formulation has an equal concentration of dissolved molecules as compared to living cells?

A. Yes.

Q. Hypertonic and isotonic formulations are not the same, right?

A. Correct.

Q. And you agree that isotonic and iso-osmolar have

roughly the same meaning?

A. Yes.

Q. You agree that osmolality considerations would not motivate the POSA to develop an isotonic formulation for intravitreal injection?

A. Could you repeat that.

Q. You agree that osmolality considerations would not motivate the POSA, the person of ordinary skill in the art, to develop an isotonic formulation for intravitreal injection?

A. Well, I just testified here today that they would. I testified that iso-osmotic conditions were clearly indicated by two different references appropriate for intravitreal administration.

Q. Doctor, osmolality is a consideration but wouldn't motivate the POSA to develop an iso-osmotic formulation for intravitreal administration, right?

A. It's a strong consideration that he would take into consideration.

Q. But it wouldn't motivate the POSA to develop an iso-osmotic formulation, right?

A. I'm not sure I detect the thrust of what you're asking.

Q. Okay.

Let's go to the doctor's transcript at page 139, line 11 through line 16.

Doctor, I asked you the question, "Okay. I think the upshot of that is that osmolality is a consideration but wouldn't motivate the POSA to develop an iso-osmotic formulation for intravitreal administration" --

A. This was taken way out of context. You -- you had presented --

Q. Doctor --

THE COURT: Gentlemen -- gentlemen, one at a time. Ask your question again, Counsel.

MR. TRASK: I was just reading from the transcript and the doctor cut me off. If I could finish.

THE COURT: That's why I said one at a time. Repeat, then we'll go from there.

MR. TRASK: Okay. Thank you, Your Honor.

BY MR. TRASK:

Q. I'll start from the beginning, Doctor. I want to read through this short snippet of testimony, and then I'd like you to confirm that I've read it correctly. Okay?

A. Yes.

"Q Okay. I think the upshot of that is that osmolality is a consideration but wouldn't motivate the POSA to develop an iso-osmotic formulation for intravitreal administration.

"A Apparently not."

Did I read that correctly?

A. Yes.

Q. We'll take that down.

The POSA would view a hypertonic formulation as suitable for intravitreal administration, right, based on the literature?

A. Would view a hypertonic solution? No. I wouldn't agree with that.

Q. Okay.

Can we put up the doctor's transcript at 136, line 19, through 137, line 2.

Doctor, at your deposition I asked:

"Q And when you say he wouldn't find it strange, you mean the POSA would view a hypertonic formulation as suitable for intravitreal administration, right, based on the literature?

"A Yes."

Did I read that correctly?

A. You read it correctly. This was taken out of context. You had shown me a document purportedly for an intravitreal dosage form that was at an extraordinarily high osmolarity. And I wasn't sure where this came from, and I was trying to think through the issues.

And I recall that it was said at some places that the eye is remarkably tolerant to hyperosmolar situations, but that

doesn't mean that one should take liberties to intentionally develop a hyperosmolar solution based upon that. One should always err on the side of being conservative.

Q. So your position, Doctor, is that you wouldn't administer a formulation that is too high in terms of its hypertonicity, right?

A. Certainly.

Q. So something over 850 milliosmoles would not be a good idea to inject intravitreally, right?

A. Right. And that doesn't mean that I would find it acceptable to administer something under that but well above what is normally considered iso-osmotic.

Q. So your testimony is that you could administer something that's hypertonic, not isotonic, but not something that's too high in terms of its hypertonicity, right?

A. The line of questions that you had put me through --

THE COURT: Doctor, that's what redirect examination is for. If you could just answer counsel's question.

THE WITNESS: Okay.

Repeat, please.

BY MR. TRASK:

Q. Your testimony is that it wouldn't be a good idea to inject a formulation that is too high in terms of its hypertonicity, but something that is somewhat hypertonic would be okay to administer?

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A. No.

Q. Doctor, is it your position that something 850 milliosmoles or higher would be a good idea to administer intravitreally?

A. No.

Q. But you said remarkably -- that the eye is remarkably tolerant to hypertonic solutions, right?

A. Yes, but one should exercise a good degree of caution and not -- and be extremely conservative with designing a dosage form that is designed to go into the eye. Just because the eye may be tolerant in some individuals is no reason to try to seek approval for something that could very well be injurious to some fraction of the patient population.

Q. So you agree, then, Doctor, that something that is just slightly outside the range of isotonicity would be okay to administer intravitreally, but you wouldn't want to administer something as high as 850 milliosmoles, right?

A. I didn't say that.

Q. The eye is remarkably tolerant to hypertonic formulations, right?

A. There's a difference between asking the question -- what would happen if I injected something into somebody's eyeball that had a tonicity of 600 milliosmoles? What would happen to that person? That's one question.

Another question is should I go out and intentionally

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develop a drug that is going to be administered to potentially millions of people with that degree of osmolarity? There's a difference there. There's a risk-benefit equation that your question does not recognize.

Q. Doctor, my question was simpler.

The eye is remarkably tolerant to hypertonic solutions, correct?

A. Yes. I said that.

Q. Let's turn to the Saishin reference. This is Defendants' Exhibit 2751. I believe this is one in both binders.

Can you put up 2751, please.

Doctor, you've relied on the Saishin reference during your direct testimony?

A. Yes.

Q. And you said it provided a motivation to administer VEGF Trap intravitreally, right?

A. Yes.

Q. Saishin was a study in mice, right?

A. Yes.

Q. And it involved administration of VEGF Trap?

A. Yes.

Q. And the authors were comparing two routes of administration for the VEGF Trap, subcutaneous and intravitreal, right?

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A. Yes.

Q. Let's look at your Slide 58, please.

Now, you pointed to each one of these passages in support of your motivation to combine, right?

A. Yes.

Q. And your view is that these passages recommend to the POSA to administer VEGF Trap intravitreally?

A. Yes.

Q. Let's look at the broader context for these passages.

So the first passage, I want to show the full paragraph.

So you see the passage at the bottom in purple is the one you quoted on your slide, right?

A. Let me read this entire passage.

Yes.

Q. This is the full paragraph containing the passage that you included on your slide, correct?

A. I don't know. I forgot what it was, but I'll take your word for it.

Q. Have you not looked at this passage recently, Doctor?

A. I have not looked at it recently, correct.

Q. You see that the passage refers throughout to systemic administration of VEGF Trap, right?

I've highlighted in yellow the words "systemic," "circulating," and "subcutaneous." Do you see that?

A. I see that the statement "local administration of VEGF Trap R1R2 by intravitreous injection is a viable alternative. A single intravitreous injection of VEGF Trap R1R2 markedly suppressed the development of choroidal neovascularization over the course of two weeks."

That's what I see.

Q. Doctor, I'm asking you about the first passage on your slide. We'll get to the other one that you just read.

Do you see there's three passages on your slide on the right?

A. Yes.

Q. I'm asking you about the one at the top. Okay?

A. Okay.

Q. Do you see that that passage is part of the larger paragraph shown on the left side of this slide from Saishin, page 7?

A. Okay.

Q. Do you see that the broader paragraph refers to systemic, circulating, and subcutaneous injection?

A. Yes.

Q. And so when -- the passage you quoted that says "these data suggest" and goes on to discuss VEGF Trap, it's talking about systemic administration, correct?

A. It's recommending both.

Q. That passage right there is referring to systemic

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administration. That's subcutaneous administration, right?

A. Well, authors typically will make a case for one route of administration. New paragraph. They will then make the case for the second route of administration. This is the first paragraph.

Q. It's your testimony, Doctor, that the concluding paragraph -- the concluding sentence of that paragraph is referring to intravitreal administration even though the entire paragraph is talking about subcutaneous administration?

A. I'm not sure what preceded this paragraph, and I'm not sure what was directly after this paragraph.

Q. Let's look at the second passage that you quoted, Doctor.

You see what I've done here is the same thing as I did on the last slide, but now we're looking at the second quoted passage from your slide? And I've shown the broader paragraph in which that passage appears from page 7 of Saishin.

Do you see that?

A. Yes.

Q. Do you see it says, "The effects of long-term systemic inhibition of VEGF are unknown. While there are theoretical reasons why it could be problematic, VEGF inhibitors have been tested as adjuncts to chemotherapy in cancer trials, and there have not been reports of severe problems clearly linked to blockade of VEGF. Should systemic

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inhibition of VEGF prove problematic, there's an alternative."

And then it goes on to discuss intravitreal, right?

A. Yes.

Q. This passage, the passage you quoted, is described as an alternative to systemic subcutaneous administration should systemic inhibition of VEGF prove problematic, right?

A. And your point is?

THE COURT: Doctor?

THE WITNESS: Yes.

THE COURT: Please just answer the question.

THE WITNESS: I'm sorry.

THE COURT: Thank you.

BY MR. TRASK:

Q. Do you agree or disagree with that, Doctor?

A. I agree with what you said.

Q. Let's look at the third passage you quoted on your slide.

You see here this is discussing recommendations pertaining to subcutaneous administration and recommendations pertaining to local delivery. That's intravitreal administration, right?

A. Yes.

Q. And what the authors are recommending here in this paragraph is for subcutaneous administration to move into clinical trials. That's trials in humans, right?

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A. Yes.
Q. That's a big step, right, from mice?
A. A big step from mice, yes.
Q. For intravitreal administration, the passage you quoted, the authors merely say that additional preclinical studies are recommended, right?
A. Yes.
Q. Preclinical studies are studies in animals?
A. Yes. Well, that makes sense.
Q. Okay.

We can take that down.

Let's look at the Ferrara 2006 publication, PTX -- Plaintiff's Exhibit 701.

You see the Ferrara paper, Doctor?
A. Yes.
Q. Now, this is a 2006 publication; is that right?
A. Yes.
Q. Now, we've referred today, and you've referred, to two other publications. The Saishin publication that we just looked at, right?
A. Yes.
Q. And Avery publication that you mentioned, right?
A. Yes.
Q. Do you know whether Ferrara was published before or after those publications?

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A. I don't know.

Q. Let's look at --

Can I have Reference 114 in the Ferrara paper, please.

Do you see the Ferrara authors are citing the Avery paper, right?

This is page 12 of Exhibit 701.

A. Okay.

Q. And there's a citation to the Avery paper that you've mentioned several times today, right?

A. Okay.

Q. Ferrara came after Avery, right?

A. I guess, yes.

Q. It had to have because it cited the Avery paper, right?

A. Yes.

Q. Do you know if the Ferrara authors discussed the Avery paper?

A. I don't recall.

Q. Did you read the Ferrara paper in full, Doctor?

A. I did, but this was quite some time ago.

Q. Let's turn to the discussion in Ferrara of the Avery paper.

Now, do you see here I've highlighted a sentence that ends in Reference 114. You'll recall that Reference 114 is the

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Avery paper, right?

A. Okay.

Q. We just looked at that.

And what Ferrara says about the Avery paper -- report, it says, "This case report attracted much interest and prompted a more recent, larger, uncontrolled open-label series of 79 subjects with neovascular AMD and 4- to 15-week follow-ups during which improvements in nonstandardized visual acuity measurements and in retinal anatomy, as assessed by optimal coherence tomography and fundus fluorescence angiography, were observed without associated inflammation or other significant safety issues."

Do you see that?

A. Yes.

Q. And then it goes on. That's the Avery paper, right, that you discussed?

A. Yes.

Q. And it goes on to say, "Although intriguing, these early findings are difficult to compare with data from rigorous double-masked controlled Phase III trials of verteporfin photodynamic therapy, pemigatinib, and more recently ranibizumab."

Do you see that?

A. Yes.

Q. It's saying that "The Avery results are preliminary

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and difficult to compare with more rigorous studies," right?

A. That's what it says.

Q. And then it goes on at the bottom of this passage on page 6 to say, "It's also noteworthy that early clinical studies with" -- some of those other drugs -- "suggested a considerably greater benefit in AMD patients than that eventually demonstrated in Phase III studies, further emphasizing the difficulty of interpreting early clinical results."

Do you see that?

A. Yes.

Q. So Ferrara explained that the results from Avery were intriguing but difficult to compare with more rigorous studies, right?

A. That's what he said.

Q. And he said that earlier drugs suggested a considerably greater benefit than eventually panned out in later studies, right?

A. That's what he said.

Q. Now, you're aware that Ferrara cites Saishin as well?

A. Correct.

Q. Let's look at that passage.

Here's Ferrara's discussion of the Saishin paper on which you rely. Saishin is Reference 80 on page 11, and the discussion of Saishin is at page 4.

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Do you see that on the screen?

A. Yes.

Q. Ferrara's understanding after reviewing the Saishin paper was different than yours, right?

A. Yes.

Q. Ferrara and the coauthors of that paper concluded that "Interestingly, these studies show that systemic administration" -- that's subcutaneous administration, right?

A. Yes.

Q. -- "of the VEGF Trap inhibits neovascularization by about 75 percent; however, intravitreal administration of the same agent resulted in about 25 percent inhibition."

Did I get that right?

A. You did, but he didn't mention anything about the difference in dosing.

Q. He also goes on to describe that "The limited efficacy observed in the intravitreal administration may be due at least in part to the existence of a barrier to the transretinal penetration of large molecules, such as the VEGF Trap."

Did I get that right?

A. You got that right.

Q. Now, the Ferrara paper that we're looking at was published in the journal *Retina*, correct?

A. Yes.

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Q. That's a peer-reviewed scientific journal?
A. Yes.
Q. The Ferrara authors were all from the biotech company Genentech?
A. Yes.
Q. In 2006 Genentech was a large, well-established biotech company, right?
A. Yes.
Q. Perhaps the most successful biotech company in history at that time, correct?
A. Correct.
Q. As of 2006 Genentech itself had a VEGF antagonist on the mark, right?
A. Yes.
Q. And they had another one in clinical trials, right?
A. Yes.
Q. Dr. Ferrara, the author of this paper, is credited as the discoverer of VEGF, right?
A. Yes.
Q. He invented the molecules in both Avastin and Lucentis, right?
A. Yes.
Q. You don't know him personally, do you?
A. No.
Q. You've never met him?

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A. No.

Q. Were you aware before I told you at your deposition that Dr. Ferrara is a member of the National Academy of Sciences?

A. No.

Q. You agree that the National Academy is considered one of the highest honors that can be accorded to a scientist?

A. Yes.

Q. Were you aware before I told you at your deposition that Dr. Ferrara is the winner of the Lasker Award?

A. Yes.

Q. You were aware of that?

A. No, I was not aware of that.

Q. Are you familiar with the Lasker Award?

A. I am aware that it is a prestigious honor.

Q. It's sometimes referred to as America's Nobel Prize, right?

A. I suppose.

Q. That's because 86 Lasker Award recipients have gone on to win the Nobel prize, right? Does that sound right to you?

A. I suppose. I haven't studied that statistically to see the correlation.

Q. Can we have PTX 3345, please.

Were you aware of this New York Times article

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reporting on Dr. Ferrara's receipt of the Lasker Award?

A. No.

Q. You can take that down.

In your opinion, Doctor, Dr. Ferrara was really scared of the upstart company Regeneron, right?

A. I believe it is reasonable to expect that Dr. Ferrara reflected the strong concern of Genentech for VEGF Trap R1R2 and even for the use of their own bevacizumab in place of ranibizumab and, in fact, refused to even contribute to the development of bevacizumab trials with Rosenfeld's work.

So there is, obviously, a concern that any competitive threat to ranibizumab should be squashed based upon what we learned from how Genentech dealt with Rosenfeld's request for funds.

Q. Doctor, in your view, Dr. Ferrara, the discoverer of VEGF and the inventor of Avastin and Lucentis, was really scared of the upstart company Regeneron, correct?

A. I didn't say that. I said that very often --

Q. Can we look at your deposition transcript, Doctor?

THE COURT: Let's let the doctor finish his answer first.

BY MR. TRASK:

Q. I'm sorry. Go ahead, Doctor.

A. I'm sorry. Very often employees of a company will reflect the corporate stance. These people receive stock

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options and, you know, continued employment and other perks as well. It's reasonable to expect that there would be a desire to reflect the corporate position. That's completely different from saying the man is a brilliant scientist.

Q. Page 317, line 12, through 318, line 1, of the doctor's transcript.

"Q And you think they" -- "they" meaning Ferrara -- "misinterpreted Saishin?

"A I think Ferrara had a completely understandable bias. He's working for Genentech, right? He's got a franchise to maintain. He's really scared of that upstart Regeneron company. He's coming in, and they're going to blow them away with a better dosage form. So, yeah, he's going to do what he needs to do to keep his management happy and publish articles that are disparaging the competition."

Did I read that right?

A. You did.

Q. You think it's reasonable to suspect that, because Dr. Ferrara and his coauthors were Genentech employees, they're rendering opinions in a peer-reviewed scientific article that might be contrary to the science, right?

A. Dr. Ferrara's articles have been critically evaluated by Avery, and there were numerous methodological issues that

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were raised against his findings that large molecules could not penetrate the retina.

He used an extraordinarily small amount of VEGF -- of HER2, the antibody that he used that was the large molecular antibody in his competition trials. This is a more -- a study where the lead author was Mordente. It was in, I think, 1989.

And what they found there was that there was no penetration from the human epidermal growth factor protein, which was on the order of about 150,000 daltons, whereas the smaller molecules were able to migrate through.

It has been since shown that the amount that he used, 25 micrograms, was too small and that you can overcome the barrier to migration in the retina if you use a sufficiently high concentration of antibodies.

So it was shown in 2004 that, if you use on the order of 1 to two milligrams of immunoglobulin G, you are able to penetrate the -- to the retina.

It was also found that Ferrara, when he did his experiment, did not use the most permeable part of the retina, which was the fovea, and instead he used the peripheral parts of the retina, in which the internal limiting membrane, the ILM, was the thickest.

If he had gone to the fovea, he would have encountered a much thinner part that would have posed much less of a barrier to large molecules.

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In addition, the inner plexiform layer is missing in the fovea as well. So the experiment was poorly designed.

MR. TRASK: Your Honor, I'd like to respectfully move to strike that testimony. It wasn't responsive at all to my question and discussed a number of references and concepts that were nowhere in his direct examination.

THE WITNESS: I -- I'm sorry, Your Honor.

THE COURT: That's a request for me.

Overruled.

MR. TRASK: Let's turn now -- getting towards the end, Your Honor -- to the Gaudreault reference. This is Plaintiff's Exhibit 1839. This one I believe is in both binders.

THE COURT: You said 1839, Counsel?

MR. TRASK: That's correct, Your Honor.

BY MR. TRASK:

Q. Doctor, do you see the Gaudreault reference on the screen?

A. I do.

Q. This too was published by Genentech scientists, right?

A. Yes.

Q. And it was published in the journal *Investigative Ophthalmology and Visual Science*?

A. Yes.

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Q. That's a reputable peer-reviewed journal?
A. Yes.
Q. Gaudreault studied the effects of ranibizumab dosed both intravenously and intravitreally in monkeys, right?
A. Yes.
Q. And Gaudreault reported that penetration of ranibizumab into the retina following intravitreal administration is critical for its clinical use, right?
A. That's what he said.
Q. The authors also reported that retinal penetration suggests the availability of ranibizumab to inactivate VEGF at the site of AMD, right?
A. That's what he wrote.
Q. Now, you disagree with that statement, right?
A. Yes.
Q. You think the Gaudreault authors overinterpreted the data, right?
A. There were several schools of thought. This was unsettled science at the time that all these publications were out. There was a faction that you are referring to where it was believed or at least promulgated that large molecules have a problem in penetrating the barrier to the retina. There were others who had done studies with rabbits, other animals, and had found that, no, we are able to see that we do get penetration.

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So it was very unsettled at the time.

Q. Doctor, I asked if you think Gaudreault overinterpreted the data. Yes or no.

A. He had a point of view. He may have overinterpreted the data, I suppose, yes.

Q. Let's turn to the Ghate reference. This is Plaintiff's Exhibit 1576. It's in plaintiff's binder.

You referenced this paper during your direct, Doctor?

A. Yes.

Q. These authors are not Genentech scientists, right?

A. Correct.

Q. They're from the Emery University Eye Center?

A. Yes.

Q. In Atlanta, right?

A. Yes.

Q. No connection to Genentech that you're aware of?

A. They may have consulted for them. I don't know.

Q. You do not know one way or the other, right?

A. No.

Q. Let's look at page 281.

THE COURT: Counsel, yes?

MR. HUNT: Apologies, Your Honor. I need to object to this. I don't recall going through the Ghate reference with the good doctor on direct.

MR. TRASK: I believe that the doctor addressed it.

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But even if I'm wrong about that, Your Honor, this goes directly to the doctor's credibility in refuting well-established science from individuals with a high degree of expertise across the nation, both at Genentech and elsewhere.

THE COURT: Overruled. If it's a credibility question, let's get to it, then.

MR. TRASK: Sure.

BY MR. TRASK:

Q. Let's look at page 281. There we are.

Do you see the authors here are discussing intravitreal injection?

A. Yes.

Q. And they say it's the most invasive route with the most serious complications, right?

A. Yes.

Q. And then let's look a little further down the page.

The authors here say that "The internal limiting membrane" -- that's the membrane in the eye that separates the vitreous from the retina -- "is impermeable to linear molecules greater than 40 kilodalton and globular molecules greater than 70 kilodalton; thus larger macromolecules will have a larger retention time, possibly weeks, but their effect on the retina after an intravitreal injection is limited."

Do you see that?

A. That's what it says.

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Q. You don't agree with that statement in this peer-reviewed literature, do you?

A. As I indicated, there were two schools of thought, one that large molecules cannot penetrate, and there was an alternative school that said they do penetrate. And it was also unambiguous at the time that humans with AMD were getting better after receiving intravitreal injections of bevacizumab as early as mid-2005.

So that would be the relevant consideration as opposed to theoretical discussions about mouse, monkey, rat, and rabbit studies, the fact that this was actually being administered, bevacizumab was actually administered to humans as early as mid-2005. And then others started taking this up and repeating it, and they too were finding excellent clinical results.

So proof of concept for large molecules, curing or certainly delaying and improving the status of AMD patients with neovascularization issues was undisputed at that time. So I'm not sure I see the relevance.

THE COURT: Doctor, you were asked whether or not you agreed with the statement. You've now described two camps. Please answer the question. Do you agree with it or not?

THE WITNESS: No.

THE COURT: Thank you. The determination of whether questions are relevant or not is up to me. I understand and

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appreciate your thoughts, but I'll handle any objections. Thank you.

Next question, Counsel.

BY MR. TRASK:

Q. Yes. Doctor, in your opinion the person of ordinary skill in the art would believe it's not necessary for a large VEGF antagonist molecule to enter the retina in order to exert its therapeutic effect, right?

A. There is a school of thought that believed that, yes.

Q. That's your opinion, right, doctor?

A. That was my opinion, and I've subsequently found that there are others who also expressed that.

Q. Subsequently to your deposition?

A. Yes.

Q. Now, in your view, Doctor, the mechanism of action for aflibercept is that the VEGF molecules are reacting with the aflibercept in the vitreous so that the aflibercept molecules never enter the retina, right?

A. I stated in my deposition that that was one alternative explanation for what was going on, yes.

Q. Doctor, you said it's the mechanism of action, didn't you, in your report?

A. No. I said that there were two possibilities. I said that either aflibercept was, in fact, penetrating through because in view of the contrasting experimental results from

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different animal studies; so that was possible. And if it was not the fact that they couldn't penetrate through, I could envision an alternative explanation, which I proceeded to give you.

Q. Can we put up the doctor's report at paragraph 105, please.

Doctor, do you see here's a copy of your reply report. And in the highlighted passage in paragraph 105, you said, "The mechanism of action being that the VEGF molecules are reacting with VEGF Trap R1R2 in the vitreous humor and the VEGF Trap R1R2 would never enter the retina."

Do you see that?

A. I did say that. That's true, yes.

Q. Take that down.

In your view, Doctor, the person of ordinary skill in the art would believe that the VEGF antagonist would remain in the vitreous and suck the VEGF out of the retinal compartment, right?

A. Yes.

Q. In your view, annihilation of the VEGF by the VEGF antagonist, you're essentially having a vacuum cleaner sucking all out of the VEGF out of the retinal compartment, right?

A. That's what I said in my deposition, correct.

Q. That's what you testified was the mechanism of action of aflibercept?

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A. I said that was one of the two possibilities. I had said -- when you asked me that, I said that was an alternative explanation, but I said it was also possible that aflibercept, in fact, did penetrate the retina, which we now understand to be, in fact, the case.

Now -- no, I'm sorry. I'm going to stop because you didn't ask me anything else.

Q. Doctor, you don't know anything about the rate at which VEGF is secreted from the eye, do you?

A. No.

Q. You don't know whether the rate that VEGF is produced in the retina is faster or slower than the rate at which it diffuses into the vitreous, right?

A. No.

Q. You're not an expert in the anatomy or physiology of the human eye?

A. No.

Q. You're not an expert in the anatomy of the human retina, right?

A. Right.

Q. You're not an expert on retinal kinetics?

A. I think, as I explained during my deposition, I understand kinetics. I'm an expert in kinetics, and I applied it to the retina.

Q. You wouldn't say you're an expert in retinal

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kinetics, right?

A. I am not sure how to answer that.

Q. You were hired for this case just a few months ago, right?

A. Correct.

Q. Earlier this year?

A. Yes.

Q. You'd never studied the anatomy or physiology of the eye outside of this case?

A. That's correct.

Q. Outside of this case, you'd never studied the transport of molecules across ocular membranes, right?

A. Correct.

Q. Outside of this case, you've never studied the transport of molecules across retinal membranes, have you?

A. Right.

Q. You're not an expert on the physical barriers between the vitreous and the retina, right?

A. Correct, only after having read about it in this case.

Q. You're an expert in this case now having read the literature in this case?

A. I wouldn't say I'm an expert. I see that what I had proposed is, in fact, advocated by other experts in the field that they had proposed that this was a viable explanation for

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what was going on. So I essentially anticipated what other experts had said.

Q. You can't identify by name the tissues that separate the vitreous part of the eye from the retina part of the eye, can you?

A. You have the inner limiting membrane, which, as I indicated, was very thin over the fovea, and because -- and you also have the plexiform layers, and there are other layers as well. But those are the two layers that have been suggested as being the barriers to migration.

Q. Did you study up on this just prior to trial?

A. Yeah, of course.

Q. You didn't know the answer to that question when I asked you at your deposition, did you?

A. Of course not, no. If I had, I would have told you.

Q. Before you were hired as an expert by Mylan in this case, you hadn't studied any of the processes in the eye at issue in this case, right?

A. That's correct.

Q. And you can't explain with certainty the role of the inner limiting membrane that you just referenced, right?

A. I'm not alone in that. Many of the experts that have been cited here cannot say with certainty what is going on.

Q. Are any of the other experts in this case offering the opinion that the VEGF antagonist works by sucking the

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VEGF --

A. Yes --

Q. -- out of the retina --

A. Yes.

Q. -- by a --

A. Yes.

THE COURT: Doctor, one at a time, gentlemen.

Counsel, please ask your question.

BY MR. TRASK:

Q. Are any of the other experts in this case, Doctor, offering the opinion that VEGF antagonists can work by sucking the VEGF out of the retina like a vacuum cleaner?

A. Yes.

Q. Before you were retained by Mylan in this case, you weren't even aware of the existence of the inner limiting membrane in the eye, right?

A. Yes.

Q. Prior to this case you had no experience with drugs for age-related macular degeneration?

A. Correct.

Q. You had no experience with diabetic macular edema or diabetic retinopathy either, right?

A. Right.

Q. Other than your work on this case, you have no experience studying the mechanism of inflammation of VEGF

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antagonists?

A. Say that again.

Q. Other than your work in this case, you have no experience studying the mechanism of inflammation of VEGF antagonists?

A. Correct.

Q. You're not sure if there are any cells in the vitreous of the human eye, right?

A. There's no cells in the vitreous of the human eye.

Q. At the time of your deposition, you weren't sure whether there were cells in the vitreous of the human eye, right?

A. Correct.

Q. You've never previously served as an expert in a case involving ocular drug administration?

A. Correct.

Q. Now, with respect to that vacuum cleaner theory that you've mentioned, Doctor, you haven't seen any literature as of 2006 stating that VEGF antagonists can sequester VEGF molecules outside the retina in the vitreous, right?

A. I'm not sure what the date was. It was around. I can't say for sure that it was before.

Q. Doctor, you testified in your deposition that you weren't aware of any literature as of 2006 stating that VEGF antagonists can sequester VEGF molecules outside the retina in

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the vitreous, right?

A. That's what I stated in the deposition, that's correct.

Q. And in your view of all the literature that's been cited in this case and in your report, the publication that you would say best supports your theory about the vacuum cleaner mechanism of action of aflibercept is your kinetics textbook from 1978, right?

A. That and the knowledge of a POSA, yes.

Q. And your kinetics textbook from 1978 isn't even of record in this case, is it, Doctor?

A. No.

MR. TRASK: Nothing further.

THE COURT: Thank you, Counsel.

We're going to take a five-minute break before we begin direct. It's my intention to complete the doctor's testimony today, just as a heads-up.

I offer that also in case anyone has flights to catch or travel arrangements, please feel free to duck out. You don't need my permission to do that, but feel free to do so. But it's my intention to complete the doctor's testimony here today.

We're going to take five so you-all can switch. Thank you.

(A recess was taken from 4:32 p.m. to

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4:44 p.m.)

THE COURT: Thank you, everyone. Please be seated.

Redirect, Counsel.

MR. HUNT: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. HUNT:

Q. Dr. Rabinow, do you remember when counsel asked you about the Court's claim construction as it relates to your invalidity opinions?

A. Yes.

Q. And counsel suggested that you did not consider both proposed constructions in forming your reply to Dr. Trout's opinions; is that right?

A. Yes.

Q. I'd like to call up DTX 7090, your reply expert report, page 13, paragraph 30. Is this your reply expert report, Dr. Rabinow?

A. Yes.

Q. Did you, in fact, set forth here in paragraph 30 both parties' claim constructions; is that right?

A. Correct.

Q. And it's your testimony that you considered both claim constructions in forming your opinions in this case, correct?

A. Yes.

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Q. That includes the opinions set forth in your reply report?

A. Yes.

Q. Okay.

Thank you, Mr. Gibson. You can take that down.

Now, Dr. Rabinow, do you remember when counsel asked you about polysorbate 20 and the cosolvent limitation of the '865 patent claims?

A. Yes.

Q. But you're not offering any opinions today about whether polysorbate 20 is, in fact, acting as a cosolvent; is that right?

A. That's correct.

Q. Instead, your understanding is that if polysorbate 20 is found to be a cosolvent under the Court's construction, then the organic cosolvent limitations in the asserted claims must be found invalid in view of the many polysorbate 20 disclosures in the prior art; is that right?

A. That is correct.

Q. And your opinions today are based on the construction that the Court -- that was ordered by the Court; is that right?

A. Yes.

Q. Now, do you recall counsel asked you some questions about the Dix '226 patent?

A. Yes.

Q. In fact, I think counsel asked you if the Dix '226 patent disclosed diabetic retinopathy. Do you recall that?
A. Yes.
Q. He also asked you if the Dix '226 patent disclosed AMD, right?
A. Yes.
Q. Now, it's the '865 patent claims that are at issue in this case, right?
A. That's correct.
Q. And do the '865 patent claims contain any limitations requiring the use of the claimed formulation in any particular disease state?
A. No.
Q. So is it relevant whether the Dix patent discloses diabetic retinopathy in your analysis?
A. No.
Q. Do you remember when counsel asked you about your deposition testimony concerning the likelihood of the Court entering Regeneron's claim construction?
A. Yes.
Q. Now, you weren't pulling your punches, though; you were just assuming that Regeneron's construction could apply, right?
A. Yes.
Q. And so that's why you prepared two reports in this

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case?

A. Correct.

Q. And as you testified earlier, your opinions are unchanged under either party's construction, right?

A. Yes.

Q. Do you remember when counsel asked you about the amino acid sequence disclosed in the '865 patent?

A. Yes.

Q. And that's sequence ID4, right?

A. Yes.

Q. And it's your opinion that the person of ordinary skill in the art would understand, based on their knowledge as of June 16th, 2006, that the disclosure of VEGF Trap R1R2 would necessarily mean that the amino acid sequence ID Number 4 is present; is that right?

A. Yes.

THE COURT: Yes, Counsel?

MR. TRASK: Your Honor, we've been tolerating a lot of this, but these are all leading questions.

THE COURT: Understood. Sustained.

BY MR. HUNT:

Q. Did you consider sequence ID Number 4 from the Dix '226 patent in your analysis, Doctor?

A. Yes.

Q. Did you do any comparison of the sequence in the

Dix '226 patent to the claims at issue here?

A. Yes.

Q. And what was the relationship between the sequence ID4 disclosed in Dix '226 and sequence ID4 disclosed in the '865 patent?

A. They were identical.

Q. So is it your opinion that the Dix '226 patent discloses the sequence ID4 claim in the '865 patent?

A. Yes.

Q. Dr. Rabinow, do you recall counsel's questions regarding the priority date of the '865 patent?

A. Yes.

Q. Have you assumed for purposes of your analysis that the '865 priority date -- well, strike that.

Have you offered any opinions in this case regarding whether Regeneron is entitled to the June 16th, 2006, priority date I believe you previously testified applies?

A. In my expert report, I discuss that, yes.

Q. Have you seen any evidence suggesting that Regeneron is entitled to anything other than the June 16th, 2006, priority date?

A. No.

Q. Now, counsel asked you some questions regarding Rudge; is that right?

A. Yes.

Q. And I believe you testified that the Rudge article was published in 2005; is that right?

A. Yes.

Q. Did Dr. Trout dispute the priority date of the Rudge reference in his responsive report?

A. I don't recall that he did.

Q. Now, counsel asked you some questions regarding the Lam reference as well, right?

A. Yes.

Q. Now, by at least 2005 what is it that the Lam reference reported with regard to stable liquid formulations?

A. That antibodies were stable for two years at 5 degrees centigrade.

Q. Okay.

And if we could call up DTX 3556, the Lam reference, at page 31. Specifically on the left side, I'd like to go to Column 7, lines 53 through 58, paragraph starting "the term 'antibody.'"

Now, Dr. Rabinow, we're at DTX 3556, page 31. Does the Lam reference define the term "antibody"?

A. It says what it includes.

Q. Does it indicate that the term "antibody" in the Lam patent is being used in its broadest sense?

A. Pretty much so, I would guess, yeah.

Q. Now, are you also using the term "antibody" in its

broadest sense today?

A. Yes.

Q. And you've testified that antibodies are like fusion proteins, right?

A. Yes.

Q. Is it your testimony that the formulation disclosures in the prior art for antibodies are relevant to formulations of aflibercept?

A. Yes.

Q. Earlier today I think counsel asked you if you consulted with any ophthalmologists. Do you remember that?

A. Yes.

Q. Now, did -- the asserted claims of the '865 patent are formulation claims, right?

A. That's correct.

Q. Are there any specific ophthalmology limitations in the '865 patent?

A. No.

Q. So in your view was it necessary to consult an ophthalmologist?

A. No.

Q. And do you understand with regard to isotonicity that iso-osmotic has the same meaning as isotonicity?

A. Yes.

Q. I'd like to briefly look at the Saishin reference,

which we can pull up on DDX 4, Slide 58.

Dr. Rabinow, these are a few passages from Saishin that you relied upon in your direct examination, correct?

A. Yes.

Q. And counsel asked them about you on cross -- or asked you about them on cross?

A. Yes.

Q. And this is DTX 2751, page 7, right?

A. Yes.

Q. Now, you relied on the phrase in the first box; is that correct?

A. Yes.

Q. Could you please read the -- read into the record the statement on the first box of DTX 2751, page 7.

A. "These data suggest that VEGF Trap R1R2 deserves consideration as a potential treatment for two complications of diabetic retinopathy, retinal neovascularization, and macular edema."

Q. Now, diabetic retinopathy, is that a disease of the eye?

A. Yes.

Q. What about retinal neovascularization?

A. Yes.

Q. And macular edema?

A. Yes.

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Q. And Saishin discusses intravitreal administration, as I believe you testified, right?

A. Yes.

Q. So what would the person of ordinary skill in the art reading Saishin, and specifically the disclosures that we just discussed, understand regarding the use of an intravitreal injection with VEGF Trap R1R2?

A. Strong recommendation for continued development with a promise of success -- or an expectation of success, shall I say.

Q. Do you recall counsel's questions regarding Genentech, Dr. Rabinow?

A. There was a lot of discussion about Genentech. I'm not sure which ones you're referring to.

Q. Well, how about when counsel asked you if Genentech was perhaps the most successful biotech company in history?

A. Yes, I recall that.

Q. Have we looked at a number of disclosures from Genentech today?

A. Yes.

Q. And those -- what sort of scientific area were those disclosures in?

A. They were in the formulation development area.

Q. And there were a multitude of them, right?

A. Yes.

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Q. And counsel on redirect even asked you about a Lasker Award winner that works at Genentech; is that right?
A. Yes.
Q. So the person of ordinary skill in the art in June 16th of 2006, is it your opinion that they would be interested in reviewing formulation disclosures from Genentech?
A. Yes.
Q. Now, the '865 patent claims, I believe we've discussed that they're formulation claims, right?
A. Yes.
Q. Do the '865 patent claims have anything to do with the anatomy of the human retina?
A. No.
Q. Do the '865 patent claims have anything to do with retinal kinetics?
A. No.
Q. Do the '865 patent claims have anything to do with transport of molecules across retinal membranes?
A. No.
Q. And does one need to be an expert in the physical barriers between the vitreous and retina to understand the '865 patent claims?
A. No.
Q. Now, Dr. Rabinow, on your direct examination do you recall discussing Dr. Trout's objective evidence opinions?

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A. Yes.
Q. Specifically safety and efficacy?
A. I recall some things. I'm not sure exactly what things you're referring to.
Q. Okay.
Mr. Gibson, could we have Slide 119, please.
I will be very quick, Doctor. I think there may have been something unclear in the record. I'd like to clear it up.
MR. TRASK: For the record, Your Honor, outside the scope of the cross. I never covered this publication or this slide during the cross-examination.
THE COURT: Go ahead, Counsel.
MR. HUNT: I apologize, Your Honor. I do believe that the Thomas publication was covered during cross; but, regardless, this will be very short. I'm just trying to clarify --
THE COURT: I believe it was. Go ahead. Overruled.
MR. HUNT: Thank you.
BY MR. HUNT:
Q. Is it your opinion that Eylea's safety and efficacy is related to the aflibercept molecule?
A. Yes.
Q. And not to the formulation; is that right?
A. That's correct.
Q. And is it correct that the aflibercept molecule's

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properties provide Eylea's safety and efficacy?

A. Yes.

Q. Now, I just have a couple more questions, Dr. Rabinow.

Do you recall counsel's questions regarding the Liu reference?

A. Yes.

Q. There's disclosure of stability data in Liu, right?

A. Yes.

Q. And Liu -- what company was Liu working for?

A. Genentech.

Q. And I believe we discussed the concentrations in Liu; is that right?

A. Yes.

Q. Is there a concentration range disclosed by the Liu reference?

A. It was 40 to 150 mg/mL.

Q. Do you consider those to be high concentration?

A. I do.

Q. So the Liu reference disclosed high-concentration protein formulations and stability data relating thereto, right?

A. That's correct.

MR. HUNT: With that, Your Honor, I have no further redirect questions. I do have some exhibits I'd like to move

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in when we're done.

THE COURT: No. Understood. I know we've got a couple of exhibit issues to cover. We'll do that after any recross.

MR. TRASK: Very briefly, Your Honor. That's a promise.

THE COURT: One which shall be enforced.

MR. TRASK: Understood, Your Honor.

THE COURT: Just kidding. Go ahead.

RECROSS-EXAMINATION

BY MR. TRASK:

Q. Doctor, do you recall counsel just asked you whether there are any specific ophthalmology limitations in the '865 patent?

A. Yes.

Q. You answered no, correct?

A. Correct.

Q. You know that Claim 1 of the '865 patent refers to intravitreal administration, right?

A. Yes, yes. That's correct.

Q. You were mistaken when you answered that question?

A. I was mistaken.

MR. TRASK: No further questions, Your Honor.

THE COURT: Thank you.

Any reredirect?

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MR. HUNT: No, Your Honor. Just the aforementioned exhibits.

THE COURT: Understood. Let me scratch off my list first. I -- I believe it was on cross there was a reference to PTX 1526 and it should actually be PTX 576.

MR. TRASK: You anticipated exactly the correction I was going to make, Your Honor.

THE COURT: Okay. All right. Well, we'll note that correction in the record. With that, Counsel, go right ahead. And I won't take credit for it. Madam Clerk and Madam Law Clerk of course get them all.

Counsel, go right ahead with the exhibit list, slowly, please.

MR. HUNT: Yes, Your Honor.

Defendants move into evidence DTX 0013, DTX 0726, DTX 0728, DTX 0729, DTX 0730, DTX 2264, DTX 2265, DTX 2751, DTX 3040, DTX 3492, DTX 3506, DTX 3510, DTX 3549, DTX 3556, DTX 3588, DTX 3592, DTX 3610, DTX 3611, DTX 3619, DTX 4041, DTX 5036, DTX 5037, DTX 5038, and, finally, DTX 5040.

THE COURT: Thank you, Counsel.

Any objection to any of those?

MR. TRASK: Could I have just a brief moment to confer?

THE COURT: Certainly.

MR. TRASK: No objection, Your Honor.

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THE COURT: Without objection, each of those exhibits are hereby deemed admitted.

(DTX 0013, DTX 0726, DTX 0728, DTX 0729, DTX 0730, DTX 2264, DTX 2265, DTX 2751, DTX 3040, DTX 3492, DTX 3506, DTX 3510, DTX 3549, DTX 3556, DTX 3588, DTX 3592, DTX 3610, DTX 3611, DTX 3619, DTX 4041, DTX 5036, DTX 5037, DTX 5038 and DTX 5040 were admitted.)

MR. HUNT: Thank you, Your Honor.

THE COURT: Thank you, Counsel.

MR. TRASK: Your Honor, I just have two cross exhibits to admit, PTX 3344, PTX 3346.

THE COURT: Any objection to those?

MR. HUNT: Your Honor, these were not previously disclosed to us; so we certainly reserve the right to object to these as new exhibits not previously disclosed. And we will endeavor to do so in an expeditious fashion.

THE COURT: Understood. Those were used as impeachment, correct, Counsel?

MR. TRASK: That's right, Your Honor.

THE COURT: Consistent with this Court's prior rulings, objection noted but overruled. Those exhibits will be deemed admitted.

(PTX 3344 and PTX 3346 were was admitted.)

THE COURT: And then we fixed the numbering on the --

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is it Ghate? Am I pronouncing that correctly?

Any other exhibits that require the good doctor to remain in that chair?

MR. HUNT: No, Your Honor.

THE COURT: All right.

Doctor, thank you so much, sir. You can step down. Thank you.

How long is Ms. Chu's deposition?

MS. MAZZOCHI: Sadly, Your Honor, it is more than an hour.

THE COURT: All right, then. That feels like a week to me. My fingers crossed for a different number, Counsel, but I understand.

MS. MAZZOCHI: Your Honor, maybe if we take the weekend we'll go back and look at it with a fine-tooth comb and see if we can shave a few minutes off.

THE COURT: Always appreciated. We'll call it a day in terms of evidence presentation in a week.

Let me ask this question: With a slight change in the Court's children's summer camp and activities schedule, any objections if we start at 9:00 a.m. next week as opposed to 9:30?

MS. MAZZOCHI: None from us.

MR. BERL: None, Your Honor.

THE COURT: Okay. We'll start at 9:00, then, next

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week. My youngest has volleyball camp up the road that starts early; so I'll be here certainly by then. So we'll start at 9:00. Monday, of course, is a federal holiday; so we begin on Tuesday.

Let me ask this question, just as sort of a planning and preview. Where do we stand in terms of remaining witnesses from Mylan during this phase?

MS. MAZZOCHI: Yes, Your Honor. Our next two live witnesses will be Dr. Jay Stewart as well as Dr. MacMichael. We do not have any reason today to doubt why they can't be both up and down, I would hope, on Tuesday. I will say we have been hoping that we could get Dr. Stewart on the stand today. We did not anticipate so much time on -- from Regeneron on their cross today. But that would be our goal, and then we have the Chu deposition.

THE COURT: Would that be the last witness in this phase from the defense?

MS. MAZZOCHI: Right. Then, again, our last live witness in terms of rebutting their commercial success witness will be Mr. Hofmann. Then the only issue is going to be -- I don't think we'll have to bring anybody back; but, again, if they bring in something new that one of our experts didn't have the ability to rebut, but that would be something we would think quick, like, 10, 15 minutes, I would hope.

THE COURT: Understood. Okay.

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MS. MAZZOCHI: But I will say this, though, Your Honor. I am very concerned because we've been trying to be pretty judicious with the use of our time. So while we believe we are on track in terms of what we've planned out for our case in chief and response and planning for crosses with Regeneron, we're very concerned that Regeneron is over their time. So I just wanted to make sure we're clear we're going to continue to get an even split of the anticipated time.

THE COURT: Y'all are keeping your own clock. So y'all keep track of that. You came to an agreement. Surely someone here is charged with keeping track.

MS. MAZZOCHI: Oh, yes. More than one.

THE COURT: I assumed that someone here had that responsibility. You may turn out to be the MVP. Congratulations.

MS. MAZZOCHI: Thank you, Your Honor.

THE COURT: Thank you.

In terms of remaining lineup that plaintiff would anticipate calling at this juncture.

MR. BERL: Yes. After defendants rest, Your Honor, we'll then call one fact witness with respect to the method of treatment family. That's Ms. Chu. One expert witness on that, Dr. Csaky, as well as, on the formulation side, we have one inventor, Dr. Graham, as well as Dr. Trout to come back and address invalidity of the '865 patent. And we have one

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commercial success expert, Dr. Manning.

THE COURT: I'm sorry. Doctor who?

MR. BERL: Manning.

THE COURT: Understood.

MR. BERL: We anticipate that we should be able to finish. I think we're obviously a little behind of where we thought we would be, but we think we should be able to finish next week perfectly fine just as planned.

THE COURT: Any time sooner than Friday would be --

MR. BERL: That, I won't promise.

THE COURT: Okay. All right. And then witness Hofmann might be the backstop after; is that correct?

MS. MAZZOCHI: That's correct, Your Honor. I suspect that after Dr. Manning goes, then it will be Dr. Hofmann's turn. Thank you.

THE COURT: All right. Okay. Anything else we need to take up at this juncture from plaintiff's perspective?

MR. BERL: Not from Regeneron, Your Honor.

THE COURT: Defense?

MR. HUNT: No, Your Honor.

THE COURT: All right. Great. Feel free to leave whatever you'd like in the courtroom. No one will be in here in the interim. So I'll leave it at that.

We'll be ready to roll on Tuesday morning at 9:00.

Happy Father's Day, all those who observe and

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celebrate. Have a wonderful weekend. We'll see everybody Tuesday morning.

(Proceedings concluded at 5:08 p.m.)

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CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 16, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 16th day of June 2023.

/s/Cindy L. Knecht

_____

Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 6

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 20, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

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(Video deposition of Karen Chu)

Tuesday Morning Session,

June 20, 2023, 9:00 a.m.

- - -

THE COURT: We convene for day one, week two, of trial. Good morning, Counsel. Happy West Virginia Day to everybody.

Mylan may call its next witness.

MS. BODA: Good morning, Your Honor. Katie Boda.

Defendants' next witness will be Karen Chu by video deposition. Regeneron identified Ms. Chu in response to our 30(b)(6) topics identified in DTX 202, including conception and reduction to practice, the patent examples, and several issues relating to aflibercept development and associated clinical trials.

THE COURT: I'll note again Regeneron's objection to playing of the video in its entirety. Objection noted.

(Video deposition of Karen Chu.)

Q. Thank you. Good morning, Ms. Chu. My name is Deanne Mazzochi. Can you please state your full name and address for the record.

A. Yes. Karen Chu, and my home address is 73 Richbell Road, White Plains, New York 10605.

Q. And then what was your initial role and responsibilities at Regeneron?

A. So when I joined the company, I joined as a senior

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clinical trial manager. And then as is true, I think, for a lot of small companies in that role, wore several different hats and had a broad range of responsibilities as it related to clinical development. And over the years moved into more of a clinical project management role, and then finally into my current role.

Q. Okay. And what -- was your initial title -- I think it was -- what was it? -- director of therapeutic area project management?

A. So that was not my first title at Regeneron.

Q. Okay. What was your first title?

A. I believe -- my recollection is that my first title was senior clinical trial manager. But the director of therapeutic area project management was promotion into a broader clinical project management role.

Q. And then did you ever have any individuals who reported to you in those roles?

A. At the time that I was a clinical trial manager I had a group of people that reported to me who -- who were more junior clinical trial managers and involved in the operations of the clinical trials.

Q. Okay. How do you differentiate what your role was versus what you call the operation of the clinical trials?

A. So within clinical research, there are several people that contribute to any aspect of conducting a clinical trial.

So the actual operations of the clinical trial, which includes everything from ensuring that clinical study sites are identified and trained appropriately to providing supplies for the clinical study sites to deciding which laboratories to use or how labs will be collected, that typically is considered part of the operations role. So they're -- really, that -- you know, they really oversee the actual execution of the clinical trials.

Q. Let's focus on VEGF Trap. And if I call VEGF Trap aflibercept, is that all right as well?

A. That is all right. I understand it to be the same molecule.

So I can confirm that the document says "Plaintiff's Rule 26(a) Initial Disclosures."

Q. Again, I'm trying to just get at what are identified as alleged inventions in Defendants' Exhibit 4, the '601 patent. You said that in your role you participated in the design of the studies, for example.

Can you tell me anything that you recall about anything inventive or unique or new or different about those particular trials that relate to the inventions set forth in the '601 patent?

A. Certainly with every new molecule, the properties of the molecule as well as considerations around its clinical use go into the design of any trial. And Eylea represented a new

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anti-VEGF treatment that we felt had real potential advantages and designed the trials in a way that we felt we could demonstrate those unique properties to the best extent possible.

Q. And is it fair to say that your clinical trials were designed to try to optimize or maximize the chance of success?

A. So I think it's true that in clinical development you're always trying to maximize your chances of success.

Q. Would Regeneron have followed or pursued a clinical trial that it thought was going to fail?

A. So there's always a risk of failure. Clearly, you know, the -- especially for Phase III trials, there is a statistical threshold that you must meet. And there's always a chance that you would not meet that for various reasons.

So I don't think it's true that Regeneron would not have pursued a trial that had a chance of failure.

Q. Yeah. Maybe we can phrase it this way: Is it fair to say that, in your time at Regeneron, if Regeneron was going to pursue a clinical trial, they believed they would be able to meet that -- the clinical end points they put in place? They wouldn't have spent the money on a clinical trial if they didn't?

A. So, again, every clinical trial, you know, we try to design it for success. But there's always a risk that a clinical trial would fail for one reason or another, whether

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that's safety or efficacy.

Q. When it comes to aflibercept, were there any clinical trials you designed that led to failure as opposed to success with regard to the ophthalmology category?

A. Can I ask for some limitations on the extent of my answer? Is there a time frame that we're referring to?

Q. Sure. Let's say 2006 forward.

A. So, actually, most recently Regeneron has reported two clinical trials with aflibercept that did not meet their primary end point.

Q. And which were those?

A. Those are trials in the treatment of retinopathy of prematurity.

Q. And what was the dosing regimen for those?

A. It's .4 milligrams either unilaterally or bilaterally for up to three monthly doses.

Q. When you say "for up to three monthly doses," you mean with three monthly doses or doses separated by three months between them?

A. Sorry. In retinopathy of prematurity, physicians treat initially with a single dose. If that does not regress the retinopathy of prematurity sufficiently, they can give a second dose a month later and a third dose a month later with similar considerations.

Q. So besides this particular study that Regeneron

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conducted for the -- at the request of the FDA for pediatric patients, are there any other studies that Regeneron has pursued for aflibercept in the eye that have failed to meet their clinical end points?

A. Not that I am aware of.

Q. All right. Ms. Chu, can you just confirm you have a document before you marked DX 202 that is marked "Karen Chu 30(b)(6) Deposition Topics"?

A. Yes, the title of the document is "Karen Chu 30(b)(6) Deposition Topics."

Q. Right. But who was the individual who ultimately came up with the idea of dosing 2 milligrams approximately every four weeks for the first three months and then the 2-milligram dose approximately once every eight weeks, or once every two months, thereafter?

A. So, again, Regeneron operates in a -- you know, cross-functional team environment; so there was input given by many different functions and many different people. But George Yancopoulos and Len Schleifer were definitely heavily involved in these discussions, and any approval would have needed to have been given by George to move ahead with the study design.

Q. Right. I understand they had to give approval, but who actually came up with the idea of this particular regimen, in Regeneron's view?

A. I don't recall.

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Q. All right. So, Ms. Chu, when it comes to Regeneron's position with regard to the '601 patent, does Regeneron have a position as to who was responsible for the conception of the full claims set forth in Claim 1 of the '601 patent?

A. George Yancopoulos is the named inventor on the '601 patent.

Q. And why does Regeneron believe that George Yancopoulos is the person who conceived of the methods set forth in Claim 1 of the '601 patent?

A. George has always and continues to play a very hands-on role in all research and development, including the development of aflibercept. And he was personally involved in many, many discussions related to the development of aflibercept across all phases of clinical trials, including the design of the Phase III studies.

Q. Okay. So is it Regeneron's position that the reason -- that the reason for George Yancopoulos being the named inventor is because he's the one who did the sign-off on the Phase III clinical design study -- sorry -- Phase III clinical study design?

A. So my knowledge is that George had tremendous input. And ultimately it was his decision to move forward with the final study design for the VIEW 1 and the VIEW 2 studies.

Q. Are there any documents that showed that it was George Yancopoulos, as opposed to someone else, who

specifically put together the 2-milligrams every four weeks for the first six months followed by 2 milligrams once every eight weeks, or every two months thereafter?

A. Off the top of my head, I don't recall specific documents.

Q. Did you try to reach out to Dr. Cedarbaum to prepare as a 30(b)(6) witness?

A. I did not reach out to Dr. Cedarbaum in preparation for this deposition.

Q. What about Mr. Ingerman, Avner Ingerman?

A. Right. Avner Ingerman.

Q. Avner Ingerman, right. Wasn't he also one of the individuals who was in favor of the eight-week interval?

A. My recollection of Dr. Ingerman's position at that time is that he was lobbying for an as-needed or prn dosing regimen, although he was part of many discussions about alternative dosing regimens that could be employed.

Q. Such as?

A. Such as every eight weeks or other potential dosing regimens.

Q. And what within the visual acuity data prompted shortening the interval from 12 weeks to eight?

A. So within the visual acuity data, even though visual acuity is a highly variable measure and this was a relatively small study in that there were about 30 patients per group, we

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looked for trends to inform us of what's happening. And my recollection is that the most important aspect of the visual acuity was that the groups that were dosed with monthly injections first overall had a greater gain in visual acuity.

Secondly, that when those patients were allowed to go longer than four weeks without a dose, we saw some decline in visual acuity over that period.

Q. Okay. And was the period a 12-week period, an eight-week period, or was it a prn period?

A. So in this study, after Week 12, patients were dosed prn. So the duration between that Week 12 dose and subsequent doses was variable.

Q. Okay. Well, why go with eight weeks as opposed to six weeks or just sticking with monthly?

A. So we did include two monthly dosing groups in the VIEW 1 and the VIEW 2 study. We tested two separate doses, .5 milligrams and 2 milligrams. As I mentioned before, there were many considerations that went into the study design. And some of those considerations have to do with the constraints of a study conduct.

So one aspect of these studies is we must conduct them as what we call double-masked studies. And we perform sham injections at visits where patients are not receiving an active injection. And it was impractical to include a group where we had a six-week dosing interval because it would have

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necessitated visits essentially every two weeks for all patients.

Q. Okay. So the every eight weeks just made the clinical trial design easier in terms of maintaining the mask?

A. It was both a dosing interval that we felt was supported by the data and also created a more practical way to conduct the study.

Q. Now, in the '601 patent, Claim 10, we have the same dosing regimen, but this time it's for a method of treating diabetic macular edema in a patient in need thereof.

Who was the one -- what is Regeneron's position as to who was the person who actually came up with the idea of applying this regimen to the DME indication?

A. So this regimen is different in that it is for 2 milligrams given every four weeks for the first five injections followed by approximately once every eight weeks, or every two months.

And my recollection is that, again, there were several discussions about the optimal study design for treating diabetic macular edema. And those conversations would have included both people from the clinical team as well as senior management.

Q. Right. Who decided that the dosing was going to be for the first five injections as opposed to three or four?

A. My recollection is that George Yancopoulos made that

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decision.

Q. Is that documented anywhere?

A. I don't recall if there is specific documentation of that.

Q. If you can take a look at the '601 patent, is the clinical trial protocol for the Phase III VIVID or VISTA studies set forth in any of the patent examples?

A. To answer that question, I would have to go through the entire patent. Is that something I should do?

Q. Sure. You can start with Example 1, which begins at Column 8.

A. So in my review of the Patent '601, I do not see a description -- or the VIVID and VISTA trials given as an example, but I do see the Phase II clinical trial in diabetic macular edema described as Example 5.

Q. And if I understand you, it was the data from this Phase II study that justified the dosing regimen for the VIVID and VISTA studies for diabetic retinopathy?

A. So data from this Phase II study did inform decisions regarding the VIVID and VISTA study designs.

Q. And why is it that Regeneron believed that the DME data could be transferred over to the diabetic retinopathy indication?

A. So as I mentioned, data from the VIVID and VISTA studies included a secondary end point of a proportion of

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patients with two or more step improvement in diabetic retinopathy. Patients with diabetic macular edema do have underlying diabetic retinopathy at various severities. And we did see a statistically significant outcome of improvement in patients that were treated with aflibercept in the VIVID and VISTA studies -- oh, I'm sorry -- in the -- yes, in the VIVID and VISTA studies. Sorry.

Q. Let me know when you have that exhibit before you.

A. I have Exhibit 204 in front of me.

Q. Okay. I'd like to take a look at Claim 6 of the '601 patent.

A. Okay. I see that.

Q. And -- yeah. So here again, I just have a question. What can be done to the dosing regimen in Claim 1 to ensure that a patient is going to be able to meet these requirements of Claim 5 and Claim 6 and -- specifically using this measurement technique that's set forth in Claim 6?

A. So I would respond the same way, that the response to treatment is highly variable with individual patients.

Q. Okay. So how are we going to know, then, if an individual patient actually meets the standard?

A. So in the treatment and monitoring of an individual patient with neovascular age-related macular degeneration, visual acuity would be assessed prior to treatment initiation and at an interval deemed appropriate by the treating physician

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during the course of treatment.

Q. Ms. Chu, can you take a look at DX 205 and confirm that it is the FDA-approved Eylea labeling?

A. So I have Exhibit 205 in front of me, and it appears -- this appears to be the Eylea USPI revised as of May 2019.

Q. Well, are you aware of any change to the formulation description that appears here as compared to when the Eylea product was first approved in 2011?

A. In my experience and knowledge, I am not aware of any changes to the formulation as described here in the USPI.

Q. And then we've got George Yancopoulos, who is listed, at least on this org chart, as the CSO. Is he still the CSO today or does he have a better title?

A. My understanding is he still has the title chief scientific officer.

Q. Okay. Anything, though, that would justify having the longer dosing interval that you recall?

A. So I can't remember if this was specifically in Neil's purview, but we did know that, based on the aflibercept molecule comparing to Lucentis, that it did have a longer half-life in the eye of animals. And so that gave us an indication that potentially a longer dosing interval might be possible. But certainly animal studies are only somewhat translatable to human studies.

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Q. Okay. And then from Regeneron's perspective, which clinical trial was it that allowed you to conclude that aflibercept might have a longer half-life in the human eye that might justify a longer dosing interval?

A. So we -- during the course of Eylea clinical development, we did not measure half-life in the human eye. That would have required sampling from ocular fluids, which, to do serially in patients, is very difficult and causes additional safety risk for patients. So the data from the 0508, or CLEAR-IT 2, study was really the clinical data that we looked at in order to decide which dosing regimens to test in Phase III.

Q. Okay. Can you confirm that Exhibit 207 is a Friday, January 30th, 2004, email from Jesse Cedarbaum to you and others involving what was described as draft VEGF Trap AMD press and some thoughts for release on the start of an AMD trial?

A. I see that the email is dated Friday, January 30th, 2004, and that I am one of the recipients of the email.

Q. Was it common for Regeneron to prepare press releases when they were about to start clinical trials?

A. Regeneron was a small company back then; so the initiation of a clinical development program would have been something that we would have disclosed.

Q. Do you have Exhibit 209 in front of you?

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A. Yes, I have Exhibit 209 in front of me.

Q. All right. Can you confirm that the top email was copied to you and others on Tuesday, August 31st, 2004?

A. Yes. I am on the cc line of this email dated -- just to say dated August 31st, 2004.

Q. Macugen was dosing its product intravitreally, correct?

A. That is correct.

Q. Did these results cause Regeneron to start thinking more closely about doing an intravitreal injection?

A. I believe that the results from the Macugen trials gave us more information about the safety and feasibility of intravitreal injections given regularly to these -- to the -- to AMD patients over the course of a year of treatment.

Q. Did the Macugen results give you any sense that there might be more willingness in the marketplace to accept an intravitreal injection?

A. The Macugen results from these Phase III studies definitely supported that intravitreal administration of a product in wet AMD patients was possible.

Q. All right. And at this time it was known to Regeneron that ranibizumab was also out there in Phase III trials, right?

A. Yes. The Lucentis trials were being conducted concurrently at this time.

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Q. And it also mentions at the end of the paragraph that Regeneron's VEGF Trap was also currently in clinical and preclinical trials, right?

A. Yes. The last sentence is "Other antiangiogenic agents currently in clinical and preclinical trials are Angstrom's A6, OXiGENE's CA4P, and Regeneron's VEGF Trap."

Q. At this point in time, were you looking at the Lucentis dosing regimen as one that you might want to copy or emulate?

A. I would say at this time we were monitoring the Lucentis clinical development program closely from a competitive intelligence perspective.

Q. Right. And certainly by the time we got to the 2010 time frame, at the time when you had submitted your Phase III clinical trials, ranibizumab had been shown to produce some consistent vision gain, right, when injected intravitreally?

A. So the pivotal Lucentis trials in neovascular AMD were the ANCHOR and MARINA trials. And they demonstrated vision gain with ranibizumab dosed every four weeks, or monthly, for the -- for a year. So Week 52 was their primary end point.

Q. Do you have that exhibit before you?

A. Yes, I have Exhibit 210.

Q. Okay. Can you confirm that Exhibit 210 contains an email string including an email from Ilham Zoughi, Z-O-U-G-H-I,

to you and others dated March 3rd, 2005?

A. Yes, I see that I am a recipient of this email from Ilham Zoughi.

Q. If you look at the bottom line, the author there said -- "We've been" -- the study clinician was quoted as saying, "We've been injecting anti-VEGF drugs into the eye for the past three years with very encouraging results."

Do you see that?

A. I do see that as part of the quote here.

Q. Right. And that quote is attributed to Philip J. Rosenfeld, MD, PhD?

A. So this email just said Rosenfeld, which I assume to mean Phil Rosenfeld.

Q. Right. Now, did Regeneron also reach out to get input from Phil Rosenfeld in the context of this clinical trial work?

A. Dr. Rosenfeld was a respected key opinion leader in the retina community, and he is someone that we interacted with occasionally to discuss aspects of the clinical development program.

Q. Do you recall there being any impact within Regeneron when it was reported that Avastin, a VEGF inhibitor, was producing positive results in the eye?

A. I don't remember this study or the data from this study having a specific impact at Regeneron.

Q. All right. But what about Avastin generally, the experience that clinicians were having with Avastin injecting it into the eye to get -- to stop vision loss?

A. So this press release is referring to systemic administration of Avastin.

Q. Right.

A. But Dr. Rosenfeld was involved in running his own investigator-initiated studies with intravitreal Avastin.

Q. Right. Right. And he indicates, in this document at least, that he had been doing that for at least three years?

A. That is what the document says.

Q. Right. So did the fact that someone like Dr. Rosenfeld and others were injecting Avastin directly into the eye, did that influence their thinking as to whether it would be useful to dose VEGF Trap into the eye?

A. Dr. Rosenfeld, as well as other retina specialists in the community, provided information that gave Regeneron more confidence regarding the feasibility of moving forward with an intravitreally delivered product.

Q. Okay.

A. So the study in Example 1 was referred to as the CLEAR-IT 1 study; the study in Example 2 was the CLEAR-IT 2 study.

Q. Okay. Perfect. Thank you.

And then if we go on to the next column, Example 4,

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the Phase III clinical trials, was that the VIEW 1 study or VIEW 2?

A. So this section under Example 4 refers to two parallel Phase III clinical trials carried out to investigate the use of VEGF-T to treat patients with neovascular -- with the neovascular form of age-related macular degeneration. So this section appears to be referring to both the VIEW 1 and the VIEW 2 studies.

Q. Okay. And then if you can jump forward to Column 14, there is an Example 5 provided there. Did that clinical study also have a name?

A. Example 5 is the Phase II clinical trial of VEGF-T in subjects with diabetic macular edema. This study was referred to as the DA VINCI trial.

Q. Okay. And then Example 6, did that clinical trial have a name?

A. So in Example 6, it's referring to a randomized multicenter double-masked trial in treatment-naive patients with macular edema secondary to CRVO. And I believe this is referring to a study that we called the COPERNICUS study, although there was a second CRVO trial conducted called the GALILEO study.

Q. Can you confirm that this is a document, an email string with the first one dated Sunday, January 8th, 2006, regarding an AMD expert meeting, from Neil Stahl to Jesse

Cedarbaum, you, and others?

A. I can confirm that the date of this email is Sunday, January 8th, 2006, the subject is regarding AMD expert meeting, it's from Neil Stahl, and I am one of the recipients of this email.

Q. One of the other questions to ask these experts was do they think that the PIER regimen of Lucentis will work?

Do you see that?

A. I do see that question.

Q. What was your understanding of PIER regimen for Lucentis?

A. So the PIER study was an investigator-initiated study conducted by Dr. Phil Rosenfeld that -- my understanding of that regimen is that it was three initial monthly doses of .5 milligrams of Lucentis followed by quarterly dosing; so every-three-month dosing.

Q. Let me know when you have that.

Are you identified as one of the individuals who participated in this advisory panel meeting?

A. Just give me a second to review this.

Okay. So I am listed as one of the Regeneron attendees for this meeting.

Q. And one of the items listed here that Regeneron wanted to get the consultant's impressions of was how will Lucentis be used in practice: Monthly as in ANCHOR and MARINA,

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induction followed by quarterly maintenance as in PIER, or induction followed by PIER and criteria-based dosing as in SAILOR.

Do you see that?

A. I do see that under 3A.

Q. Now, the title of this was "CLEAR-IT 3 Advisory Panel Meeting."

What was CLEAR-IT 3?

A. My recollection is that CLEAR-IT 3 was the initial name that Dr. Cedarbaum wanted to give the Phase III AMD studies.

Q. Okay. So CLEAR-IT 3 eventually became known as the VIEW 1 and VIEW 2 studies?

A. The Phase III studies were eventually named VIEW 1 and VIEW 2, yes.

Q. Can you confirm it's dated Friday, February 10th, 2006, from Srilatha Vuthoori to you and many others at Regeneron?

A. This email is dated Friday, February 10th, 2006. The subject is "Actions and decisions VGT team meeting." And it's from Sri Vuthoori, and I'm one of the recipients.

Q. Okay. Let me give you a document that has production numbers NYLAFL8703 through 8711, which I will mark as DX215.

A. Okay. I have Exhibit 215 in front of me.

Q. Okay. And do you see it says citation in the upper

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left-hand corner it says, "WHO drug information Volume 20, Number 2, 2006"?

A. I see that the document is labeled in the upper right-hand corner "WHO Drug Information Volume 20, Number 2, 2006."

Q. And then this was titled "International Nonproprietary Names for Pharmaceutical Substances."

A. I see the document is titled "International Nonproprietary Names for Pharmaceutical Substances."

Q. All right. Can you go ahead and turn to page 8706 as the Bates number. It's page 118 within this volume. And do you see a reference on this page to aflibercept?

A. Yes, I see on the second half of the page there is a reference to aflibercept.

Q. In the context of your clinical work, did you ever use the term "aflibercept" to refer to any chemical structure other than VEGF Trap-Eye?

A. So the terms VEGF Trap, VGFT, VEGF Trap-Eye, and aflibercept, depending on the time period, were used somewhat synonymously. VEGF Trap-Eye was almost always used to distinguish between the systemic formulation of aflibercept versus the intravitreal formulation.

Q. Right. But the underlying structure of aflibercept, the molecule, didn't change whether it was VEGF Trap-Eye or VEGF Trap or aflibercept; is that fair?

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A. It is my understanding that the active ingredient was the same in VEGF Trap-Eye and aflibercept whether that was referring to the oncology product or the intravitreally delivered product.

Q. I would like to mark as Defendant's Exhibit 218 a document with production numbers RGN-EYLEA-MYLAN-553211 through 212.

And can you confirm this is a May 9th, 2006, email from Jesse Cedarbaum to you and others discussing Rosenfeld's Lucentis PrONTO press release?

A. This is an email dated Tuesday, May 9th, 2006, with the subject "Rosenfeld's Lucentis PrONTO press release" from Jesse Cedarbaum, and I am listed as one of the recipients.

Q. Okay. Now, according to this press release, it says, "Open label on controlled study of Lucentis showed improvement in vision with five to six doses at one year."

Do you see that?

A. I see that the title is "Open label on controlled study of Lucentis showed improvement in vision with five to six doses at one year."

Q. Do you recall whether anybody ever talked about a dosing regimen that you thought might be superior to the FDA-approved regimen for Lucentis?

A. We had -- we thought it was possible that aflibercept could be superior to ranibizumab. And the design of the

Phase III clinical trials was such that we did include a 2-milligram every-four-week dosing group as well as a .5-milligram every-four-week dosing group with the ability, if we met noninferiority in those groups, to then be able to test for superiority.

I should just clarify that that would have been true for all of the groups, including the third treatment group, which was three initial monthly doses followed by a dosing every eight weeks.

Q. During your time at Regeneron, has Regeneron identified any head-to-head dosing regimen where it believes aflibercept can demonstrate superiority to Lucentis in a manner that the FDA or clinicians would accept?

A. In the protocol T study, which was a study conducted by the Diabetic Retinopathy Clinical Research Network, with aflibercept, ranibizumab, and bevacizumab dosed in the same paradigm, which was a different paradigm than Regeneron has tested in our trials, aflibercept was superior to both ranibizumab and bevacizumab.

Q. Okay. And that particular dosing regimen of aflibercept you just mentioned that was shown to be superior to Lucentis, is that an FDA-approved dosing regimen or not?

A. That dosing regimen is not specifically reflected in our labeling.

Q. Do you remember generally what was -- what they were

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doing in that one in terms of did it deviate from monthly dosing? was it number of injections?

A. My recollection is that it was monthly dosing for a certain number of doses and then criteria-based dosing based on the protocol --

Q. Okay.

A. -- which allowed for a longer treatment interval.

Q. And can you confirm this is an email from Michael Roosevelt to you, among others, dated Tuesday, May 9th, 2006?

A. Okay. I have Exhibit 219, and the date of the email is Tuesday, May 9th, 2006, with the subject "Action Items - May 9th, 2006," from Michael Roosevelt, and I am one of the recipients of this email.

Q. Then we've got the 0508 study, and that was one of the DME studies?

A. 0508 was the Phase II study in wet AMD with intravitreal aflibercept.

Q. And what was the name of that trial?

A. We referred to that as the CLEAR-IT 2 trial.

Q. Do you recall any concerns expressed internally at Regeneron about aflibercept's ability to achieve any efficacy end points by the 12-week -- with a 12 weeks' high dosing interval?

A. Are you referring to during the ongoing study?

Q. Yeah, either while the study was conducted or

afterwards.

A. So once we had -- so this email is referring to a time when the studies were ongoing. Once we received data from the studies and analyzed it, we did have some concerns that, based on the OCT data and an assessment of the visual acuity data, that the 12-week interval was one where we were seeing some loss of efficacy over that duration.

Q. And how were you defining loss of efficacy?

A. So, primarily, we were looking at the central retinal lesion thickness measured by optical coherence tomography, which was a very quantitative measure of the fluid in the retina. And one aspect of that data is that we would see a rapid reduction in retinal fluid after dosing with aflibercept, and over the longer time period without treatment, we would see some of that fluid begin to reaccumulate.

Q. And on this one I'd like to start with the email at the end of the chain from George Yancopoulos to you and others dated Tuesday, May 16th, 2006. So let me know when you're there.

A. Yes, I have Exhibit 220 in front of me, and I see the email from -- in the string from George Yancopoulos dated Wednesday, May 17th, 2006, and I am one of the recipients.

Q. Okay. And they're also talking about the PrONTO data, which was Dr. Rosenfeld's Lucentis study, right?

A. Yes, this email is referring to the PrONTO study.

Q. It looks like Dr. Yancopoulos is saying, about the PrONTO data, that Lucentis was not lasting for two months, which could provide a major opportunity for VEGF Trap interval advantage. Do you see that?

A. Yeah. So this is an email from the string dated Tuesday, May 16th, 2006, subject, "PrONTO data."

Q. Okay. So was that -- was Dr. Yancopoulos's assessment of the Lucentis PrONTO data something that caused everybody to start saying, okay, we know Lucentis can't go for more than two months?

A. So we were -- I don't recall specifically if this data in any way translated to further discussions about the dosing regimens planned for the VIEW 1 and VIEW 2 studies.

Q. Well, he says, "This indeed may provide us a major opportunity for VEGF Trap interval advantage."

Did you look at that and get excited and say, yeah, it will, or was it just more, like, whatever, you just continued on your merry way?

A. We were excited about the possibility of aflibercept having a longer treatment interval based on the properties of the molecule itself as well as the emerging data from the clinical development program.

I believe that Lucentis was approved in 2006 and was, because of their clinical trial results, slated to become standard of care. So I think that, you know, it wasn't

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specifically any outcome from Lucentis trials that made us excited, but we were certainly monitoring the competitive landscape closely.

Q. What was your -- to your recollection, what was Regeneron's rationale for why the VEGF Trap aflibercept molecule would be able to last longer as compared to Lucentis ranibizumab?

A. So my understanding of Regeneron's rationale is that, first, aflibercept is a larger molecule and, as a result, has a longer half-life than Lucentis does, as well as the fact that we have a much, much higher binding affinity and other kinetic properties of binding to VEGF that we felt would be advantageous for aflibercept and contribute to potentially a longer duration of action.

Q. And to date, as far as you're aware, has Regeneron ever validated that those two things, having a longer half-life and increased binding affinity, actually is what's allowing aflibercept to be dosed at these longer intervals as compared to ranibizumab?

A. So the evidence we have of the longer duration of action is from the clinical trial results based on outcome in the clinical studies.

Q. Now, if we can go to the front page of Defendant's Exhibit 220, you were also cc'd again on the email string, this time on May 17th, 2006, from George Yancopoulos, about the

PrONTO data, and he was responding to an email from Avner Ingerman.

Do you see that?

A. I do see the email dated 17 May 2006 from George to Avner and others where Avner is responding to an email from -- or sorry -- George is responding to an email from Avner.

Q. Now, Avner was discussing not just PrONTO but also the MARINA and ANCHOR trials. Those were also -- those were official Lucentis trials run by Genentech, right?

A. The MARINA and ANCHOR trials were the Phase III studies sponsored by Genentech for Lucentis in neovascular AMD.

Q. Okay. In discussing those trials, he said, "It may suggest that the so-called 'clinician prn practice' following 'induction dose' is as good as monthly injections for at least the first year, and that is probably the take-home message that the market will follow."

Do you see that?

A. I do see that sentence in the email.

Q. Do you know whether anybody agreed or disagreed with Avner's assessment that that's how clinicians would likely respond to this data?

A. Sorry. Can you just restate the question?

Q. Sure.

Do you recall within Regeneron whether people agreed or disagreed with Dr. Ingerman's view that clinicians would

probably perceive the clinician prn practice following induction dose was as good as monthly injections for at least the first year when it came to ranibizumab?

A. My recollection is that Dr. Yancopoulos strongly disagreed with the concept that prn dosing was as good as monthly dosing as studied in the ANCHOR and MARINA trials.

Q. So why did Dr. Yancopoulos agree to any type of prn-type dosing in the later part of the VIEW studies if he was adamant it wasn't going to work?

A. My recollection is that the most critical portion of the study and the portion of the studies that defined our initial dosing regimen in our application to the FDA was the one-year data from the VIEW 1 and the VIEW 2 studies.

Q. Let me know when you have that.

A. Okay. I have Exhibit 222 in front of me.

Q. All right. And can you confirm that there's -- that you were forwarded by Jesse Cedarbaum on or around September 5th, 2006, a message -- an email message involving Jesse Cedarbaum and Phil Rosenfeld, dated September 1st, 2006?

A. So I see the second sort of message in this string as a forwarded message from Jesse Cedarbaum, dated the 5th of September 2006. It was primarily to Len Schleifer, but I am copied.

Q. Well, one of the things that Dr. Rosenfeld told Jesse Cedarbaum which was passed on to you is he said, "You have a

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chance of use a 4-milligram dose, which is a fourfold molar excess over Lucentis, with a good chance of better durability. The more I thought about your dilemma, I would go with the 2-milligram and 4-milligram dose every two weeks or four weeks for a fixed number of doses, then see the patients back every four weeks and dose as needed. With the competition closing in on you, I think your only choice is to go for the gold and design a Phase III now."

Do you see that?

A. I do see where the email states that phrasing.

Q. Do you remember internally ever discussing the possibility of using a 2-milligram dose in your Phase III clinical trials before Jesse Cedarbaum got this feedback from Dr. Rosenfeld?

A. I don't recall specifically the timing of the discussions regarding dose selection for Phase III.

Q. All right. If you look at the top email, this is Len Schleifer saying, "This is Phil Rosenfeld's view of our diabetes opportunity." And then he says in the second line, "Jesse showed him the four-week, five-patient DME data which showed a nice response at four weeks and then a small loss by six weeks."

Do you see that?

A. I do see where that sentence is.

Q. All right. Do you know which clinical trial data

that was that was the four-week five-patient DME?

A. My assessment is that that is referring to the 0512 study, which was the Phase I study with intravitreal aflibercept in DME.

Q. Is it possible that -- well, do you recall who was responsible for designing the Phase II DME study that's referred to here in Example 5 of the '601 patent?

A. So, again, I don't recall specifically who was involved at that time, but it would have included members of the clinical development group, including myself and Dr. Vitti. Alyson Berliner, I believe was the study director. We consulted with our regulatory colleagues as well as senior management and others regarding the study design.

Q. I would like to mark as DX224 a document with production numbers RGN-EYLEA-MYLAN-65438 through 449.

What was the purpose of the global project team?

A. The global project team was a cross-functional team established as part of the Bayer collaboration to oversee development for aflibercept with our codevelopment partner.

Q. And did the Bayer people have input into what your Phase III clinical trial would look like in terms of dosing regimens?

A. As part of the Bayer collaboration, they had input into aspects of the clinical development planning, including study designs, but the ultimate scientific decision-making

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remained with Regeneron.

Q. Can you confirm on the first page of DX226, there's an email from you dated March 29th, 2007, to Jesse Cedarbaum where you were forwarding the conversation on VEGF Trap executive summary of scientific advice meeting with Swedish MPA?

A. Yes. So I have Exhibit 226 in front of me, and I see the second email in the string is a forwarded email from me to Jesse Cedarbaum on the 29th of March 2007 with the subject "VEGF Trap - Executive Summary of Scientific Advice meeting with Swedish MPA on 28 March '07."

Q. If we take a look at Jesse Cedarbaum's responsive email, can you confirm that that's dated March 29th, 2007, and went to individuals such as Avner Ingerman and George Yancopoulos?

A. Yes. So the first email in the string here is dated Thursday, March 29th, 2007, forwarded VEGF Trap executive summary of scientific advice meeting with Swedish MPA from Jesse Cedarbaum to Peter Powchik, Avner Ingerman, and others.

Q. Sure. Is Regeneron aware of anyone who put together for the Phase III VIEW 1-VIEW 2 clinical trial design a 2-milligram dose at an eight-week dosing interval before Dr. Cedarbaum's email we're looking at here of March 29th, 2007?

A. I don't recall exactly the discussions around the

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eight-week interval or whether Dr. Cedarbaum, by virtue of this email, was the first person to suggest the eight-week interval.

Q. Can Regeneron identify anybody who did it -- who put those two pieces together -- 2-milligram dose, eight-week interval -- before Dr. Cedarbaum did?

A. I can't speak on behalf of Regeneron. I can only speak for myself, and I do not recall a person who specifically put that together in this time frame.

Q. And, Ms. Chu, if you can confirm this is an email from Kathleen Lawrence to you and others, dated Monday, April 2nd, 2007?

A. So I have Exhibit 227 in front of me with a date of April 2nd, 2007, subject, "Decisions & Actions: AMD Phase III Program Meeting, April 2, '07," from Kathleen Lawrence, and I am a recipient of this email.

Q. Do you recall if you were a participant in this AMD Phase III program meeting on April 2nd, 2007?

A. I don't recall this specific meeting, but in my role I would have attended such meetings.

Q. Now, the third bullet point down says -- this is for the first time we see this, "2 milligrams q8 weeks with PIER lead-in (dose monthly for first three months)."

Do you see that?

A. I do see that the third bullet states, "2-milligram q8 weeks with PIER lead-in (dose monthly for first three

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months)."

Q. All right. Who actually assembled that particular regimen as one of the arms to consider for the VIEW 1 Phase III clinical trial?

A. I don't recall specifically who proposed that dosing regimen.

Q. Sure. In your capacity as Regeneron's 30(b)(6) witness, what's the significance of this April 4, 2007, email from George Yancopoulos to Darlene Jody?

A. So this email from George to Darlene Jody, who was a senior executive responsible for the Bayer collaboration with us, is communicating the Regeneron proposal and decisions around the optimal designs for the VIEW 1 and the VIEW 2 trials.

Q. Is there anywhere in here where Dr. Yancopoulos is advocating for starting off the regimen with three monthly 2-milligram doses and then going to the eight-week interval?

A. In my review of this email, I do not see that it includes mention of the three initial monthly doses for the q8-week group.

Q. And did you review this email in connection with preparing for your deposition in this case?

A. I have Exhibit 229, date Tuesday, April 10th, 2007, subject, "Forward: VEGF Trap-Eye GDP for REGN/Bayer" from George Yancopoulos to Darlene Jody. And, no, I did not review

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this email in preparation for today's deposition.

Q. Right. And just to be clear, that dosing regimen of VEGF Trap 2 milligrams every -- dosed every four weeks times three, then q8 thereafter, that was a dosing regimen drafted by Bob Terifay, right, in this email string?

A. My recollection of how decisions were made at Regeneron at the time was that this proposal would not have been discussed at the joint development committee meeting unless George had had input and agreed that this was the proposal for the Phase III studies.

Q. Well, if George Yancopoulos had signed off on that as the dosing regimen, why is he actually arguing against that, then, on April 10th, 2007, to Darlene Jody?

A. My read of the email didn't give me the impression that George was arguing against it. If you can point to what specifically you're referring to, I'd be happy to review it again.

Q. Nowhere in this April 10th, 2007, email to Darlene Jody is George Yancopoulos advocating for the dosing regimen that Bob Terifay identified of an aflibercept dose of 2 milligrams dosed every four weeks three times followed by a dosing every-eight-week regimen, true?

A. I can't speak to George's intent.

Q. It's not a question of intent. It's a question of what's written here in the email.

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A. It is correct that that is what -- what is written in this email is the sentence, "That is based on both U.S. and EU regulatory interactions. Such a study will definitively fulfill their requirements as one of the studies. While final dose/interval for the fourth arm of the study are a bit unsettled, we can use 2q8 for now as the most likely dose/interval."

Q. I'd like you to take a look at the email from Robert Terifay that is dated April 17th, 2007, to George Yancopoulos, Len Schleifer, Peter Powchik, Avner Ingerman, and Neil Stahl, subject, "U.S. commercial concerns regarding the Bayer compromise."

Let me know when you're there.

A. I see that email beginning on page -- the second page of this email -- the last three numbers are 333 -- from Robert Terifay, dated 17th of April 2007, to George Yancopoulos with others copied.

Q. Do you have an understanding as to why Robert Terifay would have been involved in these discussions over selecting the Phase III clinical trial regimen?

A. Bob Terifay was the head of our commercial group at that time and, as such, would have had input on the clinical development program as it related to commercial viability and commercial considerations.

Q. Again, if we look in DX230, the top email, dated

Wednesday, April 8th, 2007, from Robert Terifay to Peter Powchik, Len Schleifer, and George Yancopoulos, Avner Ingerman, Neil Stahl, and Laura Pologe, the second paragraph, he says, "From an 0508 perspective, it appears that 2q8 (especially if initiated as a 2q4 loading dose for the first three months) can offer similar improvement in visual acuity and maintain that level similarly to 2q4 and Lucentis q4. This would be a major win for VT" -- referring to aflibercept -- "versus Ran" -- referring to ranibizumab -- "in Phase III," right?

A. I see the email dated Wednesday, April 18th, 2007, from Bob Terifay to Peter Powchik and others with the first bullet stating that "From an 0508 perspective, it appears that 2q8 (especially if initiated as a 2q4 loading dose for the first three months) can offer similar improvement in visual acuity and maintain that level similarly to 2q4 and Lucentis q4."

Q. '601 patent, Claim 1.

A. So in patent '601, Claim 1, it's stated that a method for treating age-related macular degeneration in a patient in need thereof comprising intravitreally administering an effective amount of aflibercept, which is 2 milligrams approximately every four weeks for the first three months, followed by 2 milligrams approximately once every eight weeks or once every two months.

Q. Right. And that dosing regimen matches the one that

Robert Terifay is advocating for in DX230, his April 8, 2007, email, of 2q8 initiated as a 2q4 loading dose for the first three months, right?

A. My interpretation of the email from Bob Terifay is that he is describing the same dosing regimen.

Q. Ms. Chu, can you confirm that this document, DX231 is an email to you and others from Avner Ingerman, dated Thursday, August 2nd, 2007?

A. So I have Exhibit 231, which is an email dated August 2nd, 2007. The subject is "Emailing: NCT00509795.htm" from Avner Ingerman, and I am copied on this email.

Q. Okay. And in the text of this email, is he providing the information that was published at ClinicalTrials.gov in connection with ClinicalTrials.gov identifier NCT00509795?

A. So my review of this email this minute indicates that this is Dr. Ingerman forwarding the ClinicalTrials.gov posting of the VIEW 1 Phase III study.

Q. To your prior point, can you take a look at the last page of Defendants' Exhibit 231. Can you confirm that, above the last three lines, it says, "ClinicalTrials.gov processed this record on August 1st, 2007."

A. I do see where it says, "ClinicalTrials.gov processed this record on August 1st, 2007."

Q. And under the inclusion criteria, the signed informed consent, were patients obligated to keep secret their

participation in Regeneron's clinical trials?

A. No, patients were not obligated in any way to keep their participation in the study secret.

Q. Do you have it now?

A. I have Exhibit 232 in front of me.

Q. Okay. And are you identified as a coauthor on this presentation?

A. So this appears to be a poster, and I am listed as an author.

Q. And why did Regeneron want to present its data involving aflibercept and its clinical trial data at these scientific conferences?

A. So it's scientific practice that we share our results in the context of scientific congresses and publications, and thus this was part of this scientific exchange that we were contributing to.

Q. Could you try to find in your stack what they labeled as Defense Exhibit 232.

A. Okay. I have Exhibit 232.

Q. Ms. Mazzochi had some questions for you about Defense Exhibit 232. Do you know if this is a draft or final document?

A. I don't know if Exhibit 232 is draft or final.

Q. Okay. You can put that document aside.

If you could find in your stack Defense Exhibit 234.

A. Okay. I have 234.

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Q. On Defendants' Exhibit 234, do you have a habit of letting people put your name on documents or scientific presentations that you don't review and approve?

A. No. If I am an author, I definitely would have reviewed and provided input into the content of the document.

Q. Right. And you would have made sure that any statements, at least to the extent they were within your area of operation, were truthful and accurate, right?

A. Yes. Part of my review would be for accuracy.

Q. And when you were assembling that information, that was done with an understanding that the data would become public, right?

A. Sure. So in assembling data for the purpose of a presentation at a scientific congress, it was understood that that data would become public.

(Video ends.)

MS. BODA: And for administrative purposes, defendants move into evidence the following exhibits, which I believe are all agreed to: DTX 200, DTX 202, DTX 204, DTX 205, DTX 207, DTX 209, DTX 210, DTX 211, DTX 212, DTX 213, DTX 214, DTX 215, DTX 218, DTX 219, DTX 220, DTX 222, DTX 224, DTX 226, DTX 227, DTX 228, DTX 229, DTX 230, DTX 231, DTX 232, and DTX 234.

MR. GREGORY: No objection.

THE COURT: No objection to those? Okay.

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That list, Counsel, is hereby deemed admitted.

Any exhibits from the plaintiff's perspective from that deposition?

(DTX 200, DTX 202, DTX 204, DTX 205, DTX 207, DTX 209, DTX 210, DTX 211, DTX 212, DTX 213, DTX 214, DTX 215, DTX 218, DTX 219, DTX 220, DTX 222, DTX 224, DTX 226, DTX 227, DTX 228, DTX 229, DTX 230, DTX 231, DTX 232, and DTX 234 were admitted.)

MR. GREGORY: None from the plaintiff's perspective.

THE COURT: Understood. Why don't we go ahead and take our morning break at this point. We'll take ten minutes, then we'll proceed with Mylan's next witness.

(A recess was taken from 10:19 a.m. to 10:33 a.m.)

THE COURT: Mylan may call its next witness.

MS. MAZZOCHI: Thank you, Your Honor. The defendants call Dr. Jay Stewart as part of their invalidity case in chief. And Dr. Stewart's opinions specifically involve the issues relating to the dosing patent claims in compliance with 35 U.S.C. Section 112.

Your Honor, during the break, I believe we made efficient use of the binder distribution process; so hopefully you have copies up there.

THE COURT: Outstanding. Thank you all. You may proceed whenever you're ready, Counsel.

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MS. MAZZOCHI: Thank you, Your Honor.

JAY M. STEWART, MD, DEFENDANTS' WITNESS, SWORN

DIRECT EXAMINATION

BY MS. MAZZOCHI:

Q. Good morning, Dr. Stewart. Will you please state your full name for the record.

A. Jay Stewart.

Q. Are you testifying on behalf of the defendants today?

A. Yes.

Q. Did you prepare demonstrative slides to assist the Court with your testimony today?

A. Yes.

Q. All right. Let's go ahead and turn to those. Can you briefly describe your educational background.

A. Yes. I received my undergraduate degree in biochemical sciences at Harvard College, my medical degree at Harvard Medical School. And I completed an internship at Brigham and Women's hospital and then a residency in ophthalmology at the University of California San Francisco, which we call UCSF. After that I did a fellowship training in vitreoretinal diseases and surgery at Doheny Retina Institute at the University of Southern California.

Q. When did you begin your own full-time practice?

A. In 2005.

Q. And can you describe some of your clinical and

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academic positions, please.

A. Yes. So since 2005 I've been seeing patients at UCSF Medical Center. And this is a practice where we have many patients with age-related macular degeneration, or AMD, as well as other retinal conditions.

From 2009 to 2014 I was the medical director of that practice, in which capacity I oversaw decisions for the clinical practice. And since 2020 I've been the subspecialty medical director for the retina service.

Also since 2005 I've been seeing patients at San Francisco General Hospital, which is a facility where we have many patients with diabetes and diabetic retinopathy. I've been the director of the vitreoretina service at that site since 2006. And since 2014 I've been the chief of ophthalmology at that site, where I am responsible for overseeing all aspects of our department.

Q. Have you held any academic positions?

A. Yes. From 2005 to 2010 I was the assistant professor of clinical ophthalmology. From 2010 to 2016 I was the associate professor. And since 2016 I've been the professor of clinical ophthalmology.

Q. Have you received any grants to support your research?

A. Yes. I've had several grants from the National Institutes of Health to support research, one of which was a

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study evaluating ultrasound for drug delivery into the eye.

Q. Do you currently serve as the editor of any medical journals?

A. Yes. I'm the editor in chief of the *American Journal of Ophthalmology Case Reports* and the associate editor in chief of *Annals of Eye Science*.

Q. For how many years have you been working in the field of ophthalmology?

A. Over 20 years.

Q. Approximately how many patients do you see each week?

A. About 75.

Q. And have you treated patients with age-related macular degeneration, diabetic macular edema, and diabetic retinopathy?

A. Yes.

Q. Prior to 2010 have you used any VEGF drugs to treat AMD, DME, or diabetic retinopathy?

A. Yes. I was using Lucentis as well as Avastin off-label.

Q. After Eylea came on the market, did you use that as well?

A. Yes. I've been using Eylea since it came on the market. And then more recently have also been using a new drug called Vabysmo, which is spelled V-A-B-Y-S-M-O, which is also approved for some of these indications.

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Q. What do you consider to be some of your areas of expertise?

A. The diagnosis and treatment of vitreoretinal and other ophthalmologic conditions.

Q. I'd like you to take a look at DTX 7100.

And we'll put that up on the screen as well.

What is this document?

A. It's a copy of my CV.

MS. MAZZOCHI: Your Honor, at this time Mylan and Biocon proffer Dr. Stewart as an expert in the medical and surgical treatment of vitreoretinal and ophthalmic diseases.

THE COURT: Any voir dire or objection?

MR. GREGORY: No objection, Your Honor.

THE COURT: Without objection, the witness is deemed so qualified.

You may proceed, Counsel.

MS. MAZZOCHI: Thank you very much, Your Honor.

BY MS. MAZZOCHI:

Q. Dr. Stewart, have you heard the phrase "a person of ordinary skill in the art"?

A. Yes.

Q. Does the next slide, DDX 7.5, have both parties' definitions of a person of ordinary skill in the art displayed on them?

A. Yes.

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Q. Do you qualify as a person of ordinary skill in the art at least as early as of January 2011 under either definition?

A. Yes.

Q. And have you applied that perspective of a person of ordinary skill in the art here?

A. Yes.

Q. Do your opinions change whether Regeneron or defendants' person of ordinary skill in the art definition applies?

A. No.

Q. You have these in your binder. It's PTX 3, the '572 patent, and PTX 1, the '601 patent. Did you review both of these patents in this case?

A. Yes.

Q. Can you summarize some of the issues that you considered with regard to Claim 6 of the '572 patent?

A. Yes. So Claim 6 depends upon Claim 1, which describes the method for treating an angiogenic eye disorder. And I had concerns about the definition of angiogenic eye disorder. It also describes a dosing regimen which I felt lacked written description and enablement.

Q. And when it comes to the term "angiogenic eye disorder," what are some of your concerns with the term "angiogenic eye disorder"?

A. I felt that the term was too broad and, therefore, was not enabled and also lacked written description support.

Q. Do you have specific concerns with the dosing information that's found in the patent?

A. Yes, that there is no limitation on the number of doses given and, therefore, it's not enabled and also lacks written description support.

Q. Thank you very much.

Can you summarize the issues that you looked at that were specific for Claim 25 of the '572 patent as well as Claims 11 and 19 of the '601 patent.

A. Yes. So Claim 25 depends upon Claim 15. Claim 11 depends upon Claim 10. And Claim 19 depends upon Claim 18. And all of these refer to a regimen of dosing that involves five loading doses. And I believe that there is no written description support for this and that it lacks enablement.

Q. And are your enablement positions with regard to these claims tied at least in part to some of the positions that Regeneron and Dr. Csaky have taken in this case for invalidity?

A. Yes.

Q. Have you also assessed the question of indefiniteness?

A. Yes.

Q. Can you explain that, please.

A. Yes. The term "approximately" is used at multiple points throughout the claims, and I feel that terminology is indefinite.

Q. Can you summarize some of the issues that you looked at with regard to the disclosures and the specification's related applications that may bear on the question of priority.

A. Yes. There were a series of applications that were filed in which new information was added to the subsequent filing.

Q. And did you consider whether that new matter supported or enabled the claims as well?

A. Yes.

Q. All right. Let's start with some of your enablement topics. And let's focus first on angiogenic eye disorder that appears in Claim 6 of the '572 patent.

So, Dr. Stewart, in connection with your review of the '572 patent's Claim 6, did you assess whether a person of ordinary skill in the art at the time the patent applications were filed would have been able to fully make and use the claimed method to treat the full scope of angiogenic eye disorders without undue experimentation?

A. Yes, I did.

Q. Did you also consider whether a person of ordinary skill in the art at the time the various patent applications were originally filed as well as amended, whether that person

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would believe the inventor actually invented and possessed the particular dosing methods to treat the full scope of angiogenic eye disorder conditions listed?

A. Yes.

Q. All right. Now, does the '572 patent specification discuss eye disorders associated with angiogenesis?

A. Yes, it does.

Q. And is that in the '572 patent at Column 1, lines 40 to 65, and Column 5, lines 30 to 48?

A. Yes.

Q. In connection with your opinions in this case, have you reviewed Dr. Yancopoulos's trial testimony, including page 155, about what he called the common mechanism, that is, VEGF driving abnormal blood vessel growth and leak, including a statement that all these disorders shared a common mechanism?

A. Yes.

Q. In your opinion, can VEGF inhibitors driving normal -- I'm sorry -- can VEGF inhibitors driving abnormal blood vessel growth and leak be used today to treat some of the diseases listed as angiogenic eye disorders in the patent?

A. Yes. And we do use them to treat some of these disorders.

Q. Can you give a few examples of what those disorders are.

A. Wet AMD, CRVO, DME, diabetic retinopathy.

Q. Are there any other diseases on the '572 patent specification list at Column 5 that the '572 patent calls an angiogenic eye disorder where there is not so?

A. Yes. Several, including proliferative vitreoretinopathy, also known as PVR; pannus; and pterygium.

Q. Dr. Stewart, in connection with your opinions, I'd like you to assume that angiogenic eye disorders are associated with the growth and proliferation of blood vessels, that aflibercept is a VEGF inhibitor, and that a person of ordinary skill in the art has all of the teachings and examples given in the '572 patent.

With that understanding, would a person of ordinary skill in the art believe that the inventor had invented a method where the Claim 6 drug dose and schedule would apply for intravitreal aflibercept to treat proliferative vitreoretinopathy, pannus, and pterygium?

A. No.

Q. Can you explain why, please.

A. Because aflibercept, being a VEGF blocking agent, would work to block VEGF, but these conditions have more complex mechanisms of disease of which VEGF is only one component.

Q. And how about today? Have those in the field found a way to make intravitreal aflibercept work to treat proliferative vitreoretinopathy -- PVR -- pannus, or pterygium

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using the dosing regimen set forth in Claim 6?

A. No.

Q. Can you explain why that is.

A. Well, I think through an understanding, again, of the mechanism of -- action of the drug and the complex mechanism of these diseases and clinical experience in the field.

Q. To support your opinions that the term "angiogenic eye disorders" lacks written description and enablement across the full scope of the term, did you find any support in the medical literature?

A. Yes.

Q. Can you give the Court an example from the medical literature that you believe supports your opinions that the method of Claim 6 of the '572 patent does not work to treat the full scope of conditions the specification lists as an angiogenic eye disorder?

A. Yes. This publication from Shahlaee, et al.

Q. And is a copy of the Shahlaee publication in your binder at DTX 5430?

A. Yes.

Q. Can you explain why you cited this Shahlaee paper.

A. This is a paper that reviewed several methods of trying to treat proliferative vitreoretinopathy, and one of the methods that they discussed was the use of anti-VEGF treatment. And they presented the fact that several studies that looked at

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this method of treatment found no success.

Q. Do you have any other examples from the medical literature?

A. Yes. This manuscript from Shahraki, et al.

Q. And is a copy of that publication in your binder at DTX 5431?

A. Yes.

Q. Can you explain why you cited Shahraki?

A. Well, this was a --

MR. GREGORY: Your Honor, I'm sorry. I have to object. This level of disclosures is not in his expert report anywhere.

MS. MAZZOCHI: Your Honor, it's in his opening expert report at paragraphs 76, 81, as well as --

THE COURT: Could I have the report?

MS. MAZZOCHI: It should be in your binder, Your Honor.

THE COURT: There's a lot in here, Counsel. What tab am I looking for?

MS. MAZZOCHI: Sure. DTX 7099, which is his opening report.

THE COURT: Paragraphs for that again, Counsel? I'm sorry.

MS. MAZZOCHI: Let's start at paragraph 81, where he specifically cites these three references we've been reviewing

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for this very purpose, that a person of ordinary skill in the art would not think they could be treated and are currently not treated with aflibercept.

MR. GREGORY: I'm sorry. I think 7099 is his reply report.

MS. MAZZOCHI: Oh, I apologize. 7098.

THE COURT: What paragraphs, then?

MS. MAZZOCHI: Paragraph 81. Oh, no. I'm sorry. My apologies, Your Honor. Let me start that over.

In his reply report, paragraph 81 is -- Dr. Stewart specifically cited these three references I've been reviewing for this premise.

THE COURT: What's the objection, then, Counsel?

MR. GREGORY: The objection -- yes, Your Honor. My objection is that -- I'm trying to find this here. In paragraph 81 there is a very terse description -- or citation, a string cite, "see e.g.," these three references, and no description of the source that Dr. Stewart is offering now from the discovery.

THE COURT: Was Dr. Stewart deposed?

MR. GREGORY: Dr. Stewart was deposed.

THE COURT: All right. Objection overruled.

You may continue, Counsel.

MS. MAZZOCHI: Thank you, Your Honor.

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BY MS. MAZZOCHI:

Q. So, Dr. Stewart, let's just circle back. Can you just explain why you cited this publication, the Shahraki publication.

A. Yes. This was a publication that reviewed treatment approaches for the condition of pterygium.

Q. And did injecting the anti-VEGF drug improve the outcomes for pterygium patients?

A. No. They described that one of the treatment options that they were reviewing, which was the use of anti-VEGF treatment, yielded inconclusive results.

Q. Now, I believe these two publications used bevacizumab as the anti-VEGF inhibitor. Why did you choose to rely on them to opine they wouldn't work with aflibercept?

A. Because they share a common mechanism of action, which is to counteract VEGF. And so if we don't see efficacy with bevacizumab, we also wouldn't expect that with aflibercept.

Q. Do you have an example from the medical literature that is specific to aflibercept that supports your opinions that the method of Claim 6 of the '572 patent will not work to treat one or more conditions the specification lists as an angiogenic eye disorder?

A. Yes. This manuscript from Sella, et al.

Q. And is a copy of the Sella publication in your binder

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at DTX 5429?

A. Yes.

Q. Can you explain why you cited Sella in your report.

A. They used aflibercept for treatment of formed corneal neovascularization and reported that it was ineffective.

Q. And is formed corneal neovascularization a subtype of the more general description corneal neovascularization?

A. Yes.

Q. Are there any diseases in which formed corneal neovascularization also plays a role?

A. Yes. One of the conditions we mentioned earlier, which is pannus.

Q. Than what is pannus?

A. Pannus is a growth on the ocular surface that contains corneal neovascularization as well as fibrotic tissue.

Q. And did the '572 patent offer any data beyond the prior art pertaining to these specific diseases that you've just identified: formed corneal neovascularization, proliferative vitreoretinopathy, pannus, and pterygium?

A. No.

Q. How about a mechanism-of-action theory beyond anti-VEGF?

A. No.

Q. Does the specification give any hint or suggestion towards the appropriate dosing schedule that would be needed to

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treat diseases such as formed corneal neovascularization, proliferative vitreoretinopathy, pannus, or pterygium?

A. No.

Q. And in response to your expert reports in this case, did Dr. Csaky identify any data or test results, either in the specification or the medical literature, showing that intravitreal aflibercept actually will work using the Claim 6 method to treat each angiogenic eye disorder we see in the '572 patent?

A. No.

Q. In response to your expert report, did Dr. Csaky identify any specific rationale in the specification or medical literature beyond mere anti-VEGF behavior as to why a person of ordinary skill in the art could expect aflibercept to work to treat those diseases I just listed?

A. No.

Q. And to reach your conclusion that intravitreal aflibercept does not work to treat these diseases at all, did you rely on just the medical literature, or did you rely on other things?

A. I relied on an understanding of the mechanism of action of the drug as well as the complex mechanisms at issue in these particular conditions and familiarity with the field.

Q. In terms of your own personal experience, have you had to treat patients that have all four of these conditions?

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A. Yes, I have.

Q. And have you ever used aflibercept as part of their care?

A. No.

Q. In your opinion, based on what we just discussed, would a person of ordinary skill in the art reading the '572 patent specification believe that the inventor actually possessed a method of treating the full scope of these angiogenic eye disorders with aflibercept?

A. No.

Q. In your opinion, based on what we just discussed, would a person of ordinary skill in the art reading the '572 patent specification in the relevant time frame believe that the dosing method of aflibercept set forth in Claim 6 was enabled to actually work to treat the full scope of angiogenic eye disorders?

A. No.

Q. Now, for your nonenablement opinion, did you also consider factors that are used to assess the question of whether a person of ordinary skill in the art can practice the full scope of the claims without undue experimentation?

A. Yes.

Q. All right. And on your Slide Number DDX 7.29, are these eight factors listed here the undue experimentation factors that you considered?

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A. Yes.

Q. Okay. Let's start with the first three of these factors: quantity of experimentation, direction or guidance, and presence or absence of working examples.

In your opinion, if a person of ordinary skill in the art had the Claim 6 dosing regimen and a patient who presented with formed corneal neovascularization, proliferative vitreoretinopathy, pannus, or pterygium, would they find enough in the specification to give treatment direction, guidance, or working examples relevant to those disease states?

A. No.

Q. And can you explain why.

A. Because we don't receive any guidance or examples or rationale shown in those specifications regarding those conditions. And so they would need to perform an entirely new research project to figure out whether it could be used.

Q. Now, in his pretrial opinions in this case, Dr. Csaky suggested that, as long as you have the list of diseases, the steps, and understanding of the VEGF mechanism and knowledge that aflibercept worked well to treat wet AMD and other diseases we see in the examples, that would be sufficient to treat all of these other angiogenic eye disorders.

Do you agree?

A. No.

Q. Can you explain why.

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A. I think the issue is that some of these conditions involve more than just VEGF as their mechanism of causing pathogenesis in the eye. So that's one aspect which is the complexity of the disease mechanism.

Another aspect is shown in this figure, which is a picture of the eye where we see the ocular surface highlighted in yellow where several of the conditions that we were just discussing are located. And that's not proximal to the site of intravitreal injections; so we wouldn't necessarily think that administering intravitreally would be the most effective way to treat those conditions.

Q. Let's talk about the next undue experimentation factor, the predictability or unpredictability of the art.

Is there anything that a person of ordinary skill in the art could use from the specification to predict that aflibercept will perform well using the Claim 6 regimen in PVR, pterygium, formed corneal neovascularization, or pannus in a way that would let them achieve success?

A. No.

Q. And why is that?

A. Because there isn't any such guidance or examples shown that would allow us to predict that it would work for those conditions.

Q. And, also, if Regeneron argues that this art generally is unpredictable for diseases such as DME or DR, even

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if you progressed to the Phase II clinical study phase, would that increase or decrease the experimental burden on the person of ordinary skill in the art for the specifications here in your opinion?

A. That would increase the burden.

Q. And on this factor pertaining to the breadth of the claims, what would a person of ordinary skill in the art perceive about the breadth of the term "angiogenic eye disorder"?

A. I think they would perceive that term to be excessively broad.

Q. Now let's take a look at the factor relating to the nature of the invention. Directing your attention to the '572 patent abstract, what does it describe as the nature of the invention?

A. A method for treating angiogenic eye disorders by administering VEGF antagonist.

Q. So in your opinion, is any failure of the claimed methods to work to treat diseases such as pannus, pterygium, formed corneal neovascularization, or PVR something that is merely peripheral or more central to the invention?

A. It's central.

Q. For the factors involving the state of the art and the level of ordinary skill in the art, will the state of the art and high skill set of that person reduce the experimental

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burden?

A. No, because even knowing the state of the art and even if they have a high level of skill, they would still, I think, understand that there isn't information within the specifications to guide them to be able to use this treatment for those particular conditions.

Q. And we've had an issued patent out there for quite some time. Since the patent has issued, to your knowledge, has this become -- has aflibercept become the standard of care at all or otherwise used for proliferative vitreoretinopathy, pannus, or pterygium?

A. No.

Q. Let's turn, then, to your ultimate opinions when it come to the angiogenic eye disorder for Claim 6.

Do you understand that, to satisfy the written description requirement, the patent must describe an invention understandable to a skilled artisan and show that the inventor actually invented and possessed the invention claimed?

A. Yes.

Q. And in your opinion, based on what we've just reviewed, would a person of ordinary skill in the art believe that the inventor actually invented or possessed a working intravitreal dosing regimen, as we see in Claim 6, to treat the full scope of angiogenic eye disorders, including, for example, proliferative vitreoretinopathy, pannus, and pterygium?

A. No.

Q. In your opinion, based on what we just discussed, would a person of ordinary skill in the art believe that the specification enabled a person of ordinary skill in the art to practice the full scope of angiogenic eye disorders covered by Claim 6 without undue experimentation?

A. No.

Q. All right. Let's talk next about some of your opinions relating to dosing.

MS. MAZZOCHI: And, Your Honor, I'm happy to have Dr. Stewart go through and discuss the loading dose concept, but if you're good with that, I don't need to repeat it.

THE COURT: I think I've got a good grasp of it at this point.

MS. MAZZOCHI: I thought so, but I didn't want to assume.

BY MS. MAZZOCHI:

Q. Dr. Stewart, directing your attention to the summary of invention section of the '572 and '601 patents, did you find anywhere in the specification that placed any emphasis on the number of doses that should proceed the eight-week dosing interval?

A. Yes. They referred to three doses.

Q. Did the specification illustrate what this type of dosing regimen, the three doses at the start, would look like?

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A. Yes, in Figure 1.

Q. And in Figure 1 of the '572 and '601 patents, how many total loading doses, spaced four weeks apart, are illustrated before beginning the eight-week dosing regimen?

A. Three.

Q. Was there any figure that showed five?

A. No.

Q. Did you review the specification statements about loading dose or secondary dose frequency?

A. Yes.

Q. And did you also review Dr. Yancopoulos's trial testimony, including at transcript pages 235 to 236?

A. Yes.

Q. In your opinion, do the specifications for the '572 and '601 patents place any upper limit on the term "secondary" or "tertiary" doses that we see in the claims?

A. No.

Q. Did the specification provide any rationale for why you should stop with secondary dosing and switch to tertiary dosing that was not already known in the prior art?

A. No.

Q. And can you explain why a little bit.

A. Well, because the language that's used here refers to one or more secondary doses and then one or more -- so the -- there's no upper limit basically shown as to how many doses

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that you would use.

Q. And then when it comes to any adjustments that should be made to the course of treatment by the physician as we see in the -- in Column 4, does that column talk about or give any guidance or recommendations to physicians for performing those adjustments up or down or beyond what was known in the art?

A. No. It just says according to the needs of the patient following clinical examination.

Q. And where would a person of ordinary skill in the art have to go, then, for guidance or reasoning as to why they should change their loading dose regimen?

A. I think it would be difficult, not having that information provided here, to know when to do so.

Q. Separate and apart from what was known in the art?

A. Right.

Q. Does the specification provide any reason to expand or limit the number of secondary or tertiary doses to use beyond what the person of ordinary skill in the art had already thought about and used for indications, such as DME or diabetic retinopathy?

A. No.

Q. Did you see anything in the specification that explains to a person of ordinary skill in the art that they should not be concerned about risks or side effects of more loading doses for the DME or DR regimen?

A. No.

Q. Did the specification for the '572 and '601 patents articulate for the person of ordinary skill in the art any reason to choose or select four secondary doses or a total of five monthly loading doses as opposed to the many other options found in the specification, particularly in the context of a DME or diabetic retinopathy indication?

A. No.

Q. All right. I'd like to direct your attention back to Column 4, specifically lines 22 to 31 of the '572 patent, because this is some text that Dr. Csaky pointed to to suggest that the number four on this list is enough to pick or support a dosing method with five monthly loading doses versus others.

In your opinion, is that enough?

A. No, it's not.

Q. And can you explain why.

A. Because it refers to two or more doses being shown. And if we could go back to that slide, it -- in fact, it says, for example, two, three, four, five, six, seven, eight, or more secondary doses. And so there's no indication that four is being differentiated or called out as compared to all the other numbers that are there.

Q. And so then can you summarize some of the problems that you identified regarding the specification when it comes to the dosing regimens?

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A. Yes. Several. One was the fact that there were -- there was a preference for three doses, as we saw earlier, as opposed to five, and there was no particular justification or data as to why we would pull out five from the number of loading doses that was presented.

There was also no guidance across the entire scope of all the angiogenic eye disorders as to why we would choose a particular secondary or tertiary dosing regimen for each of the conditions.

There also wasn't any express guidance for DME and diabetic retinopathy on, again, choosing the five loading doses. And, in fact, there wasn't any clinical data at all regarding diabetic retinopathy shown in the specification.

So just in general, I think that the fact that there was no theory or rationale setting aside a lack of examples as to why you would transition between dosing regimens.

Q. Okay. And let's take a look at Dr. Yancopoulos's trial testimony at page 205. Does that testimony support or refute your opinions here?

A. It supports it.

Q. Can you explain why?

A. Because it refers to the fact that there are -- there wasn't any particular reasoning or rationale behind why you would go between the loading doses and the eight-week dosing.

Q. Dr. Stewart, did you find any data or rationale in

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the '572 or '601 patent specification as a whole that was identified or called out in a way that would provide a blaze mark to a person of ordinary skill in the art to guide them towards selecting a particular dosing regimen of five loading doses followed by every-eight-week dosing for the specific indications of DME or DR?

A. No.

Q. I'd also like to spend a little bit of time to discuss Example 7 because that's another one of the things that Dr. Csaky pointed to in support for the five loading doses in response to your testimony.

Now, as a preliminary matter, did you also review, as part of your opinions in this case, DTX 5330, Patent Application Number 13/940,370 filed on July 12, 2013, as a continuation-in-part application?

A. Yes.

Q. And did DTX 5330, this July 12, 2013, continuation-in-part patent application, add anything new to the existing specification?

A. Yes. Example 7.

Q. So focusing on Example 7, then, which was added to the specification in July 12, 2013, did Example 7 contain any new clinical data?

A. No.

Q. What did Example 7 contain?

A. It contained, essentially, a laundry list of dosing regimens that could be used for this treatment.

Q. Can you explain generally what this laundry list of dosing regimens in Example 7 did include?

A. Yes. There were a variety of scenarios that were presented. One of them was treating every four weeks with the injection.

Another scenario involved treating every four weeks for the first eight weeks, followed by several different options, one of which was to give an injection every eight weeks.

Another scenario was to give an injection on a less frequent basis according to the physician's determination. And another scenario was to give injections on an as-needed or pro re nata, or prn, process.

There was another scenario in which injections were given every four weeks for, essentially, a series of durations -- 12, 16, 20, 24, et cetera, weeks -- followed by injections every eight weeks.

And then finally there was one scenario where a single injection was given in which all subsequent injections would be given on an as-needed basis.

Q. And if we look, for example, at the one you have in the upper right-hand corner where it says "once every four weeks for the first 12 weeks followed," did that also include

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options for every eight weeks, physician assessments, prn dosing as well?

A. Yes.

Q. Okay. And -- sorry -- then what was the last regimen that we found in Example 7?

A. This is the single injection followed by an as-needed schedule.

Q. And that was called prn dosing?

A. Yes.

Q. Have you reviewed Dr. Yancopoulos's trial testimony at page 232?

A. Yes.

Q. Is Dr. Yancopoulos's testimony relevant to your opinion that Example 7 does not have any statements of preference?

A. Yes, it supports that.

Q. Okay. And why is that?

A. Because he said that we don't know which of these regimens would be able to produce the best visual outcomes.

Q. What did Dr. Yancopoulos identify in trial testimony you reviewed as needed to generate that guidance towards a regimen that would produce the best visual outcomes?

A. Phase III clinical trial data.

Q. Is any Phase III clinical trial data in the specification for DME?

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A. No.

Q. Is there any clinical data at all, whether Phase I, II, or III, in the specification that is specific to a diabetic retinopathy indication alone?

A. No.

Q. In your opinion, does Example 7 give the person of ordinary skill in the art any added insight as to why or when to stop monthly dosing or every-four-week dosing and switch to a longer dosing interval?

A. No, it doesn't.

Q. In your opinion, does Example 7 give the person of ordinary skill in the art any added insight as to why they should select one of these particular regimens for any particular disease without the need for more experimentation or insight?

A. No.

Q. Did Example 7 include, though, a dosing regimen that could be characterized as having five doses separated by four weeks before transitioning to eight-week dosing?

A. Yes.

Q. Now, are there any blaze marks in either Example 7 or the specification generally that, in your opinion, would explicitly guide a person of ordinary skill in the art towards that regimen with five monthly loading doses followed by eight-week dosing?

A. No.

Q. And directing your attention to Column 16, lines 35 to 51, of the '572 patent, is that section where there are instances where you could have one loading dose followed by four monthly doses for a total of five monthly loading doses?

A. Yes.

Q. And did the specification express, in your opinion, any preference amongst these five loading dose different regimens we see in Example 7, eight-week dosing versus the other two listed, such as prn?

A. No.

Q. Now let's turn to some of the clinical indications that follow Example 7.

Does the specification express any preference for using one of these Example 7 regimens with five loading doses or the one followed by the fixed eight-week dosing interval for any particular clinical indication?

A. No, it doesn't.

Q. In your opinion, does Example 7 as a whole or Example 7 in conjunction with the description of potential diseases provide sufficient blaze marks to a person of ordinary skill in the art to know which of these disease states might be preferred or the best for a physician to use with a given dosing regimen separate and apart from what was known in the prior art?

A. No.

Q. What diseases does the specification state these Example 7 dosing methods can be used for?

A. It lists a variety of eye conditions.

Q. Is DME singled out in the list anywhere or listed as preferred?

A. It does appear on the list, but it's not differentiated or called out as being preferred.

Q. Is diabetic retinopathy provided as a standalone indication?

A. No, it's not listed on this list.

Q. So if a person of ordinary skill in the art wanted to make decisions about concluding secondary to move to tertiary dosing or to select a fixed number of loading doses, in your opinion, does the specification point to any test, measurement, performance criteria they should use to make that decision that is separate and apart from what was already known in the prior art?

A. No, it doesn't.

Q. In your opinion, does the addition of Example 7 to the continuation-in-part specification that was filed in July 2013, does that help convince a person of ordinary skill in the art that the inventor possessed a method for treating all angiogenic eye disorders with any number of secondary and tertiary doses for all the diseases listed in the

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specification?

A. No, it doesn't.

Q. Now, based on what we've just discussed, is there sufficient guidance in the specification to the person of ordinary skill in the art to establish that the inventor possessed the specific regimen of the method of Claim 19 of the '601 patent that has five loading doses followed by eight-week dosing specific to the diabetic retinopathy indication?

A. No.

Q. And can you give a brief explanation as to why.

A. Well, first of all, as I mentioned, diabetic retinopathy, there was no clinical information or evidence presented at all in the specification. And, again, there would be no reason shown as to why we would choose a particular regimen for that condition over any of the other regimens that were also mentioned in the example.

Q. Now, one of the things that Dr. Csaky did point to is that the original specification had Example 5 in it.

But what was the loading dose regimen and clinical indication that was specified in Example 5 as the required number of loading doses?

A. Three.

Q. Would a person of ordinary skill in the art accept, then, that the inventor possessed the specific regimen of the method of Claim 11 of the '601 patent that requires five

loading doses followed by an eight-week dosing regimen for DME if we accept Regeneron's view that the prior art taught away from increasing the number of loading doses?

A. No.

Q. And can you explain why?

A. Well, again, because if the prior art was telling us that we needed to not increase the number of doses out of the concerns that were mentioned, that wouldn't naturally lead you toward using five loading doses. And so that would be the reason.

Q. And would your answer be the same for the '572 patent, Claim 25, which also requires DME and five loading doses followed by an eight-week dosing regimen?

A. Yes.

Q. If the named inventor had discovered something special or distinct about this species using a method with five loading doses, what would you expect to see in the specification?

A. I would expect to see examples or rationale explaining that finding that would guide us to choose that regimen.

Q. And Dr. Csaky has also alleged that the success of the five loading doses for the treatment of DME and diabetic retinopathy was unexpected.

Have you seen that opinion from him?

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A. Yes.

Q. And I believe Dr. Csaky said that it was subsequently found after the VIEW 1 and VIEW 2 trials that the five loading dose regimen for DME or DR worked, citing to publications from Brown 2015 about the VISTA and VIVID studies and Brown 2021 for the PANORAMA study.

Did you review those?

A. Yes.

Q. Did those change your opinions?

A. Well, no, because they came out in 2015 and 2021, which was after the patent at issue here.

Q. And do the Brown 2015 and Brown 2021 articles support the premise that the named inventor was in possession of a five loading dose regimen back in 2011 or 2013?

A. No.

Q. In any event, did any of this Phase III data that Dr. Csaky is relying on specific to DME and diabetic retinopathy make it into the specification of the '572 or '601 patents?

A. No.

Q. All right. So based on what you had just discussed, what did you ultimately conclude about the specification disclosures and whether there is written description support for choosing five loading doses followed by an eight-week dosing regimen in the context of the DME or DR regimens within

the specification?

A. I think, again, for diabetic retinopathy as its diagnosis, there wasn't any data shown as to the treatment of that condition. And when it comes to DME, the data that was presented used three loading doses. And so there wasn't any information -- there wasn't any guidance on why to expressly choose the five loading dose regimen over any others.

Q. So when it comes to Claim 25 of the '572 patent and Claims 11 and 19 of the '601 patent, in your ultimate opinion based on what we've discussed today, is there sufficient guidance in the specification to establish that the inventor had possession of the claims to these specific dosing regimens particularly with regard to the five monthly loading doses at the time the applications were filed in 2011?

A. No.

Q. How about for 2013?

A. No.

Q. All right. Let's focus now again on enablement and go back through those In Re: *Wands* factors. And let's start again with the first three factors relating to quantity of experimentation, direction or guidance, or the presence or absence of working examples when it comes to the dosing.

So for Claim 6, does the '572 patent specification give the person of ordinary skill in the art any guidance or reason as to why he should stop secondary dosing and move to

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tertiary dosing beyond what was already known in the prior art?

A. No, it doesn't.

Q. And what kind of experimentation would a person of ordinary skill in the art have to do to decide from the specification the number of secondary doses that are needed when treating the full scope of angiogenic disorders in Claim 6, such as the ones we discussed earlier for PVR, pannus, and pterygium?

A. They would need to conduct an entirely new research project for each of those conditions to decide how and if the treatment could be effective for it and what the dosing regimen should be.

Q. Let's talk about one of the next factors, predictability in the art. Would you be able to predict whether or not any one of the numerous dosing regimens or numerous secondary dosing options that the specification permits would work for all of the disclosed angiogenic eye disorders covered by Claim 6 of the '572 patent, including PVR, pannus, and pterygium?

A. No.

Q. Let's take a look at the rest of the factors on your chart.

Can you explain how you weighed the remaining factors -- the breadth of the claims, nature of the invention, state of the prior art, and relative skill -- for the full

scope of the Claim 6 dosing regimens?

A. Yes. As I mentioned earlier, I think that the claim is excessively broad and its inclusion of a variety of diagnoses under the category of angiogenic eye disorders. There wasn't any information presented in the prior art as to why that particular treatment regimen should be used. And I think that, even with a high level of skill, a person of ordinary skill in the art would have a difficult time knowing how they should proceed with that without conducting research and experimentation.

Q. And in that context, you're referring to the pannus, PVR, and pterygium, for example?

A. Correct.

Q. Now let's talk about the five loading dose claims.

If, as Dr. Yancopoulos suggested in his testimony, and if Dr. Csaky testifies consistently with his opinions put here on your slide that the Phase II DME data was not enough for a person of ordinary skill in the art to reasonably expect success in clinical practice that phase proof was needed, if we accept those things, what would be the experimental burden on the person of ordinary skill in the art when it comes to clinical practice of the DME and DR claims with five loading doses that we see in Claim 25 of the '572 patent and Claims 11 and 19 of the '601 patent?

A. They would be high if they have to conduct Phase III

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trials for each of those.

Q. And is there a working example or guidance or reasoning why in the specification that expressly calls out any benefit to having five doses for DME or DR beyond what was already known in the prior art?

A. No.

Q. Again, does the specification give any working examples specific to addressing diabetic retinopathy as a standalone indication?

A. No.

Q. So for these five loading dose claims, if, as we expect, Dr. Csaky is going to opine that the art taught away from and discouraged the use of five loading doses for safety reasons, in your opinion, does the specification resolve those allegedly discouraging safety concerns when it comes to using five loading doses in DME or DR patients?

A. No, it doesn't.

Q. And how do you know that?

A. Because we don't see any guidance about the safety being assured that we should use a five-loading-dose regimen.

Q. On this question of examples and guidance and direction, Dr. Csaky did point to Example 7 as containing a dosing regimen with five monthly loading doses followed by eight-week dosing, among others.

In your opinion, is that helpful here?

A. It's not.

Q. And can you explain why.

A. I think the issue is simply that the five-loading-dose regimen was one of many regimens that were presented, and there was no differentiation of that regimen over all the others. So we wouldn't know that that should be the best one to use.

Q. And was there at least any attempt to tie increased loading doses to a particular disease state such as DME or DR?

A. No.

Q. Now, in the relevant time period, did those of ordinary skill in the art change their dosing strategies if diabetic retinopathy was presented without DME?

A. Yes. I think diabetic retinopathy without DME has different clinical end points, and the clinical decision-making for injections is different. In fact, one might think that the number of loading doses might be fewer or the frequency of injections might be fewer if you're not trying to treat macular edema but rather trying to treat other biomarkers and end points in diabetic retinopathy.

Q. And either way, does the specification suggest to the person of ordinary skill in the art that they should be varying the number of loading doses depending on the type of diabetic retinopathy that the patient has?

A. No.

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Q. So then in your opinion, and particularly if, as Dr. Yancopoulos and Dr. Csaky have suggested, getting workable dosing regimens are not routine and involve years of costly and difficult advanced human Phase III clinical trial data before someone can reasonably expect a regimen to work in their clinical practice, will the person of ordinary skill in the art have a high or low experimental burden when it comes to the DME and DR claims with five loading doses we see in Claim 25 of the '572 patent and Claims 11 and 19 of the '601 patent?

A. It would be high.

Q. And can you explain why.

A. Simply because, in order to carry out these studies, it would be essentially a Phase III clinical trial for each of these indications. And to be able to arrive at that conclusion, it would be a high burden of experimentation.

Q. Now, again, in your opinion -- and, again, this is qualified by if -- as Dr. Csaky suggests here, the art suggested reducing loading doses to three or four or even less, does the specification give a person of ordinary skill in the art any type of express reason to buck that trend and pick five loading doses instead for DME or DR with a belief that it would work?

A. No.

Q. And that's true even if they have the specification in hand?

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A. Correct.

Q. Can you explain how you weighed the remaining factors, the breadth of the claims, the nature of the invention, the state of the prior art, and the relative skill for the '572 patent's Claim 25 and '601 patent Claims 11 and 19 pertaining to the five-loading-dose regimens?

A. I thought that these were more neutral with regard to those claims.

Q. Okay. And can you explain why.

A. So why I felt they were more neutral? Is that what you mean?

Q. Yes.

Actually, if we could go back one slide.

Yes, if you can explain briefly why.

A. Simply because these claims were narrower, and they were not relying upon as broad of a terminology as was present in the other claims. And that's primarily my thought process here.

Q. So in view of the testimony that you've given, what is your ultimate opinion regarding enablement for Claim 6 of the '572 patent?

A. So my concern there is that, again, because there was essentially an unlimited number of dosing regimens -- doses that could be given and dosing regimens for -- even for diseases that we wouldn't think it would be effective for, that

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that would cause problems for enablement. And, again, there was no guidance or teaching to suggest why it should do so. So this would lead to a need for excessive experimentation.

Q. In view of testimony that you've given, what is your opinion regarding whether the five loading doses for the DME claims found in Claim 25 of the '572 patent, Claim 11 of the '601 patent, are enabled by the specification, again, with the qualification if this Court were to accept Regeneron and Dr. Csaky's opinions about the art?

A. Again, because there was no specific teaching or guidance as to why that particular regimen should be chosen for DME, that would, for me, cause concerns around enablement and leading us to have to do experimentation to find that out.

Q. And likewise in view of the testimony that you've given, what is your opinion regarding whether Claim 19 of the '601 patent is enabled if -- and, again, this is if with a qualification -- this Court were to accept Dr. Csaky and Regeneron's view of the art?

A. I think similarly, because we don't see any guidance or teaching regarding diabetic retinopathy and, in fact, no clinical data at all about that condition save for the form that has DME, we again would consider this to require experimentation to determine if it could be effective or not.

Q. And, Dr. Stewart, in view of -- for all of those -- again, with the qualifications relating to what Regeneron's

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position has been and Dr. Csaky's opinions have been -- would that experimentation be undue for a person of ordinary skill in the art?

A. Yes.

Q. Dr. Stewart, in view of the testimony that you have given, do you also have any opinions regarding the priority date that should be given to Claim 25 of the '572 patent, Claim 11 of the '601 patent, and Claim 19 of the '601 patent?

A. Yes.

Q. And can you summarize that for us briefly, please.

A. Essentially that the only scenario in which five loading doses followed by an eight-week dosing regimen was shown within the specification was in Example 7. And so that was in July of 2013. So it wouldn't -- I wouldn't think that it could go to a date earlier than that for that particular regimen.

The previous submissions didn't include support for that regimen. And none of the regimens that were -- there wasn't express callout for why that regimen should be chosen, and so there wasn't anything, I think, beyond what we already knew as to why you would treat a patient in that fashion.

Q. But even though there was no dosing regimen with five loading doses until the continuation-in-part application where they added Example 7 in July 12th, 2013, even with Example 7, is it still your opinion that the -- that there is no written

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description support or enablement for those claims?

A. Yes, it is.

Q. All right. Now, do you also understand that Dr. Csaky has made some allegation that Regeneron may deserve an earlier priority date perhaps based on some internal documents from Regeneron?

A. Yes, I do.

Q. Did Dr. Csaky explain why he thought this was so?

A. No.

Q. Did you review these internal Regeneron documents?

A. Yes.

Q. And did your opinion regarding the priority date change after your review?

A. No.

Q. And can you explain why.

A. Because, again, I didn't see any justification for why those regimens should be called out for those particular conditions even from review of those documents.

Q. All right. If you take a look at DTX 5329 in your binder, can you confirm that this is U.S. Provisional Patent Application Number 61/432,245 filed January 13, 2011?

A. Yes.

Q. And if you could take a look at DTX 5332 in your binder, can you confirm that this is U.S. Provisional Patent Application Number 61/561,957, filed November 21st, 2011.

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A. Yes.

Q. And are both of these applications in the chain of applications that eventually issued as the '572 and '601 patents?

A. Yes.

Q. If you could take a look at DDX 572 in your binder.

And I think that's one of the spiral-bound ones that's in the pocket, Your Honor. Did you prepare or have prepared this demonstrative exhibit?

A. Yes.

Q. Can you explain what it shows?

A. It shows the information presented and the different submissions being highlighted in different fashion. The information from the January 2011 submission is in plain text. The information added in the November 2011 submission is highlighted in blue, and the information added in the July 2013 submission is highlighted in yellow.

Q. If you could take a look at DDX 601 in your binder. Did you similarly prepare this demonstrative exhibit for the same reasons and using the same color-coding?

A. Yes, I did.

MS. MAZZOCHI: So just to sum up for the record, Your Honor --

BY MS. MAZZOCHI:

Q. And, Dr. Stewart, if you could confirm this.

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The highlighted copies of the patents DDX 572 and 601 put new material not found in the original provisional application, DTX 5329, but found in DTX 5332 in the November 2011 application, Dr. Stewart, those are in blue highlights in your DDX exhibits?

A. Yes.

Q. And the highlighted copies of the patents, DDX 572 and 601, included new material not found in the original provisional application but which we do see in the July -- in DTX 5330, the July 2013 continuation-in-part application in yellow highlights?

A. Yes.

Q. Dr. Stewart, now let's move to our next major category, which is indefiniteness. Do you understand that patent claims are indefinite if they fail to inform a skilled artisan with reasonable certainty about the scope of the invention at the time the patent application was filed?

A. Yes.

Q. And do you understand that part of that analysis is whether a person of ordinary skill in the art would be able to determine with reasonable certainty what the claims do and do not cover?

A. Yes.

Q. Did you identify claim terms that, in your opinion, are indefinite?

A. Yes. The use of the word "approximately" that appears in multiple locations throughout the claims.

Q. And why, in your opinion, is the use of the word "approximately" a problem in the context of these claims?

A. Because it creates uncertainty around what the dosing regimen should be that would fall inside the scope of the claims.

Q. Okay. Well, to illustrate this, let's focus on Claims 10 and 11 of the '601 patent. What terms does approximately modify in Claim 10?

A. In Claim 10 it modifies every four weeks and every eight weeks.

Q. What terms does approximately modify in Claim 11?

A. In Claim 11 it modifies every four weeks, every 28 days, or monthly.

Q. Now, in the context of the '572 and '601 patent claims, why can't we say that approximately every four weeks means the same thing as approximately every 28 days or approximately monthly?

A. Because each of those has a different unit of time measure, and so it creates uncertainty around whether they mean the same thing or not.

Q. Turning to your next slide, 77, can you explain what you've shown on this slide.

A. This is a figure showing a calendar with a schedule

of injections, with the first injection being given on February 1st. The next injection four weeks later is on March 1st. And four weeks after that would be March 29th. But when we use the term "approximately every four weeks," it creates some range of error on either side of those particular injection dates.

Q. Okay. If we can turn to your next slide, 78. Can you explain what you've shown on this slide.

A. Yes. This is also a schedule showing an initial injection given on February 1st, 28 days later on March 1st, and again 28 days later on March 29th. But when we have the term "approximately every 28 days," this also creates uncertainty with a range of error on either side of those particular dates.

Q. Turning to your next slide, 79, can you explain what you've shown on this slide.

A. Yes. Again, a schedule of injection, with the first injection on February 1st, another injection four weeks later on March 1st, and four weeks after that on March 29th. But here if we think of this in the context of approximately monthly, exactly monthly would be March 1st, but with approximately monthly it creates a larger range of error around when exactly that injection would fall.

And so we can see that even the injection on March 29th, which is actually the eight-week injection, conceivably

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could fall within an approximately monthly description.

Q. Does the specification use the term "approximately" anywhere outside the claims?

A. It's used once to describe the number of subjects enrolled in a clinical trial.

Q. Does that help give you any guidance as to the appropriate range to be given the term "approximately" in the claims we've been looking at here?

A. No.

Q. Did you see the term "approximately" applied to any dosing interval in the specification where the dosing interval was allowed to have some variability?

A. No.

Q. What did Dr. Csaky say about the definition of the term "approximately"?

A. His response to provide clarification around this topic used the word "approximate." So it didn't actually clarify this further for me.

Q. Does Dr. Csaky's definition provide the person of ordinary skill in the art with any more clarity, in your opinion?

A. No.

Q. Did you also consider Dr. Csaky's comments that approximately should be used merely to accommodate scheduling issues?

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A. Yes.

Q. And he explains that the standard could be based on scheduling issues involving both the physician or the patient. Does that, in your view, help give the person of ordinary skill in the art reasonable clarity --

A. No.

Q. -- as to the scope of the claims?

A. No.

Q. And why not?

A. Because the schedule of the physician and the schedule of the patient might be subject to different constraints. A patient might not be able to come on a particular day depending on various factors. And that might create a certain range of error as far as when the patient could come back versus a doctor's schedule that might entail only having appointments available on certain days of the week and causing perhaps even a greater range of error around when the schedule would resume.

Q. And do you understand that Regeneron has also proposed that approximately should also take into account not just the ability to return to the office but a whole new metric which is a standard of retaining remarkable efficacy?

A. Yes.

Q. And does that standard of retaining remarkable efficacy provide, in your opinion, more clarity regarding the

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term "approximately"?

A. It doesn't.

Q. And why not?

A. Because that would -- could potentially determine -- depend upon how we determine efficacy. We might determine efficacy based upon vision or anatomic features of the eye, and that might lead you to different strategies such as treat and extend and other regimens that involve maintaining efficacy over a certain period of time with a lesser frequency of injection. And so having to retain efficacy doesn't actually help guide us to know what the schedule should be.

Q. And could retaining efficacy also include a prn regimen?

A. It could.

Q. All right. So if you're trying to perform the method of Claim 11 of the '601 patent and want to be sure you're inside the scope of the claims, what does the person of ordinary skill in the art need to do?

A. I think the only way to be sure you're inside the scope is to give the injection exactly every 28 days.

Q. And what if you wanted to dose aflibercept to a patient and make sure that you were outside the scope of Claim 11 of the '601 patent?

A. Well, I think that would be very challenging because of what I showed earlier with the range of error around each

scheduled injection. And so it would be hard to know whether a particular date falls inside or outside of the approximate schedule.

Q. And what if you were trying to apply the patient or doctor's scheduling metric that Dr. Csaky proposed or the efficacy metric that Regeneron has additionally proposed? Would that help?

A. No, because, again, it would be difficult to know whether a particular consideration would cause you to fall inside or outside of the scope.

Q. Okay. And are these concerns that you've raised for the term "approximately" equally applicable to the other asserted claims -- Claim 6 of the '572 patent, Claim 19 of the '601 patent, and Claim 25 of the '572 patent?

A. Yes.

Q. All right. So based on the testimony you've just provided here, what is your ultimate opinion regarding the indefiniteness of the term "approximately" that appears in Claim 6 and Claim 25 of the '572 patent and Claims 11 and 19 of the '601 patent?

A. That it creates uncertainty around what the treatment schedule should be that would fall within the scope of the claim, and so it's indefinite.

Q. And if a person of ordinary skill in the art has multiple metric standards to choose from -- whether it's number

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of days, number of weeks, number of months, scheduling issues, or efficacy issues -- does that complicate matters further or does that clarify matters further?

A. It makes it more complicated.

Q. And, Dr. Stewart, let's go ahead and sum things up, then. Can you summarize your opinions, please, for Claim 6 of the '572 patent.

A. Yes. So in this claim my concern regarding the term "angiogenic eye disorder" that I feel is too broad and incorporates conditions for which this wouldn't be enabled and lacks written description support.

The number of doses that's given was also unlimited, as we discussed. And so I feel that this is also not enabled and lacks written description support. And the use of the term "approximately" is indefinite.

Q. All right. And, Dr. Stewart, can you sum up your opinions, please, for Claim 25 of the '572 patent.

THE COURT: Just a smidge slower this time, Doctor.

THE WITNESS: I wasn't warned about that, but I'll try.

Yes. For this claim, there were no blaze marks given linking this particular condition, which is diabetic macular edema, to this specific regimen of five loading doses. And, again, that this was not enabled under Dr. Csaky's assessment of the prior art teachings.

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I also again believe that the term "approximately" is indefinite.

BY MS. MAZZOCHI:

Q. And, Dr. Stewart, can you also summarize your opinions, please, for Claim 11 of the '601 patent.

A. Yes. Similarly, the absence of any blaze marks guiding me to this -- link this particular disease with this particular five-loading-dose schedule, it was also not enabled under Dr. Csaky's assessment of the prior art. And, again, the use of the word "approximately," which is indefinite.

Q. And then let's turn to the last claim, Dr. Stewart, to wrap up. Can you summarize your opinions, please, for Claim 19 of the '601 patent.

A. Yes. And similar to the others, there again were no blaze marks linking this particular condition to the five-loading-dose regimen. In fact, there wasn't any clinical data at all in the specification about diabetic retinopathy, the fact that it wasn't enabled again under Dr. Csaky's assessment of the prior art, and the indefiniteness from the term "approximately" being included.

MS. MAZZOCHI: And with that, Your Honor, unless you have any questions, I'm happy to pass the witness.

And if you like, we can also move into evidence the exhibits that we just discussed as an administrative matter. Those would be DTX 7100, DTX 5430, DTX 5431, DTX 5429,

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DTX 5329, DTX 5330, and DTX 5332.

And I believe those are all not objected to.

THE COURT: Let's confirm. Any objection to any of those?

MR. GREGORY: No objection, Your Honor.

THE COURT: Without objection, those exhibits are hereby admitted.

Thank you, Counsel.

(DTX 7100, DTX 5430, DTX 5431, DTX 5429, DTX 5329, DTX 5330, and DTX 5332 were admitted.)

MS. MAZZOCHI: Thank you, Your Honor.

THE COURT: You want to start and stop, Counsel, or do you just want to take a break and start --

MR. GREGORY: Let's just go ahead, Your Honor, if that's all right.

THE COURT: Go ahead. But you've probably got about -- I'm going to say ten minutes before I've got to take a break and meet a 7-year-old downstairs.

MR. GREGORY: In that case, Your Honor, I don't think I have much, but I can't promise I'm going to be under ten minutes. We could take a break.

THE COURT: Why don't we go ahead and do that. I don't want to interrupt by exiting stage left -- going out that door and from there.

Doctor, this is a little bit of a gift to you. You

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get to have lunch by yourself in the quiet. And I apologize. I don't know if you've been here for any of the other days of trial. If you have, you've heard me offer this caution or the rules of this proceeding, of course, prevent anyone from talking to you while you're midstream on your testimony.

So you're a man without a country, for lack of a better term, over our lunch break. The lawyers are hereby ordered to feed you, but they're ordered to not speak to you. So you're welcome for this little break.

Why don't we go ahead and take 45 minutes at this juncture, and we'll pick back up at 12:30 if that works for everyone. We can proceed with cross at that point.

Thank you all. My apologies. It's a different Kleeh kid's schedule this week than we're used to; so we'll see everyone at 12:30.

Again, Doctor, no one is being rude or discourteous. You're just sort of on your own.

Thank you all very much.

(A recess was taken from 11:44 a.m. to 12:37 p.m.)

THE COURT: Counsel, if you're ready, you may proceed.

MR. GREGORY: Thank you, Your Honor.

CROSS-EXAMINATION

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BY MR. GREGORY:

Q. Good afternoon, Dr. Stewart. Nice to see you again.

You've offered opinions today about the '601 and the '572 patent. Those are PTX 001 and 003 respectively, right?

A. Yes.

Q. And I think we may have a number of disagreements between you and I about the legal implications of some of the words in the patents, but I want to make sure that we can agree about what the words actually are.

First, let me just be clear. You understand that the specification of the '572 patent and the '601 patents, they're effectively identical, correct?

A. I would need to compare them word for word to confirm that, but I know they are largely similar.

Q. In your discussion with defense counsel earlier this morning, you used, I believe, the '572 patent as your example for the specification of both of them; is that right?

A. I believe so.

Q. So I'd like to do the same just to save a little bit of time, if that's okay with you.

A. Okay.

Q. All right. So with that established, let's take a look at the '572 patent. You can use defense counsel's binder that they used this morning with you. Again, it's PTX 003.

Please let me know when you have it in front of you.

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A. I have it.
Q. So you studied this patent, right?
A. Yes.
Q. Closely?
A. Yes.
Q. Please take a look first at page 14, Column 2, lines 42 to 46, if you would.

So one thing we can agree on, Dr. Stewart, is that the specification does disclose that the methods of the present invention can be used to treat any angiogenic eye disorder.

We can agree on that, right?
A. Can you say which lines you're referring to?
Q. Lines 42 to 46 of Column 2 of page 14.
A. I see that that's what is stated, yes.
Q. And we also can agree that the specification describes more specifically that the methods of the present invention can be used to treat age-related macular degeneration, diabetic retinopathy, and diabetic macular edema.

You see those words, right?
A. I do.
Q. I want you now to turn to another document that I believe is in the binder that defense counsel used with you this morning. I believe it was DTX 5329. And that should be the '245 provisional application.

Do you have that in front of you?

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A. Yes.

Q. I believe you testified this morning this is the provisional application, dated January 13, 2011.

Do you recall that?

A. Yes, I do.

Q. I want to look at paragraph 6 on page 5 of this provisional patent application.

Just let me know when you're there, and we'll put it up on the screen for you as well.

A. I'm sorry. It has number two at the bottom of the page. I see what you're referring to.

Q. You see paragraph 6?

A. Yes.

Q. Another thing we can agree on here is that the provisional application includes the same disclosure that we just saw from the '572 specification, right?

A. Yes.

Q. You'd agree that this provisional application here discloses that the methods of the present invention can be used to treat any angiogenic eye disorder.

We agree on that, right?

A. That's what it says.

Q. And just like the '572 specification, it discloses that the methods of the present invention can be used to treat age-related macular degeneration, diabetic retinopathy, and

diabetic macular edema, correct?

A. Yes.

Q. Okay. Look back at the '572 patent, the one you spent a lot of time on this morning. I specifically want to direct your attention to page 16, Column 5, lines 30 to 48. We're going to put it up on the screen for you as well.

Do you have that passage in front of you, Doctor?

A. Did you say Column 5? Oh, yes, I do. Yes, I do see it in the middle of the column.

Q. And here this portion of the specification contains a slightly longer list of angiogenic eye disorders, correct?

A. Yes.

Q. And you agree -- we can agree that the '572 patent here again discloses that the method of the invention can be used to treat angiogenic eye disorders, right?

A. It does say that.

Q. And we can again agree that here, the '572 patent discloses that the methods of the invention can be used to treat age-related macular degeneration, diabetic macular edema, and diabetic retinopathies, right?

A. Yes.

Q. I want to do a little bit of comparison now between the patent and the provisional. You're welcome to flip back and forth in the binder, and I'll also put it on the screen for you.

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First I want to look at Column 2, line 57 to 60, at page 14 of the '572 patent. I want to compare it with paragraph 8 of the '245 provisional.

We can agree, Doctor, that these passages that I've just called out in both the '572 patent and the '245 provisional, they are identical, right?

A. Yes.

Q. We can agree that they both disclose topical or intraocular administration, correct?

A. Yes.

Q. We can agree that they both single out intravitreal administration, correct?

A. Yes, they cite that in the "for example" section.

Q. Okay. Another comparison.

Next, please let's look next at Column 3, line 66 over to Column 4, line 9, on page 15 of the '572 patent. I also want you to look at paragraph 16 of the '245 provisional. And, again, we'll put that on the screen for easy reference there.

Do you have that before you?

A. Yes, I do.

Q. Again, we can agree that both of these passages in the '572 patent and the '245 provisional, they're identical, right?

A. Yes.

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Q. And we can agree that both of these passages disclose an exemplary embodiment in which each secondary dose is administered three to four weeks after the immediately preceding dose, correct?

A. Yes.

Q. And, likewise, we can agree that both these passages disclose an exemplary embodiment where each tertiary dose is administered at least eight weeks after the immediately preceding dose, right?

A. At least eight is listed as one of many choices up to 14 and a half or more.

Q. It reads, "Each tertiary dose is administered at least" -- and then there's a parenthetical, and then -- "weeks after the immediately preceding dose."

That's what it says, right?

A. Yes, it does.

Q. Eight is called out specifically, right?

A. Yes, it's the first in the series of numbers.

Q. Just a few more of these, Doctor.

Let's take a look next at Column 4, line 22, at page 15 of the '572 patent -- so I think you can stay right where you are -- and also paragraph 18 of the '245 provisional. And it's up on the screen as well for ease of reference, sir.

Please let me know when you have it before you.

A. I have it.

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Q. We can again agree that these passages in the '572 patent and the '245 provisional, they're identical, right, sir?

A. Yes.

Q. And we can also agree that both the '572 patent and the '245 provisional in these passages disclose methods wherein two or more secondary doses are administered to a patient, right?

A. Yes.

Q. And we can also agree that both the '245 provisional and the '572 patent disclose methods wherein two secondary doses are administered, right?

A. That is one of the examples given.

Q. It's set out right there in black and white, right?

A. Yes. It's the first of the numbers that are listed in parentheses.

Q. And we can also agree that both the '572 patent and the '245 provisional disclose methods wherein four secondary doses are administered, correct?

A. Yes, it's also one of the many numbers that are listed there.

Q. Well, to be clear, sir, how many numbers are listed there? It's seven, right?

A. Well, it says "or more"; so that encompasses any number beyond that point.

Q. And how many numbers are specifically called out by

name?

A. Seven.

Q. And four is one of those seven that's listed, correct?

A. Yes, it is.

Q. Let's take a look -- one more at least. Let's take a look at Column 4, line 32, on page 15 of the '572 patent -- so you don't have to turn far there -- and then paragraph 19 of the '245 provisional.

Again, we can agree that these passages are identical, right, sir?

A. Yes.

Q. And we can also agree, can't we, that both the '572 patent and the '245 provisional disclose, again, in these passages administering secondary doses in four-week intervals, right?

A. Yes.

Q. And we can also agree that both the patent and the provisional application disclose in these passages administering tertiary doses in eight-week intervals, correct?

A. Yes.

Q. I want to skip all the way down now to Example 7 of the '572 patent, and that's going to be at page 21.

Would you take a look there?

A. Yes.

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Q. And you see that the '572 patent Example 1 -- Example 7, it's titled "Dosing Regimens," correct?

A. Yes.

Q. And Example 7 does, in fact, set forth various dosing regimens?

A. Yes.

Q. I think on direct examination you referred to them as a laundry list. Is that right?

A. Yes.

Q. To be clear, we may call them -- there's a specific number there. There's 20; isn't that right?

A. There are 20 entries. I think that the reason that I view it as going beyond that level is because some of these encompass various permutations that can be considered.

Q. There are 20 entries, right, sir?

A. There are 20 entries on this example.

Q. And I want to look at Column 16, lines 35 to 38. Column 16, for reference, is page 21.

Do you have that before you?

A. Yes.

Q. I believe you highlighted this particular exemplary dosing regimen during your testimony this morning; is that correct, Doctor?

A. Yes.

Q. We can agree, can we not, that this particular

regimen includes the administration of 2 milligrams of aflibercept by intravitreal injection once every four weeks for the first 16 weeks followed by 2 milligrams of aflibercept via intravitreal injection once every eight weeks.

That's what it says, right?

A. Yes.

Q. And you understand that intravitreal injections once every four weeks for the first 16 weeks, that's five loading doses, correct, sir?

A. Yes.

Q. So this particular exemplary dosing regimen set out here in Column 16 includes monthly loading doses, right?

A. Yes.

Q. It includes fixed extended dosing -- or fixed extended interval doses of every eight weeks as well, right?

A. Yes.

Q. It recites only one interval, time interval, for the loading doses. That's four weeks, right?

A. Yes.

Q. It recites only one time interval for the fixed extended doses. That's eight weeks, right?

A. Yes.

Q. It identifies the precise number of loading doses be administered. That's five, right?

A. Yes.

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Q. And take a look now, if you will, at the bottom of Column 15, which is right below -- at the bottom of Example 7. Actually, I'm sorry. Column 15 at the top of Example 7, right below the header.

Do you see that?

A. Yes.

Q. And it defines the exemplary dosing regimen we just looked at as exactly that, a example of a dosing regimen, quote, within the scope of the present invention, right?

A. Yes.

Q. Finally, let's take a look at the bottom of Example 7. So this is going to be Column 17, and then into Column 18 on page 22.

Do you have that before you?

A. Yes.

Q. And you agree with me, right, sir, that Example 7 discloses that that exemplary five loading dose method we just talked about may be used for the treatment of diabetic macular edema, right?

A. Yes. That is one of the conditions listed.

Q. And you agree with me, don't you, sir, that Example 7 discloses that this five loading dose exemplary regimen we just talked about could be used for the treatment of vascular retinopathy, right?

A. Yes. That's another of the conditions listed.

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Q. Okay. Now that we've established, I think, a little bit more about what the patents actually say, let's talk about how you reached some of your opinions in this case.

I believe you offered several opinions that various patent claims at issue here lacked written description. Is that right?

A. Yes.

Q. You offered an opinion that Claim 6 of the '572 patent lacks sufficient written description because the specification of that patent does not disclose the inventor was in possession of a method of treating angiogenic eye disorders.

That's one of the bases for your opinions, right?

A. Yes.

Q. And your understanding is that for this claim -- that is, Claim 6 of the '572 patent -- to have written description support, the specification must provide clinical data for a substantial number of the exemplary angiogenic eye disorders listed in the specification of the '572 patent, right?

A. No.

Q. Doctor, did you have your deposition taken in this matter?

A. Yes, I did.

Q. And I actually took your deposition; is that right?

A. Yes.

Q. So we met a couple months ago, and we sat in a

conference room and I asked you a series of questions, correct?

A. Yes.

Q. And you understood you were under oath during that deposition?

A. Yes.

Q. You understood you had an obligation to tell the truth?

A. Yes.

Q. To be accurate?

A. Yes.

Q. You were, in fact, truthful and accurate in that deposition; is that right?

A. Yes.

Q. I want to put on the screen pages 111 to 112 of the doctor's testimony.

Doctor, I'm going to read this, and I want you to tell me if you were asked these questions and gave these answers at your deposition:

"Q Okay. So then to cycle back to my original question, is it your view that, to have adequate written description support for Claim 1 of the '572 patent, there would need to be disclosures in the relevant disclosure of clinical data for at least the majority of the listed angiogenic eye disorders?

"A I think that the person of skill in the art would need to believe that the inventor was in possession of that information for a substantial number of the listed disorders. And to me, in my opinion, having it for only three of the numerous is not sufficient.

"Q When you say that the person of ordinary skill in the art would need to believe that the inventor was in possession of that information for the substantial number of listed disorders, what do you mean by 'that information'? Do you mean clinical data?

"A Yes."

Doctor, did you hear those questions and give those answers at your deposition?

A. Yes, I did.

Q. You've also made various assumptions about the law to reach your written description opinions, right?

A. I'm not sure which assumptions we're referring to.

Q. Any assumptions. You made assumptions about the law to reach your written description opinions in this case, correct?

A. Perhaps. I'm not sure which assumptions we're referring to.

Q. Let me be more specific.

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In performing your written description analyses in this case, one assumption you made was that the relevant disclosure being assessed for written description needed to include an example for every embodiment of the claimed invention; isn't that right?

A. I may have said that during deposition, but I'm pretty sure that I got some of my definitions mixed up when I was speaking about written description and enablement. So I'm not sure if that's what you're referring to in that moment.

Q. Let's take a look at the doctor's testimony from page 36, so between lines 8 and 13.

Doctor, I want to read this, and you can tell me if you were asked this question and gave this answer at your deposition.

"Q In performing a written description analyses in this case, you have assumed that the relevant disclosure must include examples for email embodiment, correct?

"A Yes."

Did you give that answer at your deposition, sir?

A. Yes.

MR. GREGORY: With the Court's permission, I'd like to pass out one exhibit here.

THE COURT: Understood. You may.

MS. MAZZOCHI: Your Honor, I'll just object to this

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exhibit because it's outside the scope of the opinions that the witness testified to, not only on direct but also in his report.

MR. GREGORY: Your Honor, this is an expert ophthalmologist who's been offered by defendants in this case. He testified regarding this exhibit at his deposition. He's familiar with this exhibit. At the very least for the sake of efficiency, we'd rather do this now while he's currently on the stand than either get a subpoena and bring him back in that case or --

THE COURT: What is the relevance of DTX 3498?

MR. GREGORY: This is one of their core anticipation pieces of prior art from the DME claim, sir.

THE COURT: Understood. Overruled.

BY MR. GREGORY:

Q. Doctor, do you recognize DTX 3198 which I've just passed you?

A. Yes.

Q. And you saw this document actually before your deposition, correct, sir?

A. Yes.

Q. You saw it again at your deposition, correct, sir?

A. Yes.

Q. Let's put it up on the screen.

You understand -- why don't you also take out the

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'601 patent while you're at it, and that is PTX 001.

THE COURT: Whereabouts in '601, Counsel?

MR. GREGORY: We're going to take a look at Claim 11 at the back of your packet.

THE COURT: For the record, that's on page 21 of Column 22.

MR. GREGORY: Thank you, Your Honor.

THE COURT: Thank you. Go ahead.

BY MR. GREGORY:

Q. You're familiar with Claim 11, correct, Doctor?

A. Yes.

Q. You understand that Claim 11 depends from Claim 10?

A. Yes.

Q. And thus includes all of the elements or limitations of Claim 10?

A. Yes.

Q. By the way, Doctor, I believe you testified earlier today, you have the qualifications of the person of ordinary skill in the art as to Claims 11 and 10 of the '601 patent, right?

A. Yes.

Q. Taking a look now at the press release before you -- let me back up for a second.

You understand that this is a Regeneron press release, DTX 3198, dated September 14th, 2009, right?

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A. Yes.

Q. It's titled "Enrollment Completed in Regeneron Bayer Healthcare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)," right?

A. Yes.

Q. You agree with me, don't you, Doctor, that this press release, the September 14th, 2009, press release does not disclose all of the limitations of Claim 11 of the '601 patent, correct?

MS. MAZZOCHI: Again, Your Honor, here again I'd like to object because Dr. Albini already testified about this exhibit. The witness did not testify -- did not opine on this at all in his expert reports. And when they brought this up at his deposition, we likewise objected that it was outside the scope of his expert reports.

THE COURT: Understood. It's relevant to his methodology in reaching his opinions. Overruled.

BY MR. GREGORY:

Q. I'll repeat the question if you'd like, Doctor.

You agree that the September 14th, 2009, press release does not disclose all the limitations of Claim 11 of the '601 patent, correct?

A. When you say "all the limitations," where are you referring to?

Q. I'm referring to the elements or the limitations of

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Claim 11 of the '601 patent.

Are you familiar with that claim?

A. Yes.

Q. Okay. And my question to you is whether the September 14th, 2009, press release discloses all the limitations of Claim 11 of the '601 patent.

A. The press release is about a study regarding wet age-related macular degeneration, and this claim relates to diabetic macular edema. So it's on a different topic.

Q. I'll direct your attention, sir, to the second page of the press release, the second paragraph on the second page.

Nowhere there or anywhere else in the September 14th, 2009, press release is there a disclosure of all the limitations of Claim 11 of the '601 patent, right?

A. It talks about diabetic macular edema and refers to several treatment regimens, including monthly injection every eight weeks after three monthly loading doses or as needed after three monthly loading doses, and the claim here refers to five loading doses.

Q. So is the answer to my question yes, sir?

A. Can you repeat the question?

Q. You agree with me, don't you, that nowhere in the September 14th, 2009, press release is there a disclosure of all the limitations of Claim 11 of the '601 patent?

A. The press release does not cite the specific dosing

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regimen that's listed in the claim.

Q. We can take that down.

You'd agree with me, sir, that in 2011 people -- ophthalmologists were exploring when and how to deviate from monthly injection regimens, correct?

A. Yes.

Q. And the answer to that question was not as well as established as in subsequent years when treat and extend became more established, correct?

A. Correct.

Q. I want to shift gears one more time here.

You discussed your background a little bit earlier today, your CV and some of the journals that you contribute to, right?

A. Yes.

Q. You've published a number of papers, some of which you mentioned?

A. Yes.

Q. And a number of those papers are in peer-reviewed journals, correct?

A. That's correct.

Q. And the purpose of such publications is to present replicable research, correct?

A. Sometimes they may be review articles describing other people's research, or sometimes it might be primary

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research that you're reporting on.

Q. Sometimes they may be case reports, right?

A. Yes.

Q. But regardless of the use, you strive to be accurate in your written submissions to medical journals, correct?

A. Yes.

Q. You strive to be clear in your written submissions to medical journals, correct?

A. Yes.

Q. Now, you've offered an opinion earlier today that the term "approximately" in the asserted claims of the '601 and the '572 patents is indefinite, right?

A. Yes.

Q. You opine that ophthalmologists wouldn't understand what that word meant, right?

A. No, I didn't opine that they wouldn't understand what it meant. I stated that it provided uncertainty around the specifics of a dosing schedule.

MR. GREGORY: Your Honor, with your permission, I'd like to approach and pass out a few more exhibits.

THE COURT: Okay.

BY MR. GREGORY:

Q. So, Dr. Stewart, we've passed around now a folder containing several exhibits. I'd like to talk about them each very briefly, and I do promise to be brief.

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I want to first turn to PTX 626, which I believe should be the first document in the stack. Do you have that before you?

A. Yes, I do.

Q. And could you please take a look at the first page of that document.

A. Yes.

Q. This is a paper you authored in the journal called *Ophthalmology*, correct?

A. This was a journal *Ophthalmology Retina*, and I was a coauthor on this paper.

Q. And I want you to turn to page 1040 of this paper. I believe it's page 13 in the PDF or 13 in the printout.

Do you have that?

A. Yes.

Q. And in this paper in *Ophthalmology Retina* in a table detailing patient examination and management guidelines, you wrote, "Reattempting the refill exchange after approximately" -- you instructed -- I'm sorry -- "reattempting the refill exchange after approximately seven days."

Do you see those words?

A. Yes, I do.

Q. Let's look at the next paper in the stack. That's PTX 3352. Do you have 3352 before you?

A. Yes.

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Q. This was another paper that you authored, correct?
A. Yes.
Q. It's in the journal *Investigative Ophthalmology & Visual Sciences*, right?
A. Yes.
Q. This is from 2011?
A. Correct.
Q. Okay. I want you to turn to pages 9276 and 9277.

We'll put them up on the screen for ease of reference.

Do you see that on those pages you wrote on the page first 9276, "In some instances approximately 20 minutes into the 30-minute measurement period, a single drop of bound salt solution was placed on the cornea if the investigators judged that the eye appeared dry." And then on the very next page, you wrote, "In this study, corneal permeability was quantified approximately three to six weeks after CXL."

Do you see that?
A. Yes.
Q. Those are your words?
A. Yes.
Q. There's a few more of these here, Doctor.

PTX 3350 should be the next one in the stack. Do you have that before you?
A. Yes.

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Q. This is another paper that you wrote, right?
A. Yes.
Q. This time in the journal *Retinal Cases and Brief Reports*?
A. Yes.
Q. From a few years ago, 2017, right?
A. Yes.
Q. And on page 2 -- I believe it's page 2 of the document -- sorry -- page 1 of the document -- I believe actually the very first paragraph you write, "The patient had been diagnosed with uveitis and had been treated for approximately 18 months."
Those are your words, right, Doctor?
A. Yes.
Q. Turn to the next document in the stack. It's PTX 3351. This is an abstract for an ARVO meeting that you authored, correct?
A. Yes.
Q. ARVO stands for the Association for Research in Vision and Ophthalmology; is that right?
A. Yes.
Q. You're a member of that association?
A. Yes.
Q. You submitted this abstract at their annual meeting, correct?

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A. Yes.

Q. Let's take a look at the second page of this two-page document. You write, "Postoperative intraocular pressures were reported with a pneumatonometer at approximately 4, 8, and 11 hours and twice a day thereafter for five days."

Do you see that?

A. Yes.

Q. Other than my mispronunciation, those were your words, correct, Doctor?

A. Yes.

THE COURT: Counsel, could we get a spelling of that effort of that word for the court reporter's benefit.

MR. GREGORY: Understood. The spelling is P-N-E-U-M-A-T-O-N-O-M-E-T-E-R.

THE COURT: Understood. Thank you.

BY MR. GREGORY:

Q. Look next at PTX 3348, if you would, Doctor. This is another paper that you authored, right?

A. Yes.

Q. And it's in the *International Journal of Retina and Vitreous*, right?

A. Yes.

Q. And this paper actually concerns, it looks like, anti-VEGF therapy, right?

A. Yes.

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Q. Can you take a look at the third page of the document. Here, you don't use the word "approximately"; you use the word "about," correct?

You say, "Patients received aflibercept injections every six weeks on average and were then treated with ranibizumab or bevacizumab about six weeks after their last aflibercept injection."

Those are your words, right, Doctor?

A. Yes.

Q. One more of these. Take a look at PTX 3349.

Do you recognize this document, sir?

A. I do not. I recall being involved in this project when I was a resident, but I actually didn't realize it had gone forth to this level of submission.

Q. You don't have any reason to doubt that the Jay Stewart there in the inventor and applicant line is yourself?

A. That's me.

Q. This is an international patent application -- publication?

A. It looks to be so, yes.

Q. And if we can turn to, I believe, the second page of it, you'll see a heading called "Field of the Invention."

Do you see that?

A. Yes.

Q. And it recites that "The present invention generally

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regards the field of medicine; more particularly, it regards the field of ophthalmology."

Do you see that?

A. Yes.

Q. And I want you to look at the claims in this patent application publication and in particular Claims 45, 48, and 54, which should be on pages 53 and 54 of the printout.

Do you see that?

A. Yes.

Q. And in each of these you used the modifier "about" before a measure of weeks or months. Do you see that?

A. I didn't use that modifier.

Q. This is your patent application publication, sir, isn't it?

A. As I said, I remember working on this project as a resident but didn't realize it had actually gone forward to this level. I wasn't involved in the composing of the language for this document.

Q. You didn't tell anybody that that word was too imprecise?

A. I just stated that I wasn't involved in choosing the language for this or writing it in any fashion.

Q. Okay. Shifting gears just a bit, Doctor, I want you to look at what should be the next document in the stack. That's PTX 628.

Do you recognize this document?

A. Yes.

Q. It's the label for Eylea or a label for Eylea, correct?

A. Yes.

Q. You've seen labels for Eylea before, right?

A. Yes, I have.

Q. In fact, you've reviewed them in your clinical practice, right?

A. Yes.

Q. I want you to look at the highlights of the prescribing information, the top part of the page that we have called out right now on the screen. I want you to make sure you have that in front of you as well.

Do you see that in the dosage and administration section of the highlights of prescribing information the Eylea label recites the recommended dose for Eylea is "2 milligrams administered by intravitreal injection every four weeks" -- and then there's a parenthetical -- "approximately every 28 days, monthly, for the first three months."

Do you see that?

A. Yes.

Q. Do you see that, similarly, at the very next bullet it says that "Although Eylea may be dosed as frequently as 2 milligrams every four weeks (approximately every 25 days),

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monthly, additional efficacy was not demonstrated in most patients when Eylea was dosed every four weeks compared to every eight weeks"?

Do you see that?

A. Yes.

Q. Then do you see there are, I think, three more uses of the word "approximately" on this first page of the Eylea label modifying measures of time in either days or months.

Do you see that?

A. Yes.

Q. I want you to look at another document which I think you may be familiar with, PTX 0472. It should be the next one up in the stack.

Have you seen this document before, sir?

A. Yes.

Q. This is the Yesafili label, right, or a proposed Yesafili label?

A. Yes.

Q. You understand that Yesafili is Mylan and Biocon's proposed aflibercept biosimilar product, correct?

A. Yes.

Q. And you see the same uses of "approximately" to modify measures of time in either days or months as we just saw in the Eylea label here in the Yesafili label, correct?

A. It looks very similar.

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Q. Have you told Mylan or Biocon that they should amend this language because it's unclear?

A. No.

Q. I want you to look at one more label for me. It's the last one, I believe, in the stack. It's PTX 1617.

This is a label for Lucentis, right?

A. Yes.

Q. The active ingredient is ranibizumab?

A. That's correct.

Q. And this is a label from June 2010, correct?

A. Yes, it is.

Q. This is before priority dates that you assessed in performing your various analyses in this case, right?

A. Yes.

Q. And you see again that the word "approximately" is used multiple times in the first page of the highlights of prescribing information to modify measures of time and days.

Do you see that?

A. Yes.

Q. You're familiar with Dr. Karl Csaky, right, sir?

A. I'm familiar with him as someone in the field. And as I mentioned at my deposition, I have seen him give one or more presentations at conferences in the past.

Q. You consider Dr. Csaky an expert in vitreoretinal diseases?

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A. Yes.
Q. You consider him an expert in wet age-related macular degeneration?
A. Yes.
Q. You consider him an expert in diabetic macular edema?
A. Yes.
Q. And you consider him an expert in diabetic retinopathy, right?
A. Yes.
Q. And you would agree that Dr. Csaky is well respected in the fields of wet AMD, DME, DR, and vitreoretinal diseases generally, correct, sir?
A. I believe so.
MR. GREGORY: No further questions at this time.
THE COURT: Redirect, Counsel?
MS. MAZZOCHI: You knew there would be, Your Honor. I apologize.
THE COURT: It makes the record look cleaner when I ask.
MS. MAZZOCHI: I do appreciate that.

REDIRECT EXAMINATION

BY MS. MAZZOCHI:
Q. Dr. Stewart, for all of these references that Mr. Gregory took you through, did any of them use the term "approximately" in the same inconsistent manner that the claims

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you discussed did from the '572 and '601 patents?

A. No, not that I could tell.

Q. Can you expand on that a little bit?

A. I think the issue in the patent claims that we were discussing earlier was that there were several different means of -- measures of time being modified. And in the case of a patent claim, my understanding is that we want to be able to determine if a particular schedule falls in or outside the scope of that claim; so having that uncertainty in so many units of time makes it hard to know if a particular dosing schedule does fall in or outside of that claim.

Q. And if you can pull from that stack of papers that Mr. Gregory gave you. Let's start, for example, at PTX 3348.

A. Yes.

THE COURT: Which article is that, Counsel? I'm sorry.

MS. MAZZOCHI: 3348. This one is one of Dr. Stewart's articles titled "Conversion back to bevacizumab or ranibizumab for recurrent neovascular activity with aflibercept in age-related macular degeneration: a case series."

THE COURT: Okay. A thrilling title.

Sorry. Sorry, Doctor. Couldn't resist.

BY MS. MAZZOCHI:

Q. Dr. Stewart, if you could turn to the third page of

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the exhibit, Table 1, where it talks about patient characteristics. Did you actually put a specific range or standard deviation that was permitted for the approximate interval?

A. Yes. We included the mean and the standard deviation.

Q. Does the '572 or '601 patent have that same degree of specificity or definition?

A. No.

Q. If you could take a look at the -- let's start with the Eylea labeling. And I believe that one was PTX 628. And we can go ahead and look at the dosage and administration section on the first page.

In the context of the labeling, did they apply the term "approximately" to two different types of units, as in approximately every 28 days and approximately monthly, as we see in the '572 and '601 patent claims?

A. I think it's only modifying days in these instances.

Q. Sure.

Does the label apply the term "approximately monthly" in addition to "approximately every 28 days"?

A. No.

Q. Does that change the scope, in your opinion?

A. Yes.

Q. Can you explain why.

A. Because monthly is a much larger unit of measurement. And so if you're approximating that, then you're going to have a wider error bar on your side of that timeline.

Q. But if you're looking in the context of the labeling where it says "approximately every 28 days, monthly," without the term "approximately" modifying the term "monthly," is the term "monthly" narrow in your opinion, or is it broad?

A. It's narrow.

Q. If you -- and would your answer be the same, for example, for the Yesafili labeling that you were directed to?

A. Yes.

Q. And, likewise, do you know whether the Lucentis labeling has any of that same problem that you saw in the claims of the '572 or '601 patent?

A. I think the Lucentis label is only using approximately to modify 28 days.

Q. So no worry about the scope of range on units?

A. Only one type of unit is used here.

Q. All right. Let's go back to a couple of things that Mr. Gregory asked you.

Now, Dr. Stewart, when Mr. Gregory asked you if things were disclosed on a page or disclosed in the press release, were you using the term "disclosed" in an ordinary sense or in a legal sense?

A. To me, that would be an ordinary sense.

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Q. As in just what's written on the page?

A. Yes, meaning do I see it on the page.

Q. Okay. Let's go back to Example 7, which I believe is in PTX 3, exhibit page 21.

And let's highlight that first set of language on the bottom of Column 15 that runs from around line 61 to 67.

Do you have that, sir?

A. Yes.

Q. Now, Mr. Gregory pointed you to only one little snippet of the first two lines under Example 7. Can you read the whole thing into the record.

A. "Example 7: Dosing Regimens. Specific, nonlimiting examples of dosing regimens within the scope of the present invention are as follows: VEGFT 2 milligrams (0.05 milliliters) administered by intravitreal injection once every four weeks (monthly)."

Q. Now, would the person of ordinary skill in the art read those first two lines that you read referring to specific nonlimiting examples, would the person of ordinary skill in the art view that language as limiting the number of regimens to 20 or not limiting the number of regimens to 20?

A. Not limiting because it says nonlimiting.

Q. And then, likewise, to the extent -- I think Mr. Gregory asked you if all of these regimens could be used. Is there anything that a person of ordinary skill in the art

would find in the specification that says any one of these regimens should be used or called out to be used with DME or diabetic retinopathy?

A. No.

Q. When it came to your testimony that you provided here in court today, did you assume that you had to find an example in order to find enablement or written description?

A. No, I didn't.

Q. Let's go back, then, to the press release, which was DTX 3198. And let's go to the second page of the exhibit.

And let's call up the description of the VEGF Trap-Eye in Phase II development paragraph.

Now, I believe you indicated that what was written on the page for the first indication that involved an eight-week dosing regimen was what? 2 milligrams every eight weeks after three monthly loading doses?

A. The first one was 2 milligram monthly and then 2 milligram every eight weeks after three monthly loading doses was the second option.

Q. Now, even if there's no express recitation of the number five there, does the prn dosing regimen permit dosing that would include five monthly loading doses in the context of this regimen?

A. You could happen upon a scenario where five loading doses are given through the course of using a prn approach.

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Q. And would that prn regimen also permit, then, those five loading doses being followed by an eight-week dosing regimen?

A. It could be if that's how circumstances played out for that particular patient.

MS. MAZZOCHI: Nothing further, Your Honor. Thank you.

THE COURT: Recross?

MR. GREGORY: Nothing further, Your Honor.

THE COURT: Any exhibits we need to tidy up with the doctor?

MR. GREGORY: None from us, sir.

THE COURT: Are the stack that was in the binder part of the record, or are you satisfied just --

MR. GREGORY: We are satisfied. We don't need to move them into evidence.

THE COURT: All right. Understood.

Any other exhibits from defense standpoint, then.

MS. MAZZOCHI: Your Honor, because so many of what was in the stack I've never seen before, let me -- can I just have -- to see if I need to put them in the record for this witness just to make sure that the Court has context and completeness. But, otherwise, we don't have anything further. But we'll clean that up tomorrow morning if that's all right.

THE COURT: Understood.

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MS. MAZZOCHI: Thank you.

THE COURT: Doctor, thank you. You can step down. You can leave all the documents up there. Someone will tidy those up. Thank you, sir.

If I could ask counsel to grab whatever's up here, whomever it belongs to.

While we're doing that, Mylan may call its next witness.

If everyone has finished rotating and whatnot, Counsel, you may call your next witness.

MR. SALMEN: Thank you, Your Honor. Heinz Salmen on behalf of defendants Mylan and Biocon. We call Dr. Gregory MacMichael as our next witness.

THE COURT: Doctor, if you would come all the way to the front.

You may proceed, Counsel.

MR. SALMEN: Thank you, Your Honor.

GREGORY MACMICHAEL, PhD, DEFENDANTS' WITNESS, SWORN

DIRECT EXAMINATION

BY MR. SALMEN:

Q. Good afternoon, Dr. MacMichael.

A. Good afternoon.

Q. Would you please introduce yourself to the Court.

THE WITNESS: Your Honor, my name is Greg MacMichael.

THE COURT: Good afternoon, sir.

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BY MR. SALMEN:

Q. Dr. MacMichael, are you here testifying on behalf of Mylan and Biocon?

A. Yes, I am.

Q. And did you prepare a set of demonstrative slides to assist with your testimony today?

A. Yes, I did.

Q. Okay.

If we could pull up DDX 8 on the screen.

And I believe you've been provided a binder and a printout of these slides. Dr. MacMichael, are these the slides that you prepared?

A. Yes, they are.

Q. Dr. MacMichael, where are you from?

A. I'm from New Jersey.

Q. And turning to your demonstrative slide, DDX 2, on the screen, will you please provide the Court with a summary of your educational background.

A. Yes. I went to Penn State to get a bachelor's degree in microbiology. Subsequent to that, I went to North Carolina State University to get a master's degree in microbiology and biochemistry focusing on the use of -- I went to North Carolina State to get my master's degree in microbiology and biochemistry with a focus on the use of bacteria to break down hazardous wastes and degrade oil spills.

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Q. What was your doctoral thesis in?

A. Yes. I got my PhD in microbiology and biochemistry at Mississippi State University, again working on the use of bacteria for the cleanup of hazardous waste and oil spills.

Q. After receiving your doctorate from Mississippi State University in 1984, where did you begin your career?

A. Yeah. My first job after college was working at a company called Techne.

Q. And will you please summarize for the Court your professional experience at Techne.

A. Yes. At Techne I was working with an individual named Norman Burney, who also was a famous innovator. And together we worked on the development of bioreactors for growing up animal cells to produce therapeutic proteins.

Q. How many years were you at Techne?

A. Six years.

Q. After your six years at Techne, where did you continue your career?

A. I moved over to Centocor and was the assistant director of cell culture research and development.

Q. What was the focus of your work at Centocor?

A. It was focused on developing high-cell-density, high-volumetric productivity processes for making monoclonal antibodies.

Q. Will you please explain to the Court what a

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monoclonal antibody is.

A. Yes. As you're developing a therapeutic, you will basically genetically modify numerous cells, and then you will look to see which one was the highest level of productivity. You will then pick that specific clone that was obtained from that one cell, and thus the term "monoclonal antibody."

Q. Did you have any notable achievements during your time at Centocor?

A. Yes, I did.

Q. And can you describe for the Court, please.

A. Yes. I developed the high-density upstream processes for Centoxin, the first monoclonal ever approved, Remicade, and ReoPro.

Q. And were those FDA-approved medications?

A. They were all FDA-approved medications.

Q. And what type of drug product is Centoxin?

A. Centoxin is a immunoglobulin M for the treatment of sepsis.

Q. What were your primary contributions to the development of Centoxin?

A. Developing the high cell density processes, doing the tech transfer into manufacturing, and supporting the manufacturing efforts.

Q. What type of drug product is Remicade?

A. Remicade is an IgG monoclonal antibody for the

treatment of autoimmune disorder.

Q. What were your primary contributions to the development of the Remicade product?

A. Again, developing high cell density, high volumetric productivity processes for the manufacturing of Remicade.

Q. And turning to the ReoPro product, what type of drug product is ReoPro?

A. ReoPro is a subclass of a monoclonal. It's a fragment, called Fab -- fragment of an antibody is called a Fab -- and it was actually a fusion protein. It was part human, part mouse.

Q. Can you describe to the Court what your primary contributions were to the development of ReoPro?

A. Again, my focus was on the upstream processes to develop high productivity to be able to meet market demand.

Q. After your time at Centocor, I see you moved on to Chiron. Why did you make the move to Chiron?

A. Yes. My supervisor, the head of development at Centocor, moved over to Chiron to be the senior vice president of development and manufacturing. He asked if I would join him at Chiron, and I became the director of production in vaccines development in St. Louis.

Q. What was the focus of your work at Chiron?

A. It was developing subunit vaccines in a cell line called Chinese hamster ovarian cells.

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Q. Will you please explain to the Court what a Chinese hamster ovarian, or CHO, cell is.

A. Yes. In the production of various therapeutic proteins, they use animal cells. A Chinese hamster ovarian cell was proved to be a very robust cell line, reached high levels of cell density and productivity, and also had more favorable what we call glycosylation patterns.

Q. Can you expand on that? What is a glycosylation pattern?

A. Yes. Inside each of our cells, there's a whole set of machinery that synthesizes proteins. And after the primary protein is synthesized, the cells then can further -- what's called posttranslational modification. They can modify those cells by putting sugars on those cells to change the performance in the bloodstream.

Q. Dr. MacMichael, did you invent the glycosylation pattern for the proteins you were working on?

A. No. Every cell in the human body has the ability to glycosylate proteins.

Q. And what notable achievements did you have at Chiron?

A. At Chiron we produced -- we developed multiple vaccines, but one of most interest would be hepatitis B vaccine where I led the global team, which included a clinical, regulatory, and manufacturing and development, and basically developed a new formulation for that vaccine.

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Q. Let me follow up on that, Dr. MacMichael. Were you overseeing the formulation activities during that development?

A. Yes, I was.

Q. After Chiron, I see you moved over to Eli Lilly in 1997. Why did you make the move to Lilly?

A. Yes. Eli Lilly was trying to develop a product called Xigris, activated protein C produced in HEK293 cell line, but they lacked the internal experience of how to grow those cells at high cell density. So they recruited me in to help them develop the process.

Q. What was your title at Lilly?

A. Senior director of development.

Q. What type of drug products were you working on at Lilly? What was your focus?

A. The focus was on therapeutic proteins.

Q. Will you please describe to the Court some of your notable achievements at Lilly.

A. Yes. Probably the two more notable achievements was the successful development and registration of Xigris, activated protein C for the treatment of sepsis; and additionally the development of truncated parathyroid hormone, known as Forteo, for the treatment of osteoporosis.

Q. Were those drugs approved by any regulatory authorities?

A. They were approved by the FDA and the EMA.

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Q. I see you continued your career at Wyeth. What was your title at Wyeth?

A. At Wyeth I was vice president of vaccines development.

Q. And I see you have a couple drug names listed here on Slide 3 of DDX 8. What are those drugs that you were referring to?

A. They're probably two of my more notable accomplishments while at Wyeth. Prevnar 13 is a pneumococcal vaccine that vaccinates against 13 different types of pneumococcal pneumonia.

Q. Let me ask a follow-up to that, Dr. MacMichael. What was your contribution to the development of the Prevnar 13 formulation?

A. Yes. I had responsibilities from cell line development through upstream process development, purification and final formulation and the development of the analytical -- of the assays required for in process and release testing.

Q. Did you contribute to the stable formulation for the Prevnar 13?

A. Yes.

Q. And how did you achieve a stable formulation in Prevnar 13?

A. Yes. Initially, we found that, heading into Phase I clinical trials, the vials -- just vibration in the

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refrigerators was sufficient agitation to cause some undesired aggregation. We addressed that by adding Pluronic -- by adding polysorbate 80 to prevent the aggregation.

Q. The second product on your list at Wyeth is FluMist. What type of drug product is FluMist?

A. FluMist is a more advanced version of the annual flu vaccine that many of us get. The difference with FluMist is it's -- actually, the virus is not inactivated; so it elicits a better immune response. It's sprayed up the nose, and it cannot grow in the lungs. So it gets a very good immune response protecting the recipient against the flu.

Q. Dr. MacMichael, what was the general time frame for your work on the Prevnar 13 and FluMist formulation?

A. 2002 through 2008.

Q. I see you next were the senior vice president of development and manufacturing at Cook Pharmica in 2008.

What was the focus of your work at Cook?

A. Cook was a contract development and manufacturing organization. That is, we didn't have our own products; we developed and manufactured the products for our clients.

Q. And then in 2010 you moved on to Novartis as global head of biologics. What was the focus of your work at Novartis?

A. My focus at Novartis was the development activities required to bring the biologic pipeline in Novartis, which

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included cell line development, upstream process development, purification, final formulation development, and the analytics required for all of those activities.

Q. Thank you, Dr. MacMichael.

If we turn to Slide 4 of DDX 8, can you describe to the Court what you have illustrated here on Slide 4.

A. This is a summary of some of the products that we touched on. These are eight products that I successfully developed and supported the registration and the interactions with the FDA and EMA.

Q. Let me ask about that, Dr. MacMichael. In your over 30 years of industry experience, did you gain experience on the regulatory side of product development?

A. Yes, I did.

Q. Can you describe that experience briefly.

A. Yes. To bring these types of molecules successfully forward, you have numerous interactions with the FDA and the EMA. It also requires an understanding of how to construct the various submissions that are required for successful registration.

Q. Dr. MacMichael, are you still active in the pharmaceutical industry?

A. Yes, I am. I founded my own consultancy called CMC Bioservices.

Q. And what types of companies do you generally consult

for?

A. I consult in the pharmaceutical industry everything from a large pharma company down to small startups.

Q. What technical areas do you generally consult in?

A. My focus is on therapeutic proteins, vaccines, and cell and gene therapies, from development of cell lines all the way down through the final drug product.

Q. Last question on your background Dr. MacMichael. Using your own words, how would you describe your areas of expertise?

A. Yeah. My expertise -- CMC stands for chemistry manufacturing control is the term we used for doing process development and manufacturing. My expertise starts with cell line development, and the cell lines that produce therapeutic proteins are put down in vials called cell banks. We do a cell line selection for the highest producer.

Subsequent to that, we develop across the upstream process, grow the cells up, and produce the desired protein. We then need to purify it. And then subsequent to having it purified in what we call bulk. It is then formulated into the final vial.

So in many ways, I have responsibilities from vial to vial, is one way to put it.

Q. Is that vial to vial illustrated on Slide 6 of DDX 8?

A. Yes, it is.

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Q. Dr. MacMichael, I see you've cited DTX 7087, pages 1 through 6. There's a copy of it in your binder, but we could also show that on the screen for you.

Is this a copy of your current CV?

A. Yes, it is.

MR. SALMEN: Your Honor, we move to admit DTX 7087 into evidence.

THE COURT: Any objection?

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 7087 was admitted.)

MR. SALMEN: And at this time, Your Honor, we proffer Dr. Gregory MacMichael as an expert in the formulation and development of therapeutic proteins.

THE COURT: Any voir dire or objection?

MR. BERL: No, Your Honor.

THE COURT: Without objection then, motion granted. The doctor is deemed so qualified.

You may proceed, Counsel.

MR. SALMEN: Thank you, Your Honor.

BY MR. SALMEN:

Q. Dr. MacMichael, if we turn to Slide 7 of your slide presentation, DDX 8, let's talk about the opinions that you plan to provide to the Court today.

If I could first direct your attention to PTX 2, we

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have the first page of PTX 2 here on Slide 8.

What is PTX 2?

A. PTX 2 is the '865 patent.

Q. And did you review and analyze the '865 patent, PTX 2, in forming your opinions?

A. Yes, I did.

Q. And let's also put DTX 0030 on the screen.

Dr. MacMichael, did you review and consider the document known as the prosecution history for the '865 patent in forming your opinions?

A. Yes, I did.

Q. Turning to slide -- back to Slide 8 of DDX 8, Dr. MacMichael, before we go through your opinions, let's just set the stage a little.

Did you conduct your analysis in this case from the perspective of a person of ordinary skill in the art?

A. Yes.

Q. And if we look at Slide 8, top callout, citing DDX 2679, pages 19 to 20, MacMichael opening report, is this the definition for the person of ordinary skill in the art that you applied in forming your opinions?

A. Yes, it is.

Q. And I'll read that definition into the record for you, Dr. MacMichael.

"A POSA during the relevant time period would have a

fairly high level of education and skill. Here, a POSA would have at least a PhD in chemistry, chemical engineering, biochemistry, pharmacology, or a related field, along with one to two years of experience in the development and manufacture of formulations of therapeutic proteins or a lower degree with more practical industrial experience. A POSA would have access to biologists, biochemists, physicians, pharmaceutical formulators, and the like with knowledge and experience in fields such as drug discovery and development and the treatment of ophthalmologic conditions."

Dr. MacMichael, is this the definition of a person of ordinary skill in the art that you applied in forming your opinions?

A. Yes, it is.

Q. Dr. MacMichael, did Dr. Trout also offer for a person of ordinary skill in the art?

A. Yes, he did.

Q. Do you have Dr. Trout's definition illustrated at the bottom right-hand side of Slide 8 of DTX 8, citing DTX 2251, page 11?

A. Yes, I did.

Q. How did Dr. Trout's definition compare to yours?

A. Relatively similar. Dr. Trout just had a master's degree where I had suggested a PhD for the POSA. Other than that, the two definitions were relatively similar.

Q. Dr. MacMichael, would your opinions regarding the '865 patent change at all if the Court were to adopt Dr. Trout's definition?

A. No, they would not.

Q. Now, let's move on to our second foundational point, Dr. MacMichael. Turning to Slide 9 of DDX 8, are you aware that the Court issued a claim construction order regarding certain terms of the '865 patent that are relevant to your opinions?

A. Yes, I am.

Q. And if we look here on Slide 9, we have the Court's claim construction order marked for identification at DTX 6439 here at page 20. I'll read this for you, Dr. MacMichael.

"The Court adopts Mylan's definition of 'cosolvent.' It is an organic substance added to the primary solvent to increase the solubility of the solute, here a VEGF antagonist."

Dr. MacMichael, is this the construction of the claim term "cosolvent" that you applied to your analysis regarding infringement and validity of the '865 patent?

A. Yes, it is.

Q. If we turn to Slide 10, please.

Dr. MacMichael, will you explain to the Court what you have illustrated here in the bubble at the center of Slide 10, DDX 8, citing DTX 6439, page 20.

A. Yes. I took the Court's construction for an organic

cosolvent and edited Claim 1. And as you see in the highlighted yellow -- excuse me -- red is the insertion of the Court's construct.

Q. And, Dr. MacMichael, is that the version of Claim 1 that you applied in your analysis regarding the infringement inquiry?

A. Yes, it is.

Q. If we turn to Slide 11, please, of DDX 11.

Dr. MacMichael, will you please summarize for the Court the opinions you plan to offer today regarding the alleged infringement of the '865 patent against Mylan and Biocon's Yesafili product.

A. Yes. Applying the Court's claim construction order, Yesafili does not infringe on the asserted Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent.

Q. And did you form an opinion regarding whether polysorbate 20 at 0.03 percent in Yesafili is an organic cosolvent?

A. Yes, I did.

Q. And what was your conclusion?

A. My conclusion is that polysorbate 20 at 0.03 percent in Yesafili is not an organic cosolvent.

Q. And did you form an opinion regarding whether polysorbate 20 at 0.03 percent in Yesafili is increasing solubility of the solute aflibercept in the Yesafili product?

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A. Yes, I did evaluate.

Q. And what was your conclusion in that regard?

A. My conclusion was that polysorbate 20 at 0.03 percent in Yesafili does not increase solubility of the solute aflibercept.

Q. Dr. MacMichael, I understand that you were unable to attend Dr. Trout's testimony in person. Were you nonetheless able to review Dr. Trout's trial testimony as well as his associated demonstratives?

A. Yes, I was.

Q. Was there any portion of Dr. Trout's testimony that you want to respond to specifically during your testimony today?

A. There's two points where I believe we disagree.

Q. Can you explain to the Court those two points of Dr. Trout's testimony that you would like to respond to.

A. Yes.

Q. First point, please.

A. The first point, Dr. Trout defined inhibiting aggregation as equal to increasing solubility.

Q. Do you agree or disagree with that testimony?

A. I disagree.

Q. And your second point, Dr. MacMichael?

A. The second point where I differ is reducing insolubility is equivalent to increasing solubility. I

disagree.

Q. Dr. MacMichael, I would next like to talk about some of the technology relevant to your opinions in this case. If we could turn to Slide 13. Here on Slide 13 of DDX 8 we have DTX 5172, the Bontempo reference. Dr. MacMichael, did you review and consider the Bontempo reference in forming your opinion?

A. Yes, I did.

Q. Will you please explain to the Court the information you have identified here in Slide 13 from Bontempo that's relevant to your opinions and testimony in this case.

A. Yes. I pulled a list of potential buffers that could be used in a protein formulation.

Q. And that information -- does that information come from page 7 of DTX 5172, Bontempo?

A. Yes, it does.

Q. If we turn to the next slide, Slide 14 -- actually, I'm sorry. I forgot to ask a question.

Could we go back one.

Dr. MacMichael, can you please explain the relevance of the information that you provided in the parentheticals following each of the listed buffers?

A. Yeah. The parentheticals are showing the pH ranges where each of these buffers would -- each one of these moieties would be effective as a buffer.

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Q. And, for example, if we look at succinate, what would be the buffering range for that buffer?

A. A pH of 3.2 to 6.6.

Q. And for citrate, what would be the known buffering range for a citrate buffer?

A. 2.1 to 6.2.

Q. For histidine, what would be the known buffering range for a histidine buffer?

A. 5.5 to 6.5.

Q. If we turn to Slide 14, please, of DDX 8.

Here, Dr. MacMichael, we have Exhibit DTX 5196. This is the Strickley reference. Dr. MacMichael, did you review and rely on the Strickley reference?

A. Yes, I did.

Q. And please explain to the Court the teaching in Strickley that you have highlighted here on Slide 14 from page 2 of DTX 5196.

A. Yes. I pulled out Strickley's definition of a cosolvent.

Q. And is that identified in the yellow highlighted language there?

A. Yes, it is.

Q. I'll read that for you, Dr. MacMichael.

"Cosolvents are mixtures of miscible solvents and are often used to solubilize water-insoluble drugs."

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Is that part of the information from Strickley that you relied upon?

A. Yes, it is.

Q. And is this disclosure in Strickley consistent with how a person of ordinary skill in the art would understand the use of cosolvents in pharmaceutical formulations?

A. Yes.

Q. Could we turn to Slide 15, please.

Here on Slide 15 we have another passage from the Strickley reference, DTX 5196. This time we're on page 1.

Dr. MacMichael, will you please explain to the Court the information in Strickley that you have identified here to help inform your testimony.

A. Yes. What's pulled out in the paragraph that's being shown is examples of water-soluble organic solvents. Some of the examples would be polyethylene glycol 300, polyethylene glycol 400.

Q. And with regard to the nonionic surfactants that you have highlighted there, does Strickley provide examples of nonionic surfactants?

A. Yes, they do.

Q. What are a couple of the examples of nonionic surfactants that you've highlighted here on Slide 15, DDX 8?

A. For today's discussion I highlighted polysorbate 20 and polysorbate 80.

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Q. Dr. MacMichael, are these descriptions from Strickley of polysorbate 20, polysorbate 80, and polyethylene glycol consistent with how a person of ordinary skill in the art would understand and characterize those excipients?

A. Yes.

Q. If we turn to Slide 16, please.

Here, Dr. MacMichael, we have DTX 5011. This is the Akers reference. Did you review and consider the Akers reference, DTX 5011?

A. Yes.

Q. And will you please explain to the Court the information from Akers here on page 3, DTX 5011, that you've identified to help inform your testimony.

A. Yes. Again, it defines a cosolvent and then gives additional information on how a cosolvent works in water.

Q. Let's break that down with the first highlighted language. I'll read that for you, Dr. MacMichael.

"Cosolvents are used to increase the solubility of a poorly soluble drug in water."

Is that part of the disclosure from Akers that you reviewed and considered?

A. Yes, it is.

Q. And can you describe for the Court the importance of the second passage from Strickley that you have here.

A. Yes. The second passage is showing how a cosolvent

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changes the overall physical chemistry of the solution. And the way that Akers defines it is a water-miscible cosolvent operates on the principle of lowering the dielectric constant property of water, thereby increasing the aqueous solubility of a poorly water-soluble drug.

Q. If we turn to the next slide, please, Slide 17.

Here, Dr. MacMichael, we have DTX 5012, what's known as the Ansel reference, *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. Dr. MacMichael, did you review and consider DTX 5012 in forming your opinions?

A. Yes, I did.

Q. I see you have two callouts here, Dr. MacMichael, both from page 12 of DTX 5012. Will you please explain to the Court the information from Ansel that you've identified here to help inform your testimony.

A. There's two things I wanted to accomplish. One was the definitions of a solvent and a surfactant. Then secondly to give a list of examples of potential solvents and surfactants.

Q. Let's start with the first definition applied here for solvent. I'll read that for you, Dr. MacMichael.

"Used to dissolve another substance in preparation of a solution."

Dr. MacMichael, is that definition for solvent consistent with how a person of ordinary skill in the art would

understand that excipient?

A. Yes, it is.

Q. And the second definition you've highlighted here is for surfactant. I'll read that for you as well.

"Substances that absorb to surfaces or interfaces to reduce surface or interfacial tension."

Dr. MacMichael, is that definition consistent with how a person of ordinary skill in the art would define and characterize a surfactant?

A. Yes, it is.

Q. We turn now to Slide 18, please.

Here on Slide 18 of DDX 8, we have what's already been admitted as PTX 1817. This is the Randolph and Jones reference, Dr. MacMichael.

Did you review and consider the Randolph and Jones reference to help inform your opinions and testimony?

A. Yes, I did.

Q. And will you please explain to the Court the information from Randolph and Jones that you have identified here to help inform your testimony.

A. Yes. Again, I used the Randolph and Jones to further -- give further support of the definition of a surfactant as being used as a stabilizing agent in a protein formulation, and they're typically nonionic.

Q. And let me ask you, Dr. MacMichael, what subject

matter did Randolph and Jones direct their focus on in this chapter?

A. It focused on the interaction of nonionic surfactants and proteins with respect to developing formulations.

Q. Thank you.

We move to just the next slide, please, Slide 19.

MR. SALMEN: Your Honor, if I may, at this point in time I am going to have to ask to have the courtroom sealed pursuant to Your Honor's previous order. We are going to be getting into the details of Mylan and Biocon's Yesafili product.

THE COURT: Understood.

Any objection to that from Regeneron?

MR. BERL: No objection.

THE COURT: Ladies and gentlemen, consistent with our prior -- I meant to turn that off.

Ladies and gentlemen, consistent with our prior practice, anyone who's not permitted to be in the courtroom consistent with this Court's protective order entered in this case, I would kindly ask you to step out, please. Thank you.

I would continue to ask counsel to assist the Court in policing enforcement of that requirement just with a quick look around.

THE COURT: Seeing no further objections, I'll ask court security to please seal our courtroom, sir. Thank you.

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Go right ahead, Counsel.

MR. SALMEN: Thank you, Your Honor.

(The following proceedings (1384/3 to 1416/2) were had under seal, and are filed under separate cover.)

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(Record unsealed.)

THE COURT: Counsel, if you're ready, you may proceed.

MR. SALMEN: Thank you, Your Honor.

BY MR. SALMEN:

Q. Ready, Dr. MacMichael?

A. Yes, I am.

Q. Dr. MacMichael, have you been asked to offer an opinion regarding the validity of the asserted claims of the '865 patent?

A. Yes, I have.

MR. SALMEN: I just wanted to make sure we unsealed the courtroom, Your Honor.

THE COURT: We have.

MR. SALMEN: Just double-checking.

BY MR. SALMEN:

Q. And, Dr. MacMichael, if we turn to Slide 41 of your presentation here.

Will you please provide the Court with a brief summary of your opinions that you plan to provide today.

A. Yeah. This slide shows three of my opinions.

Q. If we address them one at a time, have you formed an opinion regarding the enablement of the '865 patent?

A. Yes. My first opinion was it lacks enablement. The breadth of the asserted claims is not enabled by the '865

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patent specifications.

Q. Will you please summarize for the Court your opinion regarding the written description of the '865 patent.

A. My opinion is the asserted claims do not have sufficient written description. The '865 patent specification fails to inform the skilled person that the named inventors possessed anything but a phosphate-buffered sucrose-stabilized formulation.

Q. And then lastly, Dr. MacMichael, will you please provide a summary of your opinion regarding the indefiniteness inquiry of the '865 patent.

A. Yes. The patent's indefinite because the '865 patent specification fails to inform the skilled person what suitable for intravitreal administration means. That term is subjective and prone to multiple interpretations.

Q. If we turn to Slide 42, please.

Here on Slide 42, Dr. MacMichael, I see you have the enablement legal standard. And I'll read that for you.

"A claimed invention is not enabled and, therefore, is not patentable when the specification does not provide a sufficient description to a person of ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation."

Dr. MacMichael, is this the standard you applied in your assessment of whether the '865 patent specification

enables the asserted claims?

A. Yes, it is.

Q. If we turn to the next slide, Slide 43, please. Here on Slide 43, Dr. MacMichael, I see you have a graphic that looks like an upside-down pyramid. Can you please explain to the Court what information you are trying to convey with this graphic.

A. Yes. This graphic is showing that, as you build on the -- the claims build upon one another, there should be a narrowing in scope of the invention.

Q. And I see on the left-hand side of this Slide 43 you have identified claims of the '865 patent, the referenced Claims 2, 5, and 10, followed by the asserted Claims 4, 7, 9, 11, 14, 15, 16, and 17.

Let me ask, Dr. MacMichael, does this graphic on Slide 43 illustrate the breadth of the asserted '865 -- asserted claims of the '865 patent?

A. No, it doesn't.

Q. If we turn to Slide 44, please, please explain to the Court what you have illustrated here in Slide 44.

A. Yes. What we are seeing here, the way these claims are constructed, rather than narrowing -- rather than narrowing the overall claims of the invention, it actually broadens them.

Q. Let's break that down, Dr. MacMichael.

Here from Claim 5 to Claim 7 can you explain how the

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claims compare in scope?

A. Yeah. All the claims that are being highlighted with the word "compromises," [sic] as we know just means includes, polysorbate; so it gives various examples of components that could be used and potential concentrations and ranges of -- for example, ranges of pH. So there's an extraordinary -- not extraordinary number, but there's a large number of variables that have to be worked through. And that's not clearly defined within the scope of this claim.

Q. Thank you, Dr. MacMichael. Let's turn to your enablement analysis.

If we turn to Slide 45.

Dr. MacMichael, did you apply each -- here on Slide 45 we have identified the *Wands* factor. Did you apply each of the *Wands* factors in forming your opinion regarding the enablement of the '865 patent claims?

A. Yes, I did.

Q. And let's walk through these. If we turn to Slide 46, I'd like to start at the bottom of this list with *Wands* Factor 8, the breadth of the claims.

Dr. MacMichael, did you form an opinion regarding the breadth of the '865 patent asserted claims?

A. Yes, I did.

Q. And Dr. MacMichael, will you please explain to the Court the conclusions you reached regarding the breadth of the

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claims?

A. Yes.

THE COURT: One second, Doctor.

Yes, Counsel?

MR. BERL: Objection, Your Honor. This is leading. I mean, we haven't been sticklers about this, but this is basically having the answers on a screen and asking him to read them. That doesn't seem like an appropriate question.

THE COURT: Overruled at this point.

But it is direct examination, Counsel. Go ahead.

BY MR. SALMEN:

Q. Dr. MacMichael, let me ask the question again.

Will you please explain to the Court the conclusions you've reached regarding the breadth of the claims.

A. Yes. There's different types of formulations that are being cited. There's various types and concentrations of the buffers. Examples are given -- citrate, succinate, phosphate, histidine. However, that claim uses the word "comprise." So those are examples. Multiple other buffers could be, in fact, used.

Secondly, various types and concentrations of stabilizing agents are suggested. And then various types and concentrations of the organic cosolvent are also being suggested. But they use the word "comprises," which leaves it open-ended.

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Q. And let me ask, Dr. MacMichael, would a skilled person understand that combinations of different buffers could be used as well?

A. Yes. You could use more than one specific buffer. You can use a combination, which is actually practiced to achieve a desired pH.

Q. And under the claim language here, could combinations of different stabilizing agents be used as well?

A. Yes, they could.

Q. And same question for cosolvents, could combination of organic cosolvents be used here under the claim language?

A. Yes. In fact, we were going to use cosolvents -- various cosolvents could be used and examples were highlighted.

Q. Last question for this part, Dr. MacMichael. Now that you've identified the variables in the claims with respect to each of the required components of Claim 1, do the asserted dependent claims sufficiently narrow this universe of formulations that would lessen the burden on the person of ordinary skill in the art practicing these claims?

A. No, they would not.

Q. If we turn to Slide 47, please.

Did you also consider and apply *Wands* Factors 4, 5, 6, and 7 listed here on Slide 47 on the left-hand side?

A. Yes, I did.

Q. I'll read those for you, Dr. MacMichael. *Wands*

Factor 4, the nature of the invention. Factor 5, the state of the prior art. Factor 6, the relative skill of the art. And Factor 7, the predictability or unpredictability of the art.

Dr. MacMichael, what conclusion did you reach with respect to the amount of experimentation a person of ordinary skill in the art would need to practice the full scope of the claims?

A. There would need to be a significant amount of experimentation.

Q. Dr. MacMichael, did you identify any evidence in the record that supports your opinion that the skilled person would require a significant amount of experimentation?

A. Yes. I cite two examples that are highlighted in yellow.

Q. So let's take those one at a time. DTX 5053, this is at page 17. This is Regeneron's response to an office action.

Dr. MacMichael, did you review and consider this document?

A. Yes, I did.

Q. And I'll read that for you.

"Thus, one of ordinary skill in the art, upon reading Remington's, would expect to engage in significant nonroutine experimentation to develop a successful formulation as claimed herein."

Dr. MacMichael, was that some of the evidence that

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you identified --

A. Yes, it is.

Q. -- as support for your opinion that the skilled person would require additional -- undue experimentation?

A. Yes, it is.

Q. If we look at the bottom callout, DTX 4430, at page 3, that's a declaration of named inventor Daniel Dix.

Dr. MacMichael, did you review and consider DTX 4430 with regard to your opinions?

A. Yes, I did.

Q. And I'll read that statement for you.

"Formulation of pharmaceutical preparations and achieving a stable composition is not a simple or routine matter."

Dr. MacMichael, do you agree with that statement from Dr. Daniel Dix?

A. Yes.

Q. And is this part of the evidence that you reviewed and considered to support your opinion that the skilled person would require undue experimentation practicing the asserted claims of the '865 patent?

A. Yes.

Q. And, Dr. MacMichael, if we move to our next slide, Slide 48, did you form an opinion regarding the amount of direct -- I'm sorry.

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Did you form an opinion regarding the amount of direction or guidance presented in the '865 patent specification?

A. Yes, I did.

Q. And did you form an opinion regarding the presence of working examples in the '865 patent specification?

A. Yes, I did.

Q. Let's start with *Wands* Factor Number 3. What conclusions did you reach regarding the presence or absence of working examples in the '865 patent specification?

A. Yeah. There were examples given from the phosphate-buffered sucrose-stabilized formulations. However, for the other examples -- the other areas where the term "comprised" was used, there were no examples given.

Q. Were there any examples provided in the '865 patent specification of using any other type of buffer or stabilizer in a stable formulation?

A. I'm trying to recall. I believe it was glycol or glycerol. I'm sorry.

Q. Let me ask a more direct question, Dr. MacMichael.

Does the '865 patent specification provide any example that is not a phosphate-buffered solution?

A. No.

Q. Let's now look at *Wands* Factor 2, the amount of direction or guidance presented.

Dr. MacMichael, what conclusions did you reach regarding the amount of direction or guidance presented in the '865 patent specification?

A. That there was insufficient guidance.

Q. And here on Slide 48 of DDX 8, I see you have a callout from the patent, PTX 2, page 4, Column 2, lines 39 to 48. Will you please explain to the Court the information that you've highlighted here from the patent.

A. Yeah. I wanted to highlight the fact that there was multiple examples that are being given for some of the various constituents for both -- for the stabilizing agents as well as the organic cosolvent.

Q. And what was the purpose of highlighting the language in this passage "for example, for example, or a combination of, maybe," then "maybe, for example."

A. Because it's not specific. It's open-ended, and it allows numerous components to be considered at various concentrations.

Q. Let's turn to Slide 49.

Dr. MacMichael, did you form an opinion regarding the final *Wands* factor listed here, *Wands* Factor Number 1, the quantity of experimentation necessary?

A. Yes, I did.

Q. And what was your conclusion with respect to *Wands* Factor Number 1, the quantity of experimentation necessary?

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A. Although there would be a significant amount of experimentation that would be needed, and the screen -- the screening can be significant and the screening can be complex.

Q. Let's move on to Slide 50, please.

Dr. MacMichael, were you asked to provide an opinion regarding the written description requirement as it applies to the '865 patent?

A. Yes, I was.

Q. If we turn to Slide 51, I see here you have the legal standard for a written description. I'll read that for you, Dr. MacMichael.

"The patent must convey with reasonable clarity to persons of ordinary skill in the art that, as of the filing date, the inventor was in possession of the entire claimed genus, not just a species of the genus."

Dr. MacMichael, is this the legal standard that you applied in forming your opinion?

A. Yes, it is.

Q. Let me ask you the first question, Dr. MacMichael.

Does the '865 patent disclose a representative number of species that fall within the scope of the claimed genus of formulations covered by the '865 asserted claims?

A. No, it does not.

Q. How many species of the claimed genus are disclosed in the '865 patent?

A. I'm sorry. Please repeat your question.

Q. Sure.

How many species of the claimed genus are actually disclosed in the '865 patent?

A. I'm trying to recall. The names are given, but not the structural -- structure. So maybe if you could be a little more precise with your question.

Q. Does the patent disclose a phosphate-buffered sucrose-stabilized species?

A. Yes, it does.

Q. And does the patent disclose any other formulation that does not use a phosphate buffer?

A. No, it does not.

Q. And I'll ask you the second question of the written description legal inquiry.

Quote -- excuse me.

Does the '865 patent disclose structural features common to the members of the genus so that a person of ordinary skill in the art can visualize or recognize the members of the genus of formulations?

A. No, it does not.

Q. If we turn to Slide 52 of slide deck DDX 8, Dr. MacMichael, will you please provide the Court with a summary of your opinions with regard to the written description inquiry.

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A. My summaries are -- there's three points I'd like to make.

One is every example has phosphate buffer or sucrose stabilizer -- excuse me -- every example has phosphate buffer and a sucrose stabilizer.

Q. And how many embodiments are within the possession of the inventors of the '865 patent according to the '865 specification?

A. There's only one embodiment.

Q. And in your opinion, Dr. MacMichael, would a person of ordinary skill in the art be able to visualize or recognize any other members of the genus of formulations that's claimed by the '865 patent?

A. No.

Q. If we turn to Slide 54, please.

THE COURT: Yes, counsel?

MR. BERL: I just want to note for the record that we did not receive that slide that he just presented.

THE COURT: I'm sorry. Say that again.

MR. BERL: We did not receive the slide that he just presented. The parties have been exchanging demonstratives, objecting. We've all been playing by the rules, and I've never seen that slide before.

MR. SALMEN: Your Honor, I can explain that.

Counsel for Regeneron objected to our original slides

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there; so we tried to pare those down in response to their objections. And then we submitted them today.

THE COURT: Is the objection, Mr. Berl, to Slide 54?

MR. BERL: No. 52.

THE COURT: 52.

MR. BERL: They pared it down, I suppose, but they had information there that wasn't on the slide originally, and then they didn't send it to us after they changed it.

THE COURT: Understood.

We've run afoul of any number of agreements in the parties' joint memo. With y'all going forward from here, it is this Court's rule we're going to convene and conduct this trial pursuant to the rules of civil procedure, rules of evidence. Y'all can deal with the fallout of failing to comply and abide by the agreements you reached and the trial had been.

The Court will overrule the objection and the presentation of the slide with that noted.

MR. SALMEN: Thank you, Your Honor.

BY MR. SALMEN:

Q. If we turn to Slide 54, please.

Dr. MacMichael, were you asked to evaluate whether the patent passes the test for indefiniteness?

A. Yes.

Q. And here on Slide 54, I see you have the indefiniteness legal standard. I'll read that for you.

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"A patent is invalid for indefiniteness if it claims -- if its claims" -- I'm sorry. Let me start over.

"A patent is invalid for indefiniteness if its claims read in the light of the specification and the prosecution history fail to inform with reasonable certainty those skilled in the art about the scope of the invention."

Dr. MacMichael, is this the legal standard you applied in evaluating the indefiniteness inquiry?

A. Yes.

Q. If we turn to Slide 54, please, Dr. MacMichael, what conclusion did you reach regarding whether the asserted claims of the '865 patent passed the test for indefiniteness?

A. Yes. They weren't -- the claims are indefinite.

Q. And what part of the asserted claims, in your opinion, are indefinite?

A. Well, there's the term "suitable for intravitreal administration." However, what's suitable for intravitreal administration is undefined.

Q. Dr. MacMichael, does the patent specification provide any guidance to a skilled person to understand what is considered suitable for intravitreal administration under the asserted patent claims?

A. No. There's no information on suitability.

Q. And, Dr. MacMichael, because the term is not defined, would persons of ordinary skill in the art be able to identify

a single interpretation of what it means to be suitable -- a suitable formulation under the '865 patent?

A. Different POSAs approaching this could have potentially different interpretations of what suitable means and what's acceptable for the eye.

Q. Let's turn to Slide 57, please.

Dr. MacMichael, were you asked to evaluate the written description requirement of the '572 patent? That's the additional dosing patent that's been asserted against Mylan and Biocon's BLA product.

A. Yes.

Q. And what conclusions did you reach regarding the written description requirement of the dosing patent?

A. Yes. I highlight that it's an aqueous media for injection. There are, for example, physiological saline and isotonic solution.

Q. Dr. MacMichael, does the '572 patent disclose a representative number of species falling within the scope of the genus of isotonic solutions covered by Claim 6 which we have at the top here as PTX 3?

A. No. It only gives one mention of isotonic solution.

Q. What is that one mention of an isotonic solution?

A. Yes. It's given on the physiological saline. And as this paragraph shows, physiological saline is the isotonic solution that's being highlighted.

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Q. Dr. MacMichael, does the '572 patent disclose structural features common to the members of the genus of isotonic solutions covered by Claim 6 so that a person of ordinary skill in the art can visualize or recognize all of the members of the genus of isotonic solutions?

A. No, it does not.

Q. If we turn to Slide 58, please.

Dr. MacMichael, were you asked to review and evaluate certain Regeneron aflibercept patents?

A. Yes, I was.

Q. If we turn to Slide 59, please. Dr. MacMichael, I see you have a table here on DDX 8, Slide 59. Will you please identify the information that you're going to provide in these columns.

A. Yes. I'll go across the headers. The first column is the U.S. patent number. The second header is publication date. The third is issue date. The fourth is expiration date, and the fifth is summary of claims/disclosures.

Q. And, Dr. MacMichael, did you review and consider all of the patents and corresponding publications listed in this table?

A. Yes, I did.

Q. Let's go through these one by one, please. First, in Row 1, the '959 patent, did you review that patent?

A. Yes, I did.

Q. And did you form an opinion regarding -- excuse me.

Did you reach a conclusion as to when the information provided in the '959 patent was first published?

A. Yes, I did.

Q. And what was that publication date?

A. December 14th, 2000.

Q. And did you obtain that information from the document here, DTX 3619?

A. Yes.

Q. Did you review and consider that document?

A. Yes.

Q. And what was the summary of your review and analysis of the '959 patent disclosures?

A. Yes. The '959 was -- pertained to the isolation of the nucleic acids that actually coded for aflibercept. The expression vectors used helped to assist with that expression and met this for producing the VEGF Trap-Eye aflibercept.

Q. And based on your review and analysis of the '959 patent and its corresponding publication, would skilled persons have been aware of the isolated nucleic acids expression vectors and methods of producing VEGF Trap-Eye aflibercept as of December 14th, 2000?

A. Yes.

Q. Moving on to the next one, Dr. MacMichael, the '746 patent, did you review and analyze the '746 patent?

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A. Yes, I did.

Q. And did you reach a conclusion as to when the information provided in the '746 patent was first published?

A. Yes, I did.

Q. And did you obtain that information from DTX 4229?

A. Yes.

Q. What was the publication date of the information provided in the '746 patent?

A. August 11th, 2005.

Q. Based on your review and analysis of the '746 patent and its corresponding publication, what disclosures would have been available to the skilled person as of August 11, 2005?

A. I'm sorry. Could you please repeat that. I didn't track.

Q. Sure.

Did you provide a summary of the disclosures from the '746 patent and its corresponding publication?

A. Yes.

Q. And what was the summary of the disclosures that you concluded?

A. That the patent was a method of treating retinal neovascularization.

Q. And did that method include the use and administration of aflibercept?

A. Yes, it did.

Q. So based on your review and analysis of the '746 patent and its corresponding publication, would a person of ordinary skill in the art have known as of August 11th, 2005, the method of treating retinal neovascularization with aflibercept?

A. Yes.

Q. And turning to the next row on the table in Slide 59, DDX 8, this is the '747 patent, Dr. MacMichael. Did you review and analyze the '747 patent?

A. Yes, I did.

Q. And did you form a conclusion as to when the information provided in the '747 patent was first published?

A. Yes, I did.

Q. What was that date?

A. February 9th, 2006.

Q. And did you obtain that information from DTX 8209?

A. Yes, I did.

Q. Did you review and analyze that document?

A. Yes, I did.

Q. And what summary did you reach with regard to the disclosures of the '747 patent that would have been available as of that publication?

A. It was a therapeutic method for treating an eye disorder.

Q. And did that therapeutic method for treating an eye

disorder disclosure include the use of aflibercept?

A. Yes, it did.

Q. Turning to the next row, the '799 patent, did you review the '799 patent?

A. Yes, I did.

Q. Did you reach a conclusion as to when the information disclosed in the '799 patent was first published?

A. Yes, I did.

Q. What was that date?

A. November 24th, 2005.

Q. Did you obtain that information from DTX 8208?

A. Yes.

Q. Did you review and analyze that document?

A. Yes, I did.

Q. And what summary did you reach regarding the disclosures of the '799 patent and its corresponding publication?

A. That it was a therapeutic method for treating an eye disorder, including with aflibercept.

Q. If we turn to the next row, the '757 patent, did you review and analyze the '757 patent?

A. Yes, I did.

Q. Did you reach a conclusion as to when the information available in the '757 patent was first published?

A. Yes, I did.

Q. What was that date?
A. July 28th, 2005.
Q. Did you obtain that information from DTX 8206?
A. Yes, I did.
Q. Did you review and analyze that document as well?
A. Yes, I did.
Q. And what conclusion did you reach regarding the disclosure that was available via the '757 patent and its corresponding publication as of July 28th, 2005?
A. Yes. The patent focuses on the VEGF Trap-Eye aflibercept molecule and the nucleotide amino acid sequences that produced the aflibercept product.
Q. Two more, Dr. MacMichael.
Looking at the second-to-last row, the '758 patent, did you review and analyze that patent?
A. Yes, I did.
Q. And did you reach a conclusion as to when the information available -- I'm sorry. Did you reach a conclusion as to when the information provided in the '758 patent was first published?
A. Yes.
Q. And what was that date?
A. November 3rd, 2005.
Q. And did you obtain that information from the documents cited here, DTX 8207?

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A. Yes, I did.
Q. Did you review and analyze that document as well?
A. Yes, I did.
Q. And what conclusion did you reach regarding the scope of the disclosure of the '758 patent and its corresponding 2005 publication?
A. That it was a method for inhibiting VEGF activity in a mammal.
Q. Did that method of inhibiting VEGF activity in a mammal include a disclosure of the aflibercept molecule?
A. Yes, it did.
Q. Last one, last row, the '173 patent, Dr. MacMichael, did you review and analyze the '173 patent?
A. Yes, I did.
Q. And did you reach a conclusion as to when the information provided in the '173 patent was first published?
A. Yes, I did.
Q. What was that date?
A. April 10th, 2008.
Q. And what conclusion did you reach regarding the disclosures that were available to a skilled person as of April 10th, 2008, based on the '173 patent?
A. Yes. It was a patent focused on the composition comprising the VEGF Trap-Eye aflibercept molecule.
Q. Dr. MacMichael, one final point I wanted to ask, did

you have an opportunity to review the animations and other demonstratives that Dr. Trout presented to the Court during his direct examination?

A. Yes, I did.

Q. And have you provided your own version of those animations?

A. Yes, I did.

Q. Have you prepared a version of those animations?

A. Yes.

Q. Can you explain to the Court why you wanted to provide your own version of those animations.

A. Yes. Though Dr. Trout's animation was helpful, I thought it could be -- should be a little more realistic and show a little more detail with respect to the overall size of polysorbate with respect to the aflibercept molecule, and the fact that the polysorbate acting as a surface-active agent would have also coated the walls of the vial as well as the exposed portion of the stopper that faces the liquid.

Q. Here on the screen?

A. I'm sorry. I misstated that. It would also coat the stopper, but it would also protect inactivation at the air-water interface. And that was not shown in the diagram either.

Q. And I think we'll cover that in your version of the animation, Dr. MacMichael. Can you please identify for the

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Court what we have on the screen here.

A. Yes. What we have on the screen is this is an illustration of a vial containing aflibercept and polysorbate 80.

Q. Is this Dr. Trout's version?

THE COURT: 20, Doctor? Polysorbate 20.

THE WITNESS: I'm sorry. Polysorbate 20. My apologies.

THE COURT: Okay. Just making sure. Thank you.

BY MR. SALMEN:

Q. And if we proceed through this -- turn to the next slide -- what do we have here?

A. Yes. We have illustrated the representations of a polysorbate 20 molecule and an aflibercept molecule.

Q. Is the polysorbate 20 -- again, this is Dr. Trout's characterization of the polysorbate 20 in the aflibercept?

A. Yes. And what Dr. Trout did was he showed where the hydrophobic patches would be shown on the molecule itself are highlighted in red as well as the hydrophobic tail of the polysorbate is highlighted in red.

Q. And how did you want to modify this presentation that Dr. Trout gave to the Court?

A. Just to show a little more realistic representation of the size of the molecules and some of the additional functionality of the surface-active agent of polysorbate 20.

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Q. And here on DDX 10, Slide Number 3, is this a replication of one of Dr. Trout's slides, PDX 5004?

A. Yes, it is.

Q. Is this where you obtained the proportionality between the polysorbate 20 and the aflibercept?

A. Yes, it is.

Q. And if we carry on to the next slide here, DDX 10-4, can you please explain to the Court how you modified Dr. Trout's explanation?

A. Yes. We replaced the original illustrations with the previous -- the one from the previous slide which actually show the molecular spinal structure of aflibercept.

Q. And we also have the molecular structure of polysorbate here?

A. As well as polysorbate 20.

Q. And then how did we modify the animation in the box?

A. We basically replaced the illustrations of the aflibercept and the polysorbate with the more representative and more realistic size ratio using the electron cloud structures of the aflibercept and polysorbate 20.

Q. Dr. MacMichael, did you review Dr. Trout's testimony regarding these presentations?

A. Yes, I did.

Q. And what clarification did you want to make with regard to the animated portion of Dr. Trout's presentation?

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A. Well, there's two things. One is these -- in chemistry there can be chemical bonds that are called covalent bonds, and it takes energy to break them. What we have here is not a covalent interaction. It's called a hydrophobic interaction. So the light likes to dissolve light. So the hydrophobic portions of the molecule of the polysorbate are being attracted to the hydrophobic portions of the aflibercept.

Q. Okay.

If we run the animation here, Mr. Gibson.

Can you explain to the Court what you've illustrated here, Dr. MacMichael.

A. Yes. What we're showing is, though the aflibercept binds hydrophobically to the hydrophobic patches -- I'm sorry -- the polysorbate 20 binds to the hydrophobic patches of the aflibercept, it can disassociate from those -- and then reassociate to those hydrophobic patches of the aflibercept.

Q. Would you describe this as a static or a dynamic environment?

A. It's dynamic.

Q. If we turn to the next slide here, were there any additional clarifications that you wanted to make?

A. Yeah. I wanted to show that, in fact, the polysorbate 20 puts a layer on the surface of the vial as well as the surface of the stopper and at the surface area interface.

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Q. And if we could run the animation here, Dr. MacMichael, would you please explain to the Court.

A. Yes. What we're seeing here is that, by polysorbate adhering to the walls of the vessel and at the air interface, the hydrophobic portions of the polysorbate are interacting with the surface of the vial and the hydrophilic -- or loves water is what hydrophilic means -- is facing out into the aqueous environment.

But the polysorbate is coating the walls of the vessel and the stopper, preventing the aflibercept from adhering to the wall. Though it's not absolute, some aflibercept may -- the polysorbate can disassociate from the wall and reassociate to the wall -- I'm sorry -- the polysorbate can disassociate from the wall and reassociate to the wall.

Q. And this is on Slide 15 and 16 of DDX 10.

Dr. MacMichael, any last clarifications to the animations here?

A. Just that you also can see that it's protecting the aflibercept from denaturation by putting a layer of polysorbate at the air-liquid interface.

MR. SALMEN: Thank you, Dr. MacMichael.

Your Honor, at this time I pass the witness.

THE COURT: Understood.

Cross. Go right ahead, Counsel.

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CROSS-EXAMINATION

BY MR. BERL:

Q. Good afternoon, Dr. MacMichael.

A. Good afternoon, Mr. Berl.

Q. First of all, I hope you're having a speedy recovery from your surgery.

A. Yes. Thank you.

Q. Doctor, you're not Mylan-Biocon's only formulation expert on the '865 patent in this case, are you?

A. No.

Q. Dr. Rabinow also testified, correct?

A. Yes.

Q. And you've read Dr. Rabinow's expert report in this case?

A. Yes.

Q. There's a section of your report entitled "State of the Art," right?

A. Yes.

Q. And in that section you undertake an analysis of scores of references, correct?

A. Correct.

Q. Including some of the references you discussed today, right?

A. I'd have to -- yes.

Q. Now, Doctor, if we go to the first slide, there's a

section of Dr. Rabinow's report that's also about the state of the art, right?

A. Yes.

Q. And if we look here on the screen, page 12 of your report is identical, virtually word for word, to page 19 of Dr. Rabinow's report, right?

A. I would have to read through them and do a comparative analysis; but for sake of time, I'll assume you're making an accurate statement.

Q. Let's go to the next page. Page 13 of your report is identical, word for word, with page 20 of Dr. Rabinow's report, right?

A. I would have to read through them; but for today, I'll assume that you're correct.

Q. Looks like it, right?

A. There seem to be similarities as I'm taking a very quick look at it.

Q. And page 21 of Dr. Rabinow's report, if we go to the next, is essentially identical to page 14 of your report, right?

A. Again, I would have to read through it. High level, just taking a quick look, there seems to be similarity.

Q. And, Doctor, the entire section, page after page after page after page of your report, is identical word for word with Dr. Rabinow's report, right?

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THE COURT: One second, Doctor.

Yes, Counsel?

MR. SALMEN: Object to that question, Your Honor. He's already stated he would need to do a comparison of this. That's quite a generalization to present to the doctor at this time.

THE COURT: Why don't we go one at a time, Mr. Berl, given that limitation. I mean, I don't have all the reports. I've made that abundantly clear, but I understand the point thus far. But I'm going to sustain the objection.

Ask your next question, sir.

BY MR. BERL:

Q. Doctor, are you aware of any differences of any words of that long substantive section of your report compared to Dr. Rabinow's?

MR. SALMEN: Same objection, Your Honor.

THE COURT: Overruled.

THE WITNESS: I would have to read through both documents and do a comparative analysis.

BY MR. BERL:

Q. You don't deny, Dr. MacMichael, that there are other substantive sections of your report that are identical to the sections of Dr. Rabinow's report, right?

A. I would have to look at both reports and look at the various sections. You just asked me I don't deny that they're

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identical. I would have to look at both reports.

Q. You read his report, right, Dr. MacMichael?

A. Yes.

Q. And you have no basis to tell me right now that there are -- or to deny that there are large sections of the report -- multiple sections of your report that are identical to Dr. Rabinow's report, right?

A. I would have to read both reports and do a cross -- a cross comparison of the two reports.

Q. Doctor, the first draft of your expert reports was generated by the lawyers at RMMS, right?

A. No, it wasn't.

Q. The first draft of your expert report was not generated by RMMS?

A. RMMS, using my opinions and my information, helped write the report.

Q. Okay. So my question is really simple.

The first draft of your expert report was generated by RMMS, correct?

A. They took my opinions and put them into the report.

Q. The final report was written by the RMMS attorneys too, right?

A. With my opinions and input.

Q. But they wrote it, right?

A. If you mean wrote it by actually typing it up into

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the document, then the answer would be yes.

Q. The actual writing of your reports was performed by an RMMS attorney actually writing the report, right?

A. With strong input from myself.

Q. Well, Doctor, all of the materials considered in preparing your reports were provided for you by the lawyers at RMMS, correct?

A. All the citations that are in these various documents that were cited were also provided in our reading room.

Q. In fact, Doctor, at your deposition you weren't able to point to a single section, paragraph, or even sentence of your expert reports that you yourself wrote. Isn't that true?

A. During my deposition I can't recall that conversation occurring.

Q. Do you deny that at your deposition you were unable to point to a single section, paragraph, or even sentence of your expert reports that you wrote?

A. I'll repeat it. That conversation, I don't recall. So I can't deny it.

Q. Let's take a look at your deposition, Doctor, on page 21. You recall that I deposed you just a few months ago, right?

A. Yes.

Q. In Chicago. It was already spring and warm, right?

A. It was Easter.

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Q. Okay.

THE COURT: Doctor, if I could ask you -- I know you're relying on that screen there, but if you wouldn't mind adjusting that mic just to make sure everyone can hear you, in particular Madam Court Reporter.

Thank you so much, sir.

I'm sorry, Mr. Berl. I think we were discussing the weather in Chicago.

MR. BERL: Yes.

BY MR. BERL:

Q. We had a nice day inside while the sun was shining in Chicago; is that right?

A. We had a day inside.

Q. I enjoyed a day inside.

THE COURT: It sounds like a lovely day. Let's get to the substance of the matter.

MR. BERL: The court reporter did not enjoy it.

BY MR. BERL:

Q. Doctor, you were under oath through that day, correct?

A. Yes, I was.

Q. And you were testifying truthfully that day?

A. Yes, I was.

Q. And let's put up page 21 of your deposition starting on line 10 to page -- to line 16.

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Doctor, I asked you, "Can you point to any section, paragraph, even sentence of your report and say that's my writing? I wrote those words?"

"A No. But if given time, I'll walk through here and show you the sections that are in here that were my concepts that were then put down by the RMMS attorneys into the document."

Did I ask you that question, and did you give that answer, Doctor?

THE COURT: One second, Doctor.

Yes, Counsel?

Will you repeat that, Mr. Berl.

BY MR. BERL:

Q. Did I ask you that question and did you provide that answer?

A. Well, if this is the written deposition, then I'm going to have to say yes.

MR. SALMEN: I would just object to that as improper impeachment. He stated in response to the first answer that he didn't recall.

THE COURT: Understood. Overruled.

Mr. Berl.

MR. BERL: I'm moving to infringement now. I don't think I'm going to get in for a while into the -- what's been considered by Mylan to be highly confidential material. But I

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don't know what the witness is going to say in response to my questions; so I'm not sure what to do. I'm fine proceeding open. But if they want to close it, I have no objection.

THE COURT: Fair enough. But given the interest of a free flow of exchange on cross, it seems that if -- we should seal the courtroom out of abundance of caution unless Mylan has an objection to that.

MR. SALMEN: No objection. That would be our preference, Your Honor.

THE COURT: Understood.

Ladies and gentlemen, those of you who have been kind enough to come and go, if I could ask you to go once again given that we may get into some of the subject matter subject to this Court's protective order. So if you're not permitted to be here pursuant to that order, if I could ask you to step out. Thank you all so very much.

I'll ask court security to seal our courtroom again. Thank you.

(The following proceedings (1451/19 to 1480/8) were had under seal, and are filed under separate cover.)

(Record unsealed.)

THE COURT: Apologies. With my 7-year-old here, there was a line to my private restroom; so it took me longer to get here than I expected.

Mr. Berl, go right ahead.

BY MR. BERL:

Q. Doctor, I would like to discuss the effect of the word "comprising" in the claims which you addressed on direct, right?

A. Yes, I did.

Q. You're not a legal expert on the effect of the word "comprising," correct?

A. No, but I'm getting a lot smarter. You guys are advising me on this stuff.

Q. Someone is.

Doctor, in your view, because of the use of the word "comprising," there are a litany of compounds that could be added to the formulation, right?

A. That's the way I understand it.

Q. For example, you could add hydrochloric acid which would denature the protein?

A. Well, if you look at the claims, there's broad categories that are being proposed and examples given for comprised. There was no example of adding an acid to it.

Q. But your view is, as an example, you could add hydrochloric acid in these claims and denature the protein, right?

A. If you're adjusting the pH, you could, yeah.

Q. Okay. And in your view, the patent doesn't exclude those kinds of inoperative embodiments, right?

A. Well, when you use the word "comprise," which then opens -- very broadly opens up multiple potential compounds that can be used, without experimentation, you could wind up with a formulation that would be detrimental to the protein.

Q. Right. And you think the patent is not enabled because it doesn't exclude those kinds of embodiments that will work, right?

A. What I'm saying is that the claims using the term "comprised" -- and they give examples, four, five, six examples in each of the comprises -- that there's an inordinate number of potential possible formulations. It would require experimentation to determine the ideal formulation.

Q. Okay. Doctor, your enablement analysis is premised on the scope or breadth of the claims as shown in Slide 44 that

you showed, right?

A. I'm sorry.

Yes.

Q. And your Slide 44 suggests that the claims that are asserted like Claim 4 are no narrower than Claim 1, right?

A. That's what we're graphically trying to show.

Q. Okay. But Claim 1 doesn't require 40 mg/mL of aflibercept and Claim 4 does, right?

A. Claim 1 -- I'm sorry. Yeah. Claim 2 is dependent on Claim 1, but -- yeah, you're right.

Q. And, likewise, Claim 1 doesn't require .03 to .1 percent polysorbate but Claim 4 does, right?

A. Yeah, I don't have Claim 1 memorized and it's not on this graphic; so I don't want to answer from memory.

Q. Okay. But you understand that Claim 2 adds the comprises polysorbate limitation, right?

A. Yes. But, again, I'd have to see the entirety, and we're missing Claim 1. I apologize.

Q. Doctor, you know that Dr. Rabinow testified on Friday, right?

A. That's what I was told, yes.

Q. And let's take a look at some of what he said if we go to page 1164 of the transcript.

He was asked, "As of 2006, in your opinion, optimizing the stability of a protein formulation was routine

for the POSA?"

And he answered, "Yes."

Do you see that?

A. It's routine. Yes, I see it.

Q. Do you agree with Dr. Rabinow?

A. Routine in the fact that an organization -- a biotechnology company or a biopharmaceutical company engaged in developing multiple proteins would have a routine for how they screen those products.

Q. So do you agree or do you not with Dr. Rabinow, Doctor?

A. In general.

Q. In general yes?

A. Yes.

Q. And let's take a look at the next thing he said on page 1168.

He was asked, "And it wouldn't require undue experimentation to make formulations falling within the scope of the asserted claims, right?"

And he answered, "Correct."

Do you agree with him?

A. "Undue" is a relative term. It would take a significant amount of experimentation looking at all the possible variables that are proposed in the claims to come up with a formulation that is satisfactory; so I would say

significant experimentation.

Q. Do you agree with Dr. Rabinow or do you disagree?

A. I'm saying it requires significant experimentation. So undue experimentation, meaning that it's impossible? No. But significant experimentation. So I guess with that nuance, I'll agree with Dr. Rabinow.

Q. Okay. Well, I want to make sure I understand your opinion.

You don't have an opinion in this case that making the formulations to practice the claims that are asserted of the '865 patent would be undue experimentation, right?

A. What I've said all along is it would take a significant amount of experimentation.

Q. So you don't have an opinion -- you're not telling the Court as an expert that it would require undue experimentation, right?

A. Well, like I said, "undue" is a relative term. My term "significant" really means a significant amount of work.

Q. I have a single question, Doctor. It's a yes or no.

Are you telling the Court that practicing claim -- the claims that are asserted in the '865 patent would require undue experimentation, or are you not telling the Court that?

A. It would require undue experimentation. It would require a significant amount of experimentation. That's my testimony.

Q. That's as far as you'll go, right?

A. Well, undue means an inordinate number of experiments. But every organization that works in therapeutic proteins has staff and equipment on board with the proper resources to do that significant amount of work to develop the formulations. So undue would mean something that is beyond the realm of being able to be achieved.

Q. In your view, undue experimentation is a very amorphous term, right?

A. It's left open to interpretation.

Q. Undue experimentation, as you've applied the phrase in this case, depends on whether you're a big company or a small company?

A. That's not what I said.

Q. Okay. Let's take a look at your deposition, page 233, line 1. We'll go to line 11.

"Q Right. And why the experimentation to fill in any gaps between the examples would not be undue experimentation, that burden was on Regeneron to show that?

"A Undue experimentation depends -- is a very amorphous term. If I'm a little company, undue; and if I'm a big company, it might not be a big deal to run an inordinate number of experiments. So the word "undue," let's take

that out of it. Additional experiments."

Was that my question and was that your answer, Doctor?

A. Yes. And I believe that you're citing this on this slide. I believe that it agrees with the statement I just made.

Q. Okay. Now, Doctor, you understand that the Court here may have to decide whether the experimentation to practice the claims is routine experimentation or undue experimentation, right?

A. Yes. So what we're saying is that the patent fails to give sufficient information on how to make the formulation; so the patent in itself is indefinite. You have to go out and do experiments to determine which of these various comprises, various stabilizing agents, et cetera, would be acceptable in a final formulation.

So as we've been saying for the last two or three minutes, undue versus significant, these are relative terms. It would take work.

Q. Okay. So it would take work, but you're not taking a position on the question of whether that work would be undue or routine, right?

A. The term "undue" is being -- you know, the term "undue" means if the patent had been properly constructed and gave information to the reader of how to actually develop the

cited product in the patent, then it wouldn't require significant experimentation. But the patent fails to do that. And, therefore, significant experimentation would be required.

Q. Okay. Let me -- I'll give you one more chance to answer the question, and then I'm going to move on.

If the Court has to decide between routine experimentation and undue experimentation, you're not putting your finger on the scale of undue experimentation, right? You're not giving an opinion?

A. I'm saying -- you can use the word "undue," but I'm -- it's undue because the patent wasn't properly constructed. But a significant amount of work would have to be done to do that work.

Q. Now, Doctor, your opinion is that "protein formulations are routinely optimized to improve stability of their active ingredients"?

A. Protein -- can you show me that quote.

Q. Sure. I'll read it again.

"Protein formulations are routinely optimized to improve stability of their active ingredients."

A. Is that from one of my depositions or one article I wrote?

Q. I'm asking whether you agree with that statement, Doctor.

A. Could you repeat it one more time.

Q. Sure.

"Protein formulations are routinely optimized to improve stability of their active ingredients."

A. Yes.

Q. Okay. Now, you and Dr. Rabinow both relied on the Kaisheva reference; isn't that right?

A. Yes. I read the Rabinow testimony, but I can't pull out off the top of my head if he, in fact, looked at that document.

Q. Okay. Let's take a look at what Dr. Rabinow said about it. And that's on page 1020 of the transcript from last week.

And he says, "Kaisheva provides a recipe for how you go about developing protein formulations in terms of a three-step process."

Is that right?

A. That's what it says.

Q. And you said essentially the same thing in your expert report if we pull up paragraph 63 of your first expert report. And you cite Kaisheva at the end of that paragraph.

Do you see that?

A. Yes.

Q. And it says, "The optimization process further involves combining a therapeutic protein with excipients and then varying the concentrations of the excipients. The

formulation development approach is as follows: Selecting the optimum solution pH, selecting buffer type and concentration, evaluating the effect of various excipients of the liquid and lyophilized stability, and optimizing the concentration of the screened excipients."

That's your opinion, correct?

A. Yes. If I had a new protein coming over from discovery that had not been properly formulated and we were needing to get into animal studies and clinical trials, it would require a series of activities to get that into a successful formulation.

Q. But if you know the optimum pH, then you can take that linear approach to select a buffer type and concentration, then various other excipients, then optimize the concentration, right?

A. And what -- these two sentences in this paragraph are talking about is a significant amount of work. Now, that work may be routine, meaning the formulation organization does that work on a repeated basis, thus the term "routine." Let's not take away the fact that it's a significant amount of work.

Q. Okay. In this case, Doctor, the patent already discloses the optimum pH for aflibercept, 6.2 to 6.3, right?

A. So that's one point of the overall formulation. We have the pH.

Q. You agree with me, right?

A. I'd have to go back to the patent, but I do recall that one of the formulations was at pH 6.2. But I don't want to make a sweeping statement.

Q. Now, that information, as far as you know, was not known before the '865 patent, correct?

A. The optimum -- the pI of aflibercept.

Q. The optimum pH formulations for aflibercept for ophthalmologic administration, right?

A. I'd have to look at the sequence, go back and look at the literature, but the pI, where the protein's neutral, meaning it has the same positive and negative charge and there it's neutral, that pI dictate what pH you want to hold it at. And if I was to go back and search the literature, you're asking me was there any previous art that showed aflibercept had a pI that was acceptable at pH 6.2. I just don't have that information in front of me.

Q. Okay. Doctor, in choosing excipients in that process that we've just described from Kaisheva, the POSA would narrow down choices on the basis of their knowledge from the literature, right?

A. If they had a new novel protein coming in, this is how they would approach it. But if they had a protein that had a patent on it, one would expect that there would be more guidance in that patent on how to actually do it without having to go back and de novo do additional experiments to get to that

final point.

Q. Okay. Doctor, you can't imagine a scenario where someone would be working on products for helping with diseases of the eye without referring to the previous literature, right?

A. I've never met a scientist that's developing something that doesn't look at the previous literature.

Q. That would actually be irresponsible not to look at the previous literature, including the prior products that have been approved, right?

A. Well, yeah. I think the hypothetical, if one of my formulation people came to me and said, hey, I didn't look at anything; I'm just going to go ahead and start formulating, I'd be a little uncomfortable with that answer. Well, have you looked at other similar molecules and gotten some guidance on what may be successful?

Q. And included within that literature that the POSA would consult is information about what excipients have been used in intravitreal products, right?

A. Yes.

Q. But in conducting your analysis in this case, you didn't look at all the intravitreal products that FDA had approved and look at all the formulations, right?

A. I looked at a majority of them. I can't recall if I looked at every approved intravitreal eye formulation. I cannot tell you that I have.

Q. Doctor, in fact, other than Lucentis, you couldn't identify any FDA-approved formulation that you looked at in connection with your expert reports in this case, right?

A. I looked at Regeneron's product Eylea. I looked at Lucentis.

Q. That's it, right?

A. Those were two that I looked at, yes.

Q. And neither one of those was approved as of the priority date in the middle of 2006, right?

A. I'd have to go back and look at the approval dates, et cetera.

Q. Doctor, the POSA engaging in experimentation to practice the claim would not make formulations at random, right?

A. Any good formulation scientist would be a POSA, according to either Dr. Trout's or my definition, would have -- you know, in either of our definitions, such a POSA that would be working in your formulation group would at least have some sense of what excipients to use.

I believe that was your question.

Q. And they wouldn't make formulations at random, right?

A. They would do it in a logical manner.

Q. And if you've worked in proteins, you'll have a good understanding of what excipients have been used successfully and what buffers have been used successfully, right?

A. Yes. Yes.

Q. Doctor, in the patent, the '865 patent, there are no new classes of excipients, right?

A. Everything in that patent is -- all the compounds cited in the patent are known molecules. There's no novel new molecule being introduced.

Is that your question? I'm not sure.

Q. Yeah, they're pretty much all household names in excipients and stabilizers, right?

A. Yes, they are.

Q. Now, I'd like to talk about choosing a buffer, which you address.

Another consideration for formulating to avoid aggregation is the choice of a buffer to keep the formulation within the narrow pH range to keep your formulation stable, right?

A. Ideally you want to keep it in a narrow pH range. If you go too basic or too acidic, you can get undesirable changes in the charge of the molecule and undesirable interactions.

Q. And various buffers are available to adjust the pH of protein formulations?

A. There's multiple compounds out there that can be used as a buffering agent.

Q. And, typically, you pick a range for a buffer that's applicable to the pH you're trying to achieve?

A. Yes. What you look at, again, is what they call the pI. That's where the neutral pH of a protein is. Where is it neutral? And from that, you pick a candidate buffer that would then be where the pI of that protein would fall within the range of that buffer.

Q. And the POSA reading the claims and the specification would have considered four buffers as suitable for formulations of the asserted claims: succinate, citrate, phosphate, and histidine. Right?

A. There's other buffers out there that could have been considered.

Q. But those are the ones that the person of skill reading the patent would want to use, correct?

A. You can pull up the claims so I can read it because it comprised those, but I believe it was open-ended.

Q. My question is those are the four buffers that the POSA practicing the claim would want to use, correct?

A. Those were examples that were given by the author. They are buffers that could potentially be used.

Q. Those are the ones that the POSA would want to use, correct?

A. Those are four examples that were used by the authors to give examples of the other potential buffers that could be used. The word "comprised" means that many other buffers could be considered as well.

Q. To choose a buffer, you would look at the prior art for which buffers were used successfully in previous products for injection into the eye, right?

A. That would be a useful guidepost.

Q. And that can narrow down the overall number of candidates you need to screen?

A. It can if you say such and such buffer was used in an approved product by the FDA; therefore, there's precedent for that buffer being previously used in an intravitreal application.

Q. But you never undertook that analysis to look at prior products, correct?

A. I didn't look at all the prior products.

Q. And with respect to a stabilizing agent, Doctor, considerations for formulating a protein to avoid aggregation typically include a choice of a stabilizing agent, right?

A. Yeah, if you're reading off of a document, it would be very helpful if you could share it up on the screen. Is that possible?

Q. Doctor, I'm asking you a question whether you agree or not. Considerations for formulating a protein to avoid aggregation typically include a choice of a stabilizing agent, right?

A. Is that a quote from my deposition?

Q. I just want an answer to my question, Doctor.

A. Say it again, please.

Q. Yes.

Considerations for formulating a protein to avoid aggregation typically include a choice of a stabilizing agent, right?

A. It can require a stabilizing agent. Depending on whether it's a liquid or a lyophilized formulation, you may use certain sugars that you might not use in a liquid formulation.

Q. The patent says the stabilizing agent may be sucrose, sorbitol, glycerol, trehalose, or mannitol, right?

A. That's not what it says. It says "comprises," and it gives examples of those sugars.

Q. Doctor, those are the examples of sugars -- or of stabilizing agents provided in the patent, right?

A. Those were examples that were provided in the patent under the word "comprises," meaning that any other sugar could be considered as well as a stabilizing agent.

Q. Doctor, all five of those options were well-known stabilizing agents?

A. They were known to be stabilizing agents.

Q. If one was developing a formulation, one would screen those stabilizing agents and see which one gave the overall satisfactory performance, right?

A. If those were the five I wanted to look at, I would screen those five.

Q. Now, you also reference in your slides -- so I don't think you actually talked about it today -- something called formulation design systems, right?

A. Are you talking about factorial design?

Q. A formulation design system. You know, something called DOE or --

A. Design of -- yes, there's a book out there that I wrote for cell gene therapy called *Aging* that describes the use and the design of experiments.

Q. Through the design of experiments, or DOE, the whole purpose is to minimize the amount of testing you have to do, right?

A. Yes. Because if we were to run the hypothetical amount of experiments that would have to be ran if you were to make each individual formulation, it would be an inordinate number.

Q. You yourself have either done or supervised design of experiments going all the way back to 1990, right?

A. Yes.

Q. And the bottom line for design of experiments is you look at multiple variables, like what excipients and what buffers, and using various software out there, you can actually achieve a screening of what is successful and not successful, correct?

A. Yes. If I could explain to the Court what a design

of experiment is and how it's used, it might be helpful.

THE COURT: Go ahead, doctor.

THE WITNESS: Yes. A design of experiment you have, Your Honor, have you in a numerous number of variables. And in a traditional manner, you would only -- you would hold everything constant but one variable and then change that variable to see how it influences the outcome.

In a design of experiment, you can change multiple variables, two or three, and then look at the results. And there's software out there. There's one very popular one called JNT, J-N-T, that lets you look at the results. And, therefore, you can then sift through more results quicker and have more variables in play rather than looking at one at a time.

I believe, Mr. Berl, that's what you're referring to.

BY MR. BERL:

Q. Yes, it is. Thank you for the explanation, Dr. MacMichael.

DOE is an intelligent technique to use to minimize the amount of screening that's necessary?

A. Yes. It reduces -- it doesn't reduce the number of candidates; it reduces the amount of work.

Q. It will exclude things that don't work?

A. Yes. The results will show which variables are not getting you to the desired outcome.

Q. And so using design of experiments, you wouldn't have to make every formulation, right?

A. That's correct.

Q. And anybody in the street knows that DOE is what everybody does?

A. Everybody on the street -- I don't know about everybody; but yes, scientists would know that a DOE can be used to effectively reduce the number of variables that have to be looked at in an actual physical wet chemistry lab.

Q. The POSA would conduct the design of experiments, right?

A. The POSA could do a design of experiment.

Q. And, Doctor, you couldn't tell me at your deposition how many formulations the POSA would have to make to practice the claim using design of experiments, correct?

A. Yeah, because you -- and I couldn't answer that today. I'd have to sit down, design the experiments, and look at the number of components -- both the stabilizing agent, the surfactants, et cetera -- and design that and look at which variables I wanted to look at and how I wanted to vary those variables.

Q. All you could say at your deposition was that with design of experiments, the POSA would have to conduct multiple experiments. You couldn't give any more specificity than that, right?

A. And I just gave a little more specificity, yes.

Q. Not much, right? You don't have a number for me, do you, in terms of how many experiments the POSA would have to conduct?

THE COURT: One second, Doctor.

Yes, Counsel?

MR. SALMEN: Objection, Your Honor. He answered the question, and it was consistent with his testimony at his deposition.

THE COURT: Overruled.

Ask your question again, Mr. Berl.

BY MR. BERL:

Q. You don't have a number for me or for the Court today about how many experiments a POSA would have to conduct to practice the claims using a design of experiments, do you?

A. It's a large number. If I took six to seven stabilizers and I took three to five surfactants, et cetera, and I moved that down and multiplied it through, very quickly you get to a very large number.

Q. With design of experiments you don't have a number of how many experiments the POSA would have to conduct to practice the claims, do you?

A. Well, I just explained to you, you're asking me to, off the top of my head, tell you I was going to design a complex experiment with five to six variables with multiple

candidates in each variable and that you would have to sit down and intelligently design that experiment to determine which variables you wanted to change in each experiment.

Q. You haven't undertaken that analysis in this case, right?

A. We've looked at some hypotheticals. I was just going to say, hypothetically, you would come to a very large number.

Q. But with design of experiments, the number is smaller, and you have not provided a number about how many experiments the POSA would have to conduct with design of experiments, correct?

A. As I've explained three times -- I'll explain again -- I would have to sit down and look -- remember, they say comprised; so it isn't just glucose, sucrose, and mannitol; it could be glucose, sucrose, mannitol, galactose, et cetera, because it says "comprises." So the question is how broad am I going on all the various claims that use the term "comprised"? I could -- not just the examples given. Those are just examples. I could wind up with an inordinate number.

Q. Doctor, you didn't consider any studies Regeneron did other than those described in the '865 patent, right?

A. I did not have access to all the experiments that Regeneron did.

Q. You never asked your counsel whether there was SEC data for formulations that met requirements of the claim that

you didn't have already in the patent, right?

A. I don't recall.

Q. Doctor, you did look instead, when you talked today, about various statements and file histories, correct?

A. Various statements and file histories?

Q. Do you remember you presented that earlier today?

A. Yes.

Q. Okay. Let's look at your Slide 47. You relied there on a statement from --

THE COURT: One second, Mr. Berl.

Go ahead.

BY MR. BERL:

Q. You relied here, Doctor, in DTX 5053 on a statement from a different file history, not the file history of the '865 patent, right?

A. These are two documents that were cited on the -- looking at the *Wands* factors and looking on whether or not it would take undue experimentation. And there's two citations here.

Q. My question is, Doctor, that first citation, 5053, is from the prosecution history of a different patent, not the '865 patent, right?

A. I'll take your word for it.

Q. Okay. It's not even in the same family as the '865 patent, right?

A. I don't understand where you're heading with the question. I'd love to answer it, but I'm not quite sure what you're looking for.

Q. Okay. Doctor, you showed a statement on the screen here that one of ordinary skill upon reading Remington's would expect to engage -- would expect to engage in significant nonroutine experimentation to develop a successful formulation as claimed herein.

Is that what you showed?

A. That's what I showed.

Q. Now, Remington's is not the '865 patent, right?

A. No, it's not the '865 patent.

Q. Remington's does not disclose ophthalmologic formulations of aflibercept, right?

A. I can't recall all the content of the Remington article.

Q. As far as you know, Remington's does not disclose the optimal pH range for ophthalmologic formulations of aflibercept, right?

A. Off the top of my head, I can't recall that that document cites that, no.

Q. Now, Doctor, you also cite in the second part of this slide a statement from DTX 4430 that formulations of pharmaceutical preparations and achieving a stable composition is not a simple or routine matter. Is that right?

A. That's what it says.

Q. And you cited that from paragraph 10 of 4430, right?

A. 4430, page 003. I'm not sure -- it's enumerated 10, yes.

Q. Okay.

Can we pull up the entirety of paragraph 10 rather than the expurgated version that was presented by Dr. MacMichael.

Do you see -- you showed the Court the first sentence of paragraph 10; is that right?

A. I showed the first sentence of that paragraph.

Q. And in the last sentence it says, "I am familiar with these literature articles, all in peer-review journals, which indicate that arriving at a stable formulation is not a straightforward matter, and it is not, for instance, possible to apply a formulation for one drug to another."

Do you see that?

A. Yes.

Q. And in practicing the '865 patent, the POSA wouldn't have to go from one drug in the specification to another in the claims. It's aflibercept in the specification and aflibercept in the claims, right?

A. Yes. But I'm not quite sure what the question is.

Q. Okay. You answered it.

Doctor, you understand that Mylan conducted research

in connection with its 40 mg/mL aflibercept formulation, right?

A. Yes.

Q. And you never investigated how much research was required for Mylan with the '865 patent in hand to make formulations within the scope of the claim, right?

A. I read through their formulation development history report. It was a significant amount of work that was required.

Q. Well, you never had any conversation with Mylan personnel about the research, correct?

A. I did not interact with Mylan personnel.

Q. You never had conversations with the RMMS attorneys about Mylan's research, correct?

A. No. We reviewed the development and history report together and went through the content and discussed the meanings of the results.

Q. Well, you never asked the attorneys to show you the experimentation performed by Mylan, did you?

THE COURT: One second.

Yes, Counsel?

MR. SALMEN: I would object that this is getting into attorney work product. I mean, I don't understand the basis for this question.

THE COURT: I think --

MR. SALMEN: What information he's asking of his attorneys.

THE COURT: Understood.

Mr. Berl?

MR. BERL: First of all, it's not privileged. But second of all, if it were, it's waived because this is right from his deposition.

THE COURT: Yeah, I don't believe there is any privilege. He's already testified about it here today, and we've heard from the deposition. I believe it's relevant, as it probes the bases for the doctor's opinions in this case.

Objection overruled.

BY MR. BERL:

Q. Doctor, you never asked the attorneys to show you the experimentation performed by Mylan, correct?

A. I was given the Mylan development history report; I didn't have to ask for it. And I read through it, and we had extensive discussions with the attorneys on the content and how the results could be interpreted.

Q. Doctor, you assumed that the Mylan attorneys would have access to additional information that you didn't have, right?

A. My assumption is yes, they have additional information I'm not privy to.

Q. And you believe that the Mylan -- that the research Mylan conducted to obtain its proposed aflibercept formulation was relevant to the analysis you were conducting in this case,

right?

A. It had some relevancy to it, yes.

Q. And you agree that it would be useful?

A. The data would be useful.

Q. And in retrospect, it would have been beneficial to look at that, right?

A. I'm sorry. I did look at it. I don't understand what you're saying. I did look at it.

Q. Okay.

Let's take a look at the doctor's deposition again. And let's take a look at page 335. Let's start at line 6, go to line 14.

"Q Yeah, the research that Mylan conducted to obtain its proposed aflibercept formulation of 40 mg/mL, did you think that was relevant to the analysis you were conducting in this case or not relevant?

"A It has relevancy. It would be useful.

"Q It would be --

"A In retrospect, would it be beneficial to take a look at that? Sure."

Were those my questions and were those your answers, Doctor?

A. They look familiar, yes, they do, Mr. Berl.

Q. If you could go back in time and ask Mylan's

attorneys whether they had additional information about Mylan's research that led to their proposed aflibercept formulation, maybe you would do that, right?

A. I have done that, and I have read through the development history report multiple times and discussed it at length with the RMMS attorneys.

Q. Doctor, turning to a separate topic, you didn't identify today any particular formulation that would require undue experimentation to make, correct?

A. As opposed to what? With respect to aflibercept or any hypothetical protein or --

Q. Within the claims. You didn't identify a formulation that has the ingredients of the claim that would require undue experimentation to make, did you?

A. All of those examples are examples. So what we have is maybe 12 recipes making a cake, but you're not telling me how to go about making that cake.

Q. Okay. I have a simple question, Doctor.

Did you identify -- because I didn't hear it, but tell me if I missed it.

Did you identify any particular formulation that has the ingredients required by the claims that, in your view, would require undue experimentation to make?

A. If you're asking me just to make that formulation? Is that the question?

Q. Yes, Doctor.

A. Well, how -- making it and how -- ensuring its stability takes experimentation. I'm not following you.

Q. Okay. Doctor, Claim 1 requires a buffer, correct?

A. Claim 1 requires a buffer.

Is it possible to put the claims up on the screen?

Q. Sure. Let me put up the claim that has 1, 2, and 4 together.

There you go, Doctor.

A. Yes. Thank you.

Q. Claim 1 requires a buffer, correct?

A. Yes.

Q. And buffers refer to a known set of structures, right?

A. There's various types of buffers out there, and there's various categories of buffers. There's not one specific category of buffers.

Q. Let me try it again.

Buffers refers to a known set of structures, right, Doctor?

A. No. There's multiple -- there's various types of molecules out there that can function as buffers.

Q. Okay. Let's go to the doctor's deposition again at page 428, line 20. Go into 429, line 3.

Doctor, I asked you:

"Q And I think we've talked about these before, but that was a known set of structures, buffers, right?

"A Uh-huh.

"Q Yes?

"A Yes."

Were those my questions and were those your answers, Doctor?

A. Yes, they were.

Q. Okay. And Claim 1 requires a stabilizing agent, correct?

A. Are we going to put the claims back up on the screen?

Q. We'll try to do that.

You know that Claim 1 requires -- the claims require a stabilizing agent, right, Doctor?

A. It states that Claim 1 requires a stabilizing agent.

Q. And that's a known set of structures too, right?

A. When you say a known set of structures, when you give a specific example, a POSA would know the structure that -- when you start talking about various categories, you have to give examples of what those might be.

So your question was a buffer is a known set of structures. A buffer is a term that can encompass multiple types of molecules; so maybe -- does the word "buffer" give me the structures? The answer is no.

Q. Doctor, I'm asking about the stabilizing agent now. We're past buffers. My question is simple.

Stabilizing agent is a known set of structures, right?

A. There's multiple molecules that can be used as stabilizing agent. Stabilizing agent is very broad. Sugars are stabilizing agents. Surfactants are stabilizing agents.

Q. Is that a known set of structures, Doctor, or not?

A. There's multiple sets of structures.

Q. So no or yes?

A. What I'm saying is this patent fails to define what all the potential structures are.

Q. Okay.

Let's take a look at the doctor's deposition again, right after where we were, page 429, line 4 down to line 11.

"Q Claim 1 requires a stabilizing agent, correct?

"A Yes, it does.

"Q That's a known set of structures too?

"A Well -- I'm going down looking at dependent claims. Yes, it does."

Were those my questions and were those your answers?

A. Those were my answers.

Q. Doctor, Claim 1 recites various structural requirements with respect to both the active ingredient and

with respect to excipients.

A. I'm sorry. Where are we --

Q. Claim 1, Doctor, recites various structural requirements with respect to both the active ingredient and with respect to the excipients, correct?

A. I'm getting lost in your question, Mr. Berl.

Q. Okay. Here it is. I'll try to do it slow.

Claim 1 recites various structural requirements with respect to both the active ingredient and with respect to the excipients, right?

A. Are you reading the claims or is this your statement?

Q. That's my question.

A. Could you repeat it, please.

Q. Yes.

Claim 1 recites various structural requirements with respect to both the active ingredient and with respect to the excipients?

A. Does it require -- yes.

Q. If those structural requirements are met, one is -- well, sorry.

If those structural requirements are not met, one is not within the scope of the claims, right?

A. I'm not aware, but that's my understanding.

Q. Okay. So each formulation, to your understanding, in order to be within the genus of formulations of Claim 1, must

meet every structural requirement of Claim 1, the organic cosolvent, the buffer, the stabilizing agent, and the VEGF antagonist fusion protein with a particular sequence, right?

A. Your question was it has to meet all of the criteria in Claim 1? Was that your question?

Q. Yes.

A. The answer is yes.

Q. So all of the formulations within Claim 1 have those structural features, correct?

A. No.

Q. Okay. Doctor, you talked about the '572 patent for a moment. You have one slide on that, I believe. It's Slide 57.

Can we put that up.

Now, you understand that the '572 patent priority date is several years after the priority date of the '865 patent, right?

A. Yes, I do.

Q. And the POSA practicing the claims of the '572 patent would not make a new formulation, right; they'd use an existing formulation?

A. I cannot read the minds of the inventors, but I'll follow your train of thought.

Q. By 2011 many aflibercept formulations were known, right?

A. Yes. But you're referring to a patent that obviously

had done some variations; so I'm not quite sure where you're heading.

Q. You think the '572 patent had made new formulations?

A. No. I'd have to pull up the '572 patent and look at it to be able to follow your question.

Q. Okay. Doctor, you agree that as of 2011 there were formulations of aflibercept known that the person of skill practicing the '572 patent would use, right?

A. As of?

Q. 2011 or 2013.

A. And if they did have to use what? The '865 patent or the '572?

Q. Sure. They could use the '865 patent.

A. The '865 is patent is not enabled; so they wouldn't know how to make those buffers.

Q. So you don't think that the person of skill could have used the formulations from the '865 patent in practicing the '572 patent?

A. They could with a significant amount of work and effort and studies and screening.

Q. You haven't asserted that the Dix patent is not enabled, have you?

A. Well, let's pull -- I'm not sure -- which Dix patent are you referring to? Doesn't Dix have multiple patents?

Q. The Dix '226 patent that you addressed thoroughly in

your expert report. You don't think that's not enabled, do you?

THE COURT: One second.

Yes, Counsel?

MR. SALMEN: Objection, Your Honor. It's outside the scope of his direct examination.

THE COURT: How is this now -- Mr. Berl, how are we within the scope of his direct?

MR. BERL: Because he opined about how the person of skill would practice this -- the Claim 6 of the '572 patent. And he says it would be really hard. It doesn't disclose anything. And I'm exploring what the person of skill actually would have done.

THE COURT: Overruled.

THE WITNESS: I don't have the '572 patent in front of me; so I'm not going to address the specific detailed content unless we can -- if you have specifics you want to pull up.

Can you rephrase your question again.

BY MR. BERL:

Q. Sure.

A. I'm trying to answer your question, but I just want to get a little more --

Q. I think I asked you whether the person of skill practicing the '572 patent would use the '865 patent

formulations which have been published by that point. And you said no because they're not enabled.

Are we with each other so far?

A. What I said is -- you said, well, they can just use one of the buffers in the '865 patent. And I said no, they're not enabled.

Q. That's not what I said, but let me try it again to make sure we're on the same page.

A. Let's try it again.

Q. In your view, would the person of skill practicing the '572 patent in 2011 or 2013 use as an ophthalmologic formulation the formulations disclosed in the '865 patent which had published by that time?

A. They may have. I don't know that they would have, but they would certainly -- especially because the patents were issued to the same company, one would expect that they were using it at least as a reference document.

Q. And they could use the Dix patent too which was also issued to the same company, Regeneron, correct?

A. Yeah. One would expect, with the normal business practice, to be referring to your own internal prior art.

Q. And it's not your view that the POSA would have had a preference for one of those formulations from the '865 patent or the Dix patent over the others in practicing the '865 patent, right?

A. I would expect that Regeneron personnel might have had some preferences. But you're asking me to ask if a hypothetical POSA would have a preferred buffer? I can't answer what the hypothetical POSA would want.

Q. So you have no -- as someone who opined on the '572 patent as to what formulation in 2011 the POSA would have wanted to use for treating ophthalmic diseases using aflibercept, right?

A. Well, yes. What we're highlighting here is one of -- they're called the quantity attributes of the final product. One of the characteristics. Yes, you'd want an isotonic solution that's physiological with respect to the eye.

Q. Let me try that question again.

Do you have an opinion about whether the POSA would prefer one formulation in the prior art, such as Dix, or a different formulation, such as one of the '865 formulations?

THE COURT: One second.

Yes?

MR. SALMEN: Your Honor, I'd just renew my objection. This goes to the obviousness analysis. And Dr. MacMichael had testified here with regard to a written description of the '572 patent, but we're going way far afield of any opinion that was disclosed in his reports or during direct examination.

MR. BERL: I disagree. He's talking about how the person of skill would practice this. He says basically the

person of skill could practice this. I don't see how they would.

THE COURT: And I disagree.

Sustained.

BY MR. BERL:

Q. Now, Doctor, let me ask you about one final topic, which is indefiniteness.

A. May I correct your inaccurate quote of what I said?

Q. No.

THE COURT: No. I sustained the objection, Doctor.

So moving forward.

BY MR. BERL:

Q. Finally, I want to address indefiniteness.

You're not an expert about the medical aspect of whether something is suitable for intravitreal administration, correct?

A. I am a development and manufacturing expert. I do work very closely with colleagues that are physicians. And so I do have an understanding of what's acceptable from working with physicians and regulatory and quality members. You're never an individual working alone; you're working with a team.

Q. Right. But you on your own don't have that knowledge of what excipients or what formulations would be suitable for intravitreal administration, right?

A. I am not an ophthalmologist.

Q. And you on your own don't have that knowledge of what excipients or what formulations would be suitable for intravitreal administration, right?

A. I have a working knowledge of what excipients and which buffers, et cetera, are acceptable in the human body from all the multiple products I've developed over my career.

Q. I'm asking about intravitreal formulations, Doctor. Let me try it one more time.

You on your own don't have that knowledge of what excipients or what formulations would be suitable for intravitreal administration, right?

A. It's available in the literature.

Q. But you would -- you said at your deposition you would consult other people on a team who have that expertise, like ophthalmologists?

A. Yes. That's what I just said.

Q. Okay. But you didn't consult with an ophthalmologist in preparing your expert reports as to the '865 patent, right?

A. No, I didn't consult with an ophthalmologist.

Q. And you didn't consult with a toxicologist?

A. No, I did not consult with a toxicologist.

Q. You didn't interact or consult with anyone other than the attorneys in connection with your opinions in this case, right?

A. I was asked questions that were related to my

background and expertise in how to manufacture and formulate drug products.

Q. You understand, Doctor, that the issue of indefiniteness is whether the POSA would understand the scope of the claims, right?

A. Yes.

Q. And the POSA would understand the scope of the '865 patent claims, right?

A. They would understand that they're very broad and open, using the term "comprised" in multiple claims.

Q. But they would understand the scope of the claims, right, Doctor?

A. No, they wouldn't, because the scope of the claims is extremely broad and they're open-ended.

Q. Doctor, you're a POSA and you understand the scope of the claims, right?

A. No. I believe the scope of many of the claims is -- because it uses the term "comprises" and gives several examples but it's open-ended. So it's not narrow. It's very broad.

Q. Okay.

Let's take a look at the doctor's deposition hopefully one last time, page 486, line 21, through 487, line 1.

Doctor, I asked:

"Q And the POSA would understand the scope

of the claims?

"A Well, I am a POSA, and I understand this."

Was that my question and was that your answer?

A. Yes. The scope of the claims is open-ended and broad.

Q. Thank you.

MR. BERL: No further questions at this time.

THE COURT: Thank you.

Counsel, I assume redirect would be longer than five minutes?

MR. SALMEN: Unfortunately, yes, Your Honor.

THE COURT: Well, I wasn't going to put an adjective on it.

Doctor, we're going to break for the day. You remain midstream in your testimony; so that means you get through the evening without anyone bothering you.

THE WITNESS: Being a lonely guy.

THE COURT: You do. You are alone. Whether you prefer that or not, I'll leave to you. I won't ask. But just so you understand, no one can talk to you about your testimony because you remain midstream.

We'll resume at 9:00 tomorrow.

You can go ahead and step down, sir.

THE WITNESS: Thank you, Your Honor.

THE COURT: Thank you.

It was my understanding this was Mylan's last witness in this phase of the case; is that correct?

MS. MAZZOCHI: Yes, Your Honor. This is going to be Mylan's last witness as part of its invalidity/infringement response. We do have one live witness for sure, Dr. Hofmann, who is going to be responding to their witness on commercial success.

Whether we need to bring Dr. Albini or Dr. Stewart back after we hear from Dr. Csaky, for example, or any of the other witnesses, particularly on the issue of secondary considerations, we don't know. We're hoping we don't have to. But one of the things that I certainly would say, though, Your Honor, in terms of timing, again, we're very concerned that Regeneron has been really stacking up a lot --

THE COURT: The timekeepers are keeping track of it, Counsel. We are where we are. I've told you guys how much time you have.

MS. MAZZOCHI: We're on track. I just don't want to get stuck.

There are a couple things, though, Your Honor, that have come up, and I did want to preview them for you because I'd like to get some guidance.

THE COURT: I don't need a preview at this point, Counsel. We're going to break for the day. I'm just trying to

get a good feel for where we're headed. We can take those issues up at 9:00 tomorrow morning just before the doctor resumes his testimony.

MS. MAZZOCHI: That's fine. Thank you, Your Honor.

THE COURT: Is Regeneron's plan still the same, Ms. Chu, Dr. Csaky, Dr. Trout. And if Mr. Graham and Mr. Manning are doctors, I apologize to those witnesses.

MR. BERL: Dr. Graham will be after Dr. Chu.

THE COURT: The order was --

MR. BERL: The order was not --

THE COURT: Okay.

MR. BERL: But we're calling those people.

THE COURT: Understood.

All right. We're going to break for the day. I'll see everyone at 9:00 tomorrow.

(Proceedings concluded at 5:22 p.m.)

CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 20, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 20th day of June 2023.

/s/Cindy L. Knecht
_____
Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and

Biocon Biologics, Volume 7

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 21, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

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Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

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Regeneron Pharmaceuticals, Inc. Exhibit 2009 Page 1329
Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

Wednesday Afternoon Session,

June 21, 2023, 9:00 a.m.

- - -

THE COURT: Day seven, I think, we convene for trial. Counsel is present. Dr. MacMichael is on the stand. I believe we're ready for redirect.

Is that correct, Counsel?

Madam Court Reporter is ready. You may proceed.

MR. SALMEN: Yes, Your Honor. For the first portion of my redirect, I'm probably going to have to get into some information that has been designated confidential. So pursuant to your previous order, we ask for a sealed courtroom.

THE COURT: Understood.

In an effort to get everyone their steps in early this morning, those of you not permitted to be here under the Court's protective order, if I could ask you to step out. We would certainly appreciate it.

We'll also ask the court security, once those folks have vacated the premises, to seal our courtroom, please. Thank you so much.

(The following proceedings (1527/23 to 1533/12) were had under seal, and are filed under separate cover.)

Regeneron Pharmaceuticals, Inc. Exhibit 2009 Page 1330
Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

(Courtroom unsealed.)

THE COURT: Welcome back, everybody.

Counsel, you may proceed.

MR. SALMEN: Thank you, Your Honor.

BY MR. SALMEN:

Q. Dr. MacMichael, do you recall Mr. Berl asking you the question "Polysorbate in Claim 1 is being used as a surface-active agent to prevent aggregation and denaturation?"

A. I don't recall the specific question.

Q. That appears at trial transcript page 1455. Why don't we put that on the screen to refresh your recollection.

I'll give you a moment to read that.

A. Yes.

Q. Do you recall this question?

A. Yes.

Q. Let's take a look at the '865 patent Claim 1, please.

Claim 1 of the '865 patent does not require polysorbate, does it?

A. It does not call out polysorbate.

Q. Dr. MacMichael, you were asked about Dr. Rabinow's testimony. And to refresh your recollection, let's pull up page 1482 to 1483.

Do you recall being shown this testimony from Dr. Rabinow?

A. Yes, I do.

Q. And you see here Dr. Rabinow was being asked about optimizing the stability of a protein formulation, a single formulation, right?

A. Yes.

Q. Were you asked to provide an opinion regarding whether the patent enables just a single formulation or whether the patent enables the full scope of the universe of formulations covered by the asserted claims?

A. Yes, I was asked.

Q. Were you asked whether the patent enables a single formulation or whether the patent enables the full scope of formulations covered by the asserted claims?

A. I apologize. I can't recall the specificity of that question, but I can answer the question. But I believe it does

not give a description on how to make multiple formulations.

Q. Thank you.

Now, Dr. MacMichael, Mr. Berl asked you about undue experimentation and your interpretation of that term. Do you remember those questions?

A. Yes.

Q. Now, you've formed an opinion regarding the amounts of experimentation required to practice the full scope of the asserted claims; is that correct?

A. Correct.

Q. What level of experimentation, in your opinion, is required for the person of ordinary skill in the art to practice the full scope of the asserted claims?

A. It would take a significant amount of experimentation.

Q. When you previously suggested that -- I'm sorry. What was the term you used?

A. I used "significant" as opposed to "undue."

Q. Okay. When you previously suggested that significant experimentation would be necessary, do you consider significant experimentation to be undue in view of the full scope -- the full scope of the '865 patent claims?

A. Yeah. I remember we had quite some discussion on that.

Undue means so much experimentation that you wouldn't

be able to achieve it. What I was testifying yesterday is it would be a significant amount of work, whether it was undue, but it would take a lot of work on the part of the formulation department. So --

Q. Now, Doctor -- I'm sorry.

A. I was just going to say whether you call that undue or significant is a relative term.

Q. Dr. MacMichael, you were also asked by Mr. Berl whether you identified any formulation that you would not be able to make.

Do you recall those questions?

A. Yes.

Q. And is that the evaluation that you were asked to make in determining enablement, whether you could not make a certain formulation, or were you asked to form an opinion regarding whether the skilled person could practice the full scope of the claims?

A. I don't know if I can get to the specifics of the question of how -- what was asked yesterday, but the second part of the question was?

Q. Were you asked whether the skilled person could practice the full scope of the asserted claims?

A. I believe I was.

Q. Dr. MacMichael, you were also asked about the Kaisheva reference. Do you remember that one?

A. Yes.

Q. And in this line of questions Mr. Berl suggested that the '865 patent informed the skilled person of an optimum pH for the formulations in the asserted claims.

Do you recall that?

A. Yes, I do.

Q. And that appears for the record at trial transcript pages 1488 to 1489.

Now, let's take a look at the '865 patent, Claim 1, Dr. MacMichael.

Dr. MacMichael, is Claim 1 limited to a formulation with a pH of 6.2 to 6.3?

A. No.

Q. The full scope of the formulation pH under Claim 1 would be much broader, right?

A. Well, it's not -- I don't see a definition for the value of the pH in Claim 1, so one would assume it's broad.

Q. Now, let's take a look at Claim 4.

Is Claim 4 limited to a specific pH?

A. No.

Q. Let's take a look at Claim 5. Is Claim 5 limited to a specific pH?

A. No.

Q. Let's take a look at the Kaisheva reference, Claim 1 of Kaisheva. This is DTX 3610, page 20 to 21. There is a copy

of it, Dr. MacMichael, in your cross-examination binder, Volume 1, if that helps.

A. That's Volume 2. I'm sorry. Could you give me the --

Q. Yes. DTX 3610. And I think Mr. Gibson has it up on the screen now.

A. Okay. Okay.

Q. And you see there in the third line of Claim 1 it reads "About 5 to 25 millimolar histidine buffer, having a pH from about 5.5 to 6.5."

Do you see that?

A. Yes, I do.

Q. So, Dr. MacMichael, does the claim in the Kaisheva reference identify the specific pH range?

A. Yes, it does -- it uses the term "about." Yes, it does. It gives 5.5 to about 6.5.

Q. Right. And we don't see that specificity in the '865 patent Claims 4 or 5, right?

A. No.

Q. Okay.

We can take that down.

Dr. MacMichael, you recall when Mr. Berl asked you about certain internal documents from Regeneron where they used the term "cosolvent," right?

A. Yes.

MR. SALMEN: And for the record, Your Honor, this is at trial transcript pages 1476.

BY MR. SALMEN:

Q. Dr. MacMichael, you provided your opinion in this case that polysorbate 20 is not -- sorry.

And you provided your opinion in this case that polysorbate 20 is not an organic cosolvent in Mylan's product under the Court's claim construction, right?

A. That's correct.

Q. Okay.

Mr. Gibson, you can take that down.

Were Mr. Berl's questions regarding the internal Regeneron documents specific to the Court's claim construction?

A. I don't believe so.

Q. Do you have any idea whether Regeneron was applying the Court's claim construction when it used the term "cosolvent" in those internal documents?

A. No. I don't know the mind of the Regeneron personnel.

Q. And would the person of ordinary skill in the art have access to the Regeneron internal documents?

A. Well, they're internal documents. They're confidential.

Q. Thank you.

Now, Dr. MacMichael, I'd like to ask you about when

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Mr. Berl asked you several questions about preventing aggregation using polysorbate. And I want to first ask you to consider a hypothetical formulation of aflibercept without polysorbate.

A. Okay.

Q. Are you with me?

A. Yes, I am.

Q. That solution would have to be in some kind of a container, right?

A. Yes.

Q. And I believe you testified yesterday that protein interactions with the surface of the container or interactions with the air can result in protein adsorption which can lead to aggregation. Was that right?

A. Yes. And denaturation.

Q. And denaturation. If I had the same solution in three different containers -- one in a smooth glass, a second in a jagged plastic container, and a third in a completely rubber container -- are you still with me?

A. Yes, I am.

Q. The propensity for the protein to aggregate in those various containers is going to be different, right?

A. Yes, it will be.

Q. Now, if I pick the best container, the one where the protein showed the least amount of aggregation -- let's say the

glass. Okay? And I put my solutions in only glass, I would have reduced the propensity for the protein to aggregate by eliminating the rubber or the jagged plastic, right?

A. What you're saying -- you're saying -- through experimentation, we demonstrated that we saw a greater propensity in one container versus another? Is that your question?

Q. Yes.

A. Yes.

Q. And so by putting it in the best container, I would have reduced the propensity for the protein to aggregate now that it's in the glass, right?

MR. BERL: Objection, Your Honor. This is leading.

THE COURT: Sustained.

BY MR. SALMEN:

Q. So, Dr. MacMichael, would you equate removing the rubber interface which reduced the likelihood of protein to aggregate the equivalent of using a cosolvent to increase the protein solubility?

A. No, because if you start getting aggregation, that container, once -- you might change the rate -- depending on the container without polysorbate -- and, again, we're talking hypothetical experimentation here -- once you initiated aggregation, if you're going to see aggregation lesser in the glass and faster in the rubber, ultimately, in the glass you're

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still going to get -- hint at the final amount of aggregation. So the rate might be different. So you'd need to add a surfactant whether using glass or rubber to prevent that aggregation.

Q. And would the fact that the surface is glass versus rubber be the equivalent of adding a cosolvent to increase solubility of the protein?

A. Well, first of all, adding a cosolvent -- we're using a generic term -- "cosolvent" here -- to increase solubility?

Q. Yes.

A. The answer would be no.

Q. Thank you.

I think you also testified in response to Mr. Berl's questions that adding hydrochloric acid to protein solutions might cause aggregation by denaturing the protein; is that right?

A. Yes. When you're adjusting the pH of a protein solution, you have to be very careful that there's not -- as you're adding it, that there's not high concentrations of acid before it diffuses. In those areas, you can get denaturation.

Q. But would you then say that not adding hydrochloric acid to my formulation would be the equivalent of using a cosolvent to increase solubility?

A. No. It's two different things. The hydrochloric acid would be a denaturing agent. And not using the

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hydrochloric acid doesn't make it equivalent to using a surfactant if that is the question.

Q. Thank you, Dr. MacMichael.

Last questions here, Dr. MacMichael.

You recall the analogy Mr. Berl presented to you about driving your separate cars through a snowstorm, right?

A. Yes.

Q. Let me pose a similar hypothetical. But in mine let's put the person skilled in the art of driving in snowy conditions behind the wheel of the car. Okay?

Now, a person skilled in the art of driving through snow would know that having a good set of snow tires on your car is going to make that car sufficiently stable in the event a snowstorm does occur, right?

A. Correct.

Q. And the skilled person might even have studded snow tires which have been road tested and proven to be sufficiently stable in pretty serious weather conditions, right?

A. Correct.

Q. And the skilled person of driving in the snow would know the snow tires alone would be sufficient to prevent the car from sliding off the road, right?

A. Correct.

Q. So adding chains on top of those snow tires would merely provide the skilled person some added assurance; isn't

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that right?

A. Correct.

MR. SALMEN: That's the end of my redirect, Your Honor.

THE COURT: Thank you, Counsel.

Recross?

MR. BERL: Your Honor, I was going to start where Mr. Salmen started; but, unfortunately, that's the confidential document.

THE COURT: No. Understood.

Time for more steps, everyone. I'd like to ask you to step out of the courtroom and ask court security to seal our courtroom once everyone's had a chance to depart.

(The following proceedings (1544/16 to 1550/4) were had under seal, and are filed under separate cover.)

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(Courtroom unsealed.)

THE COURT: Thank you, Officer.

Mr. Berl, you may proceed.

BY MR. BERL:

Q. Do you recall a few moments ago you were asked questions about the pH range and whether the claims in the '865 patent were limited to a particular pH range?

A. I recall the questioning around the pH, yes.

Q. You agree that the specification limits the formulation pH to within the range of 5.8 to 7, right?

A. If you could pull up the claims and the specifications, I'd like to see them so I can confirm.

Q. Let's just pull up your expert report, your reply report, PTX 62. This is your reply expert report, sir, correct?

A. I believe so, yes.

Q. And in the second to last bullet point on page 10 it says, "The pH. The specification only limits the formulation of pH to within the wide range of 5.8 and 7.0."

Do you see that?

A. Yes, I do.

Q. And that's a correct statement, right?

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A. I made it.

Q. Now, finally, I want to ask you about the testimony you gave about trying to distinguish between a formulation and whether that's routine to make and multiple formulations.

Do you recall that in Mr. Salmen's questioning of you?

A. Yes, I do.

Q. Doctor, just so everyone's clear, your opinion is that protein formulations are routinely optimized to improve the stability of their active ingredients, correct?

A. Yes.

Q. Not a protein formulation; protein formulations. Right?

A. When I said protein formulations, I was talking about the body of biotechnology and multiple companies and multiple products. That's why I used the term in plural. Formulations require significant amount of work. That was what I was referring to.

Q. Okay. So final question. Protein formulations are routinely optimized to improve the stability of their active ingredients.

Do I have that right?

A. That's a fair statement.

MR. BERL: No more questions, Your Honor.

THE COURT: Rereredirect.

MR. SALMEN: No questions, Your Honor.

THE COURT: All right. Do we have any exhibits that we need to -- one second, Doctor. Sorry.

MR. BERL: I just have two, Your Honor. I imagine Mr. Salmen has a lot more than that. So maybe I'll just get my two done, which are PTX 672 and PTX 1948.

THE COURT: Understood.

Any objection to those two documents?

MR. SALMEN: Let me just check, please.

THE COURT: Sure.

MR. SALMEN: Actually, Your Honor, we do object to admitting those documents into evidence with this expert. Those are the two Regeneron internal documents that Dr. MacMichael stated he had not seen before. I don't think this is the witness to properly authenticate those documents.

THE COURT: Mr. Berl.

MR. BERL: Yes, Your Honor. We can admit them through someone else, but the point is we've been admitting throughout the trial cross-examination testimony or -- and the associated documents.

THE COURT: Is there any suggestion that these documents are not actually authentic? That is a low evidentiary hurdle the opponent has to climb over.

MR. SALMEN: We have no objection to their authenticity, Your Honor. It's just -- and that was not the

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basis of the objection, but these --

THE COURT: Then what is the basis?

MR. SALMEN: The lack of foundation with this expert.

THE COURT: With respect to authenticity. What other foundation? They were used to cross the bases of the doctor's many opinions, correct, Mr. Berl?

MR. SALMEN: I'll withdraw the objection, Your Honor.

THE COURT: With objection withdrawn, both of those exhibits are hereby deemed admitted.

And, Counsel, if you want to review your list very slowly, please.

(PTX 672 and PTX 1948 were admitted.)

MR. SALMEN: Yes. I'll go through them slowly, Your Honor. DTX 0007, DTX 0030, DTX 2687, DTX 3463, DTX 3465, DTX 3466, DTX 4116, DTX 4229, DTX 4430, DTX 5011, DTX 5012, DTX 5053, DTX 5172, DTX 5196, DTX 5273, DTX 7087, DTX 8206, DTX 8207, DTX 8208, and DTX 8209.

THE COURT: Any objection to any of those items on the list?

MR. BERL: No, Your Honor.

THE COURT: Without objection, each of those shall be deemed admitted.

(DTX 0007, DTX 0030, DTX 2687, DTX 3463, DTX 3465, DTX 3466, DTX 4116, DTX 4229, DTX 4430, DTX 5011, DTX 5012, DTX 5053, DTX 5172, DTX 5196, DTX 5273, DTX 7087, DTX 8206,

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DTX 8207, DTX 8208, and DTX 8209 were admitted.)

THE COURT: Anything further we need from the good doctor?

MR. SALMEN: No, Your Honor.

THE COURT: All right. Doctor, thank you so much, sir. You can step down. I throw you back into the waters. They're free to talk to you again.

THE WITNESS: Thank you.

THE COURT: Mylan may call its next witness.

MS. MAZZOCHI: Your Honor, Mylan does not have any further live witnesses for its case in chief. I did, however, before we closed yesterday we had talked about introducing exhibits that were raised by Regeneron at Dr. Stewart's cross.

THE COURT: Correct.

MS. MAZZOCHI: We would like to move into evidence PTX 3348, which is one of his publications that was used on cross.

THE COURT: Any objection to 3348?

MR. GREGORY: No objection.

THE COURT: Without objection, 3348 deemed admitted.

(PTX 3348 was admitted.)

THE COURT: Were there any other loose ends from Dr. Stewart's testimony in terms of exhibits?

MS. MAZZOCHI: I don't believe so. I think we got all the rest of his exhibits into evidence.

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THE COURT: Okay. Understood.

Regeneron, any remaining?

MR. GREGORY: Yes, Your Honor. Given that they're moving 448, I'd like to take an opportunity to go back and take a look at the other exhibits moved on cross and see if you wanted to move a couple of those into evidence as well.

THE COURT: Continue to have Dr. Stewart's exhibits at loose end then. That's fine.

So Mylan is resting its case in chief, correct?

MS. MAZZOCHI: Yes. With that, Your Honor, we would rest our case in chief. And then as we had indicated yesterday, however, Mylan does have some objections to the witnesses and some of the deposition designations that Regeneron is proposing to offer today.

I believe one of their next witnesses was going to be Ms. Chu. There were objections that we had to Regeneron calling her in her individual capacity to talk on particular topics. I believe we filed a motion on that this morning.

THE COURT: I believe that you did, 6:49 a.m. It's 21 pages in length with attachments.

MS. MAZZOCHI: Yes. And I can certainly summarize briefly what the issues are. And it's basically this.

THE COURT: Let's pause on that.

Given that Mylan has rested, are there any motions from Regeneron at this juncture?

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We'll come back to that.

MR. BERL: Yes, Your Honor. Regeneron moves for judgment under Rule 52(c). I understand, Your Honor, that this is a bench trial; so I'll be brief.

But I would note that beginning with the formulation case, as it relates to invalidity, Mylan's combinations are plainly deficient. Even taking their expert's testimony as true, he failed to show multiple limitations of the claim were met by the asserted combinations, including, but not limited to, the requirement of an ophthalmologic formulation, which is present in neither Fraser nor the Liu reference with which it was combined; and the at least 98 percent native conformation limitation, which is not present with respect to aflibercept in any of their combinations and is not even tested for any product or any molecule or any formulation with respect to the combination of Fraser and Lucentis.

Absent a showing that all limitations of the claim, the claim as a whole, is obvious, an obviousness case simply cannot succeed.

With respect to the Dix reference, Mylan advanced no evidence, zero, that the Dix application and the application at issue here were not commonly owned or were not subject to a common assignment by the same company, Regeneron. It's clear from the face of that; they're all Regeneron's applications. And, accordingly, under 35 U.S.C. 103(c), it cannot be used as

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prior art for purposes of obviousness.

With respect to anticipation of Dix, even taking as true everything their expert Dr. Rabinow said, regarding the 40 mg/mL limitation of the claim, it's just not there. He relies only on the disclosure of 10 to 50 mg/mL, a range which is not directed to aflibercept.

But in any event, the law is clear. Disclosure of a range is not the disclosure of any number within that range, and any anticipation argument that Mylan attempts to advance simply is inconsistent with that controlling precedent, and so it cannot succeed either.

Now, with respect to Section 112, Your Honor just heard Dr. MacMichael, and the testimony was clear. He had numerous opportunities, both on cross-examination and again this morning on redirect, to tell Your Honor that the experimentation to practice the claim was undue. He repeatedly declined. And that's the standard from the *Wands* case all the way down to *Alcon v. Barr*. It's routine experimentation or undue experimentation.

They had two experts testify. We haven't gone yet, of course. Their first expert, Dr. Rabinow, said it's routine. Their second expert didn't disagree with that, and he doesn't say it's undue experimentation either. You can't have an enablement case without undue experimentation, and there's no evidence that there is.

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With respect to written description, he likewise agreed that this claim recites structure and it's structurally limited. The buffer is a known set of structures. The stabilizing agent is a known set of structures. The organic cosolvent in Claim 4 limited to polysorbate, that's a known structure. The active ingredient, aflibercept, that's a known structure.

These are known structures. A written description case cannot lie where you are reciting structures in your claim because the test for written description is whether a person of skill can envisage or envision what you're claiming. Can they recognize what it is?

And all of the foundational case from the Federal Circuit, beginning with the *Wyeth* case and rapamycin all the way to their en banc *Lilly v. Ariad* case stand for the proposition that you can't just claim function, you can't say I claim anything that will work without regard to what structures it is, because the person of skill can't envision what structures you are claiming.

That's not what we have here, according to Dr. MacMichael himself. We have structures that are being claimed. And Your Honor will search in vain for any claim that is limited to structure which the Federal Circuit has said doesn't meet the written description requirement in a situation like this because, of course, you can envision is. He agreed

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it's limited to structures.

The structures are known. And so it's, by definition, something that the skilled artisan can envision. They know this is in or this is out. If it doesn't have a stabilizing agent, it's out. If it has one, it meets that limitation. This is not some amorphous effort to claim only function; and therefore, the written description requirement is met as a matter of law.

Finally, with respect to indefiniteness, Dr. MacMichael agreed that the person of ordinary skill can understand the claims. He agreed that he lacks the expertise to determine what is suitable and what is not suitable. And he didn't consult with anyone, such as an ophthalmologist, who would have that expertise.

So I submit, Your Honor, that we should have judgment with regard to invalidity.

Regarding infringement, I actually think there are not many factual disputes here between Dr. Trout and Dr. MacMichael. Everyone agrees that, if you have polysorbate in the formulation that Mylan has, more of the aflibercept would be in solution under various conditions, conditions that Your Honor has heard from every witness in the case are important, such as going through the needle and creating the shear stress that can make things fall out of solution.

THE COURT: Let me ask you this, Mr. Berl. Does the

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label applied to polysorbate 20 matter? Is that a significant issue or dispute?

MR. BERL: No.

THE COURT: Why not?

MR. BERL: The reason is that the question under the Court's claim construction is does it increase the solubility of the aflibercept?

It doesn't matter whether someone labels it a stabilizing agent, a surfactant, or an organic cosolvent. The reason is those are words. Words don't matter. Actions matter. Is it actually increasing the solubility?

And Dr. MacMichael's own Graph 34 showed that it is. Without polysorbate, it was going down like this. And I'm showing for the record the curve where it's crashing out of solution in the black on Slide 34. And he showed with polysorbate, more is in solution. He agreed that that's what happened, and Dr. Trout says that's what happened.

You could call it a stabilizing agent, a surfactant. You can call it a duck. All that matters under Your Honor's construction is is there more polysorbate -- is there more aflibercept in solution with polysorbate than without? The answer to that question I would say undisputedly, according to this record, is yes.

I would also observe that "stabilizing agent" is a general term. And one needs to ask what is it stabilizing

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against? And I think both experts agreed what it's stabilizing against is aggregation. And if it stabilizes against aggregation, both experts testified clearly that aggregation then leads to precipitation, which is the opposite of solubility. You're either in solution or you precipitated out of solution.

I don't think there's anything at all inconsistent with calling this a stabilizing agent. That's not a problem because it's stabilizing against it coming out of solution. Put another way, it's stopping it from coming out of solution; it's keeping it in solution. It is increasing the solubility because there will be more with polysorbate in solution than without polysorbate under various relevant conditions such as shear stress.

So I don't think the label matters. As I've said repeatedly, this is not some anthropomorphic exercise where the polysorbate is running around saying, "I wonder what someone calls me." That's not going on here.

We know what it's doing. It's stopping aggregation; it's stopping precipitation; it's keeping the aflibercept in solution. That's what the claim requires, more in solution with than without and under relevant conditions.

I think both experts agreed. You can look at Slide 34. That's exactly what's going on. Y axis there is solubility of the aflibercept. If there's more with

polysorbate than without, I think that ends the infringement inquiry, respectfully.

With respect to the method of treatment, happy to answer any other questions Your Honor has.

THE COURT: Go ahead.

MR. BERL: With respect to the method of treatment, Your Honor, we explained in our infringement case that their label instructs practicing these claims. We heard no response from them in their case, no expert testimony, no other testimony indicating otherwise. The evidence is undisputed that their label instructs use of the claim.

Now, if they have some argument that not everyone practices the claim, that's not a defense to infringement under 35 U.S.C. 271(e), which is the section that we're addressing here in this case. The *AstraZeneca* case clearly stands for that proposition. We cited that in our pretrial papers.

It doesn't matter whether everyone practices the claim. What matters is whether anyone practices the claim. And the testimony was clear that some doctors practice the claim. If that were not right, we would have heard an expert for Mylan come in here and tell you that, but they withdrew their noninfringement expert.

And so they have no contrary interpretation of the evidence because the evidence is undisputed that some doctors will practice this claim. They haven't disputed that their

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label sets forth the claim. Under the *Warner-Lambert* case and its progeny, that reflects Mylan's intent.

You can't say I didn't mean it, I don't really care if people do it, I don't want to do it. That's not what happens under Section 271(e). Your label reflects your intent. The evidence is undisputed that their label hits every limitation of the claim and instructs doctors to practice the claim. That's sufficient for intent. That's the beginning and the end of that inquiry.

With respect to invalidity on the method of treatment claim, they have not advanced any argument that there are five loading doses in the prior art for the DME and diabetic retinopathy. It's just not there. They try to massage every single reference they can to make three five or to may pro re nata, prn, dosing somehow turn into five.

You heard yesterday from the witness stand from Dr. Stewart that it's just not there. That's not what it says, and they can't change what the prior art says. And based on the record that they have created, there is no case of obviousness because, again, every limitation in the claim as a whole has to be obvious.

Finally, as to the Claim 6 of the '572 patent, you've heard a lot of testimony about where the prior art was. It was unclear what treatment regimens would go forward. The art was trending away from the dosing regimen that is in the claim

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here. Genentech had failed with their efforts to do extended fixed dosing. People were moving toward pro re nata dosing.

Again, I don't think there are all that many factual disputes on this point, and under the facts in the record, there is no obviousness. It was not moving in the direction where the claims went. And we did that, not anyone else.

With respect to their argument on the isotonic limitation, Your Honor, they have not established how far outside of the range of isotonic you would want to go or not want to go. They had one witness testifying about this, Dr. Albini, who said you wouldn't want to use something too isotonic, over 800, because it could create some problems and he provided a reference, but he declined to say how far outside of that range of isotonic -- and we've seen what that is in the record -- you would be willing to go or not willing to go.

And so while they have made some case crediting all their evidence, as one does at the Rule 52 stage, that you wouldn't want to venture too far, all the way over 800, they have not made any case that you can't venture at all outside of the isotonic range to practice the claims. So I think their argument there is deficient as well.

So with that, obviously, open to any questions, but we believe that we should have judgment at this stage on both patents.

THE COURT: Understood. Thank you, Mr. Berl,

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Counsel.

Ms. Mazzochi, my apologies. I had some reading materials we discussed early this morning. This is my first cup of coffee; so I somehow combined your name with Mr. Rakoczy, name into one. I assume I'm not the first person to do that, but with my apologies, ma'am, go right ahead.

MS. MAZZOCHI: No worries, Your Honor. I am used to it. I got over that in about third grade, people mispronouncing both my first and last names. So I'm good. As long as you're not shooing me out in the courtroom, I'm happy.

All right. Your Honor, under 52(c), first of all, I'll go in reverse order.

The plaintiffs have suggested -- as we stated in our Rule 52(c) motion, we do not believe the plaintiffs have met their burden, and similarly the evidence that we have set forth in connection with our case in chief actually undermines plaintiff's claims that it would be improper on the infringement side to infer an intent to induce, not only because of the miniscule number of individuals that they, in theory, tried to come up with who might be practicing the claims. They don't dispute that you have to first have a direct infringer before you can have an active indirect infringement. They simply don't have the proof on that.

Furthermore, the Federal Circuit case law is also clear that, even if you want to assume a label indication is an

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infringing one, if you have noninfringing label uses -- and that discretion is left up to the clinical judgment of the prescribing physician, which Dr. Csaky admitted it would be -- then there is no inference of an intent to deceive.

Furthermore, with regard to their issues with regard to invalidity, they don't dispute that we really met our burden because, again, they keep focusing on what was expressly stated in a reference as opposed to what was inherently disclosed in a reference. They have -- our experts were firm on that issue that there was inherency through Dixon and other references. Even their attempt to try to get Dr. Stewart to agree with them backfired because he admitted that, as a person who is a prescribing physician, if he was going to apply a prn dosing regimen, he could easily envision how you could get to five loading doses before you go to eight-week dosing. So that pretty much backfired on them.

When it comes to obviousness, again, I'm not quite sure exactly what Mr. Berl is really trying to argue here with regard to the term "isotonic." If someone would have been motivated to make the formulation isotonic, and the undisputed evidence is that they would be, to say, "Well, I can come up with some theory as to why something might not be isotonic" does not negate the motivation of a person of ordinary skill in the art to actually make the formulation obvious.

Likewise, when it comes to these particular dosing

regimens, the motivation in the art was very clear that there was going to be -- that the doctors were already using extension methods, including after a monthly loading dose period. So the fact that Regeneron thinks that maybe they optimized them at five, routine optimization is not something that can be grounds for patentability.

With regard to indefiniteness and some of the other Section 112 issues that Dr. Stewart identified, as Dr. Stewart mentioned, Dr. Csaky has nothing in his expert report suggesting that the particular disease indications he identified will not work. So that nixes Claim 6.

And when it comes to the specification, again, the fact that the number 4 or the number 5 might appear somewhere in a specification does not satisfy the Federal Circuit's blaze marks test.

So we have met our burden to show indefiniteness. We have -- I'm sorry -- nonenablement, written description. We put forth the evidence of indefiniteness. That wasn't even addressed in terms of their inconsistent metrics that Regeneron is trying to propose for the term "approximately." So we have certainly met our burden on each of the elements with regard to the dosing patents and all the defenses that we have raised.

With regard to the formulation, the '865 patent claim, I'm sure Mr. Salmen will kick me off the podium if I say anything wrong, and we'll probably want to add to it, but let

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me just try to --

THE COURT: Probably in the form of a sticky note, but go ahead.

MS. MAZZOCHI: We love those sticky notes, especially if they are not going to keep a protein from falling out of solution.

But, you know, on this question of aggregation, again, what I think that Regeneron is really trying to do is they are trying to renegotiate, reopen, and modify the Court's claim construction. The claim construction was clear because the scientific literature is clear that a cosolvent is something that will in fact increase the amount of substance that you have in solution.

And for all of the drama that's been going on back here, nobody's disputing what the phenomenon is. It's just that Dr. Trout is trying to say that, when you're preventing aggregation, that's somehow the flip side of improving solubility. It simply is not.

You know, Mr. Berl keeps saying you put more in there. You are not putting more in there in the context of our formulation. It starts in solution. It stays in solution. And the fact that you've said, well, maybe you've put some bumper guards up to make sure that you don't come out of solution, that is not increasing the overall solubility of the substance.

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We're not starting at 30 mg/mL putting a material in there and now it's getting us to 40 mg/mL. That's not -- what's what you actually use a cosolvent for. We're not starting out with a lyophilized formulation that maybe was at half the concentration stored that way for stability purposes. Now we're going to add a cosolvent to it as we reconstitute it so that we can expand the nature of the formulation. That's not what's happening here.

All that's happening is we started at 40 mg/mL. We stay at that concentration. And we don't need to have the polysorbate in there to increase the concentration because we're not increasing the concentration. We're not using it to stuff more aflibercept into the existing formulation.

So, furthermore, when it comes to some of the questions with regard to anticipation, again, I'm going to take issue with Mr. Berl's suggestion that, when the prior art disclosed 10 to 50, that that somehow is not good enough to anticipate a milligram range of 40.

And the arguments that they're trying to make here again, they either have an obvious and anticipation problem or they have a Section 112 enablement problem and they also are not going to be able to claim the benefit back to their earlier applications. Because here again -- when the Federal Circuit has identified situations where you have a range and you are going to now say I've found something within the range I'm

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going to call patentable, you also have the burden to come forward and show that it's called a result-effective variable, that there's something unique or special about this particular point in the range that's not shared by other formulations that are within the same scope of the range.

There is no evidence in the record that there's something magical here about 40 mg/mL formulations that's unique, distinct, and different from the 10- to 50-milligram ones. And if it is, then their specification certainly hasn't enabled the person of ordinary skill in the art how to identify it, find it, or get there. And that's part of what our Section 112 arguments are all about.

That's likewise the same argument that condemns their ability to claim backwards in their priority applications. If they're going to start to say that our particular combination -- I call it their particular combination of the jigsaw puzzle that's sitting in the claims.

If they want to say there's really something special about each particular range that we've pinpointed as against the prior art background of this being part of the normal recipe that people were using -- a surfactant, a solubilizer, a buffer -- then their specification doesn't enable it. And that's why, again, they don't have any reason to say that these are unique or distinct. And if they are, then it fails under Section 112.

And that's why, Your Honor, we do keep getting back to -- you know, again, Mr. Berl was saying, oh, well, look, we can find some instances where somebody will routinely optimize a formulation. Yeah, if you actually have an existing formulation, there are routine steps that somebody can go through to try to optimize it.

The problem is that these claims are not limited to just a narrow scope or a narrow range. These claims in the '865 patent are directed to an incredibly broad range. And they have not actually taught the person of ordinary skill in the art how to do that.

That's why -- when you start going through the undue experimentation factors, that's why they exist to determine is -- in the ultimate legal question for you, is it undue? Is the amount of burden that the person of ordinary skill in the art has to go through? Do we have broad claims? We sure do.

Are they saying the art is unpredictable when it comes to the obviousness analysis? They sure are.

Are they saying things like, oh, a person of ordinary skill in the art wouldn't be able to do these things because they were teaching away with motivations against it? Yes.

So even when you have, then, the '865 patent in hand and you ask the person of ordinary skill in the art would you be able to make the full scope of what is claimed? the answer then becomes no, not without a significant massive amount of

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experimentation, where you are now back in trial-and-error land.

So yes, could the person of ordinary skill in the art take, for example, the existing census formulations that were designed for intravitreal purposes and actually put them forward -- you know, use them -- put aflibercept into them, for example, or take the Fraser formulation that's existing and optimize that? Of course they could.

But if you want to then say but what about -- but Regeneron didn't limit themselves to just the narrow claim. They went broad. And because they went broad, that's what the *Amgen* case is all about. The minute you decide you're going to go with a very broad claim, you better have the specification disclosure to support it. And here, they simply don't.

So, Your Honor, I know that you're going -- I'm assuming you're going to take all these under advisement and these will be the subject of posttrial briefing; but, again, that's essentially an outline of where things are here.

THE COURT: I'll ask you the same question counsel asked Mr. Berl.

Why should polysorbate care what name we ascribe to it?

MS. MAZZOCHI: I think that what we care about is the Court's claim construction. The Court --

THE COURT: That's a living and breathing

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construction, correct?

MS. MAZZOCHI: The Court's claim construction contemplates a behavior profile.

THE COURT: Right. But that can change through completion of trial, correct?

MS. MAZZOCHI: And that's exactly the point, is that there are instances where polysorbate can behave as a cosolvent, when it is driving more aflibercept versus your starting point into solution.

That's not -- that is not what is happening here. So -- and that's where we fundamentally just object to what Dr. Trout is trying to do. He is trying to say that preventing a protein from denaturing or preventing an existing amount of protein from crashing out of solution, that that is somehow equivalent to increasing the amount in solution. They're fundamentally different things.

And I think that what you see, then, at least in Mylan's BLA, is when we're using, for example, the terminology that we do -- and I don't want to get -- I don't remember which part is public or not.

But when we are talking about our -- things within our BLA, we are making representations to the FDA this is the behavioral consequence of what's happening. This is how it is working. This is how it's functioning. This is how it's behaving.

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So our terminology that we have presented to the FDA is describing how it's behaving in solution. And what we never said is we are using this to make sure we can fit enough aflibercept in the formulation in order to meet our specification goals. If we did, it would be called a cosolvent; since we're not, that's why it's not there.

So I agree that the Court should be looking at the behavior of what's going on, but what they're trying to do is refine the term "cosolvent" to give it a new scientifically inaccurate reading. They're trying to basically graft the function and behavior of a stabilizer, of a surfactant, into the definition of cosolvent through semantic games. And we just fundamentally disagree that that's appropriate to happen here.

So I don't know if I've -- I don't know If I've answered your question. Maybe I haven't answered your question. But that to me is fundamentally where we're coming from here.

THE COURT: It strikes me at this juncture -- I mean, polysorbate 20, Tween 20, whatever we want to call it in terms of what the substance is, is on the list of ingredients, right?

MS. MAZZOCHI: Sure.

THE COURT: There's no dispute about that. What strikes me is the more operative dispute here is does it matter whether or not the claims of the patent ascribe the right

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moniker to it as to what its function is? Is that as dispositive as I intuit at this point?

MS. MAZZOCHI: Yeah. And I think that it is important because when the claim uses the term "cosolvent" -- and remember, Your Honor, they have claims that are specific to polysorbate. That's Claim 51. So they had the ability to say -- and they do have claims that say, "I hereby claim a formulation with polysorbate in it, and we don't care about its function. We don't care about its role."

They have those claims. Those aren't asserted here.

They've tried to use broader claims where they did impart a functional concept, buffer, cosolvent, stabilizing agent. They're trying to take those broad functionally defined terms and say we're now going to cover this ingredient.

By the way, Your Honor, they also clearly thought that the term "cosolvent" was different from a stabilizer. They used both of those terms in Claim 1. So for Regeneron to now turn around and say, oh, well, now I'm going to treat them as if they are synonymous terms violates a whole host of claim construction rules.

So here again, I understand -- and this is where I think, Your Honor, there has been a lot that the parties have agreed on. But what we fundamentally don't -- I mean, when it comes to --

THE COURT: I may not need my second cup of coffee

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after this, Counsel, all recently filed pleadings to the contrary. But go ahead. We might just hear what all we've agreed upon.

MS. MAZZOCHI: In the sense of the parties -- the parties are not disputing what's in the formulation. They're not disputing amounts in the formulation. And Regeneron, for example, is not disputing that we have histidine. Histidine is also helping to -- it performs a role within the formulation.

But if you start then getting away from, well, I'm going to let them say that cosolvent can just mean anything that helps or anything that prevents aggregation or anything that helps prevent denaturation, that's fundamentally rewriting the claims.

So they chose to put terms in their claims that had functional aspects to them -- buffer, stabilizer, cosolvent. Our evidence and everything that we've submitted to the FDA, we submit, confirms we are not using that function with that ingredient. We're not using polysorbate to achieve the functional role of a cosolvent.

What is that functional role? It has to be increasing, not keeping it in, not -- if you've got the same number of players on the team or on the roster and you say I want to increase the roster, that means you're putting more on.

But, by contrast, all we're saying is we've got nonplayers on the field and we're just trying to make sure none

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of them has to run off. That's not putting more people on the roster; that's just trying to keep everything status quo.

What they're trying to say is that, well, if you're trying to maintain the status quo, then somehow you're increasing and you're changing something. It's just -- it's not.

So that's why, you know, when it comes to what's going on here, it is very important what they actually put in their claim. And we can't start erasing those claim limitations. We just can't.

And frankly, Your Honor, if they had wanted to make a doctrine of equivalence argument, which it seems like they might be trying to now make, they had every opportunity to do that months ago. But then they also would have had to comply with the Federal Circuit standards on equivalent function, equivalent way, equivalent result, showing that they didn't disclose but not claim things, which are legal restrictions. They wouldn't have been able to meet those standards, which is why we don't have a doctrine of equivalence analysis here.

So they offered literal infringement. They have a claim construction. The claim construction requires that a cosolvent has to actually help dissolve, get more things into solution. And they haven't demonstrated that our ingredients are going to do that.

Hopefully, that answers your question.

THE COURT: Understood.

MS. MAZZOCHI: Thank you.

THE COURT: Given the context of a bench trial proceeding and the myriad of questions the Court has to sift through, the Court's going to, under 52(c), decline to render judgment at this point but proceed with hearing evidence on that front.

Who will Regeneron's first rebuttal witness be?

MR. BERL: Your Honor, the first witness will be Karen Chu.

THE COURT: All right. We're going to take ten minutes at this point. I'll give Regeneron an opportunity to respond to the motion concerning Ms. Chu, and we'll go from there. We'll be at ease for ten minutes. Thank you.

(A recess was taken from 10:17 a.m. to 10:36 a.m.)

THE COURT: Regeneron's response to Motion 546.

MR. GREGORY: Good morning again, Your Honor.

THE COURT: Good morning.

MR. GREGORY: Your Honor, obviously, we have not had a chance to fully brief this issue in response to the motion that we received this morning at -- I believe it was around 7:00 a.m.

THE COURT: 6:49.

MR. GREGORY: I was close.

Respectfully, Your Honor, I think that we have a road map for dealing with exactly this situation. We've -- we're having this trial already. It's the same road map that we used with Dr. Yancopoulos and Dr. Furfine. And that is, respectfully, Your Honor, this is a bench trial. And I think Ms. Chu should be able to take the stand, provide her testimony.

If defense counsel feels that, in fact, we verge into issues or material or documents that are inappropriate somehow to use with Ms. Chu or to address through Ms. Chu, they could raise that in the posttrial briefing or in the course of her testimony.

I think that is, frankly, the beginning and end of the issue. I'm happy to discuss with particularity some of the arguments that I can discern from this brief that I've had a little bit of time to digest now.

The overriding argument seems to be that Ms. Chu's testimony -- the subject matter of her testimony is some sort of surprise. I'm not sure how that can be the case. So the facts are as follows:

Ms. Chu has been on our initial disclosures -- our Rule 26 disclosures since --

THE COURT: Yes. I don't think there's any dispute about that. She was deposed.

MR. GREGORY: And she was deposed for over seven

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hours, a full day. You heard an hour of her testimony yesterday.

THE COURT: I have not heard what the weather was in the city of her deposition.

Sorry. I couldn't resist. Go ahead.

MR. GREGORY: So -- but to be clear, in those initial disclosures starting back in September, in an interrogatory response filed in January, in her deposition, in all these places, Mylan-Biocon was informed what the subject matter of her testimony would be. That's the conception, reduction to practice of the inventions found in the '601 and the '572 patents as well as the clinical properties of aflibercept. That's been consistent in every one of these written communications.

Ms. Chu has been on both parties' witness lists since the first witness lists were exchanged. I candidly don't know how much more I can explain about what Ms. Chu's going to testify to without actually putting on her testimony and walking through it with Your Honor and with defense counsel here.

THE COURT: Understood.

Counsel, she's been disclosed as a witness. You've had the opportunity to depose her. I'll be candid with you. I'm at a loss.

MS. MAZZOCHI: Sure. Your Honor, we were able to

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depose her as a 30(b)(6) witness and a 30(b)(1). But at the outset of her deposition, I put the initial disclosures in front of her and said okay, what are you going to testify to at trial?

THE COURT: Did you ask her what knowledge she had about it?

MS. MAZZOCHI: Yeah. She didn't even --

THE COURT: The words matter. It's a completely different question. I've read the exchange not only in the last volley we had over Ms. Chu's testimony but also the motion that was filed this morning.

The words matter. The objection to what are you going to testify to at trial is, I think, a valid one. But there's different questions that could have been asked, I guess, is my point.

Let me get to this point as well. Ms. Chu testified under oath. If she gets up here and all of a sudden has learned a whole lot of new things that she didn't know at the time, that sounds like a very compelling and rich cross-examination that will weigh heavily in this Court's assessment of her credibility.

But I'm not inclined -- I'll say I'm going to deny the motion at this juncture. I don't think, as a matter of law, it is proper to preclude her testimony consistent with the Court's prior rulings. She was disclosed. She was deposed.

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If she's changed her story or augmented her knowledge that she did not have at the time, counsel is certainly welcome and no doubt capable to expose that direct cross. So that motion will be denied.

We'll take up the other motion with respect to Drs. Ryder and Russell when we get to them if Regeneron intends to call them.

Mylan may call its next witness -- I'm sorry.

Regeneron may call its next witness.

MR. GREGORY: Thank you, Your Honor.

Regeneron calls Ms. Karen Chu.

THE COURT: Counsel, before you begin, just a warning, if I get a message that indicates I need to walk out of here in 18 minutes because of traffic to retrieve a kid, I'll let everybody know, but then we may take an early lunch break today. Just FYI.

With apologies to you, Ms. Chu.

MR. GREGORY: Understand, Your Honor. I have a 4-year-old myself and I know how it goes.

THE COURT: Understood. I-79 has been a joy the last few weeks.

With that, Counsel, you may proceed.

MR. GREGORY: Thank you.

KAREN CHU, PLAINTIFF'S WITNESS, SWORN

DIRECT EXAMINATION

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BY MR. GREGORY:

Q. Ms. Chu, could you please introduce yourself to the Court.

A. Yes. Good morning. My name is Karen Chu.

Q. Where do you currently work, Ms. Chu?

A. I currently work at Regeneron Pharmaceuticals in Tarrytown, New York.

Q. And I want to come back and talk about how you got there and your role. But just first, what is your job title at Regeneron?

A. My current title is executive director of clinical strategy and execution for ophthalmology.

Q. And what are your current responsibilities generally in that role?

A. My responsibilities are that I oversee all of ophthalmology clinical development alongside our therapeutic area head. And that includes interacting with our research and preclinical groups for molecules coming into the clinic as well as the design, strategy, and execution of clinical trials.

Q. You mentioned just now clinical trials and clinical development. Just so we're clear on what we're talking about, what are clinical trials?

A. So clinical trials are the studies done in humans to support bringing a therapeutic product to potential commercialization.

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Q. So I want to back up now and talk a little bit about how you got to where you are today. So can you give us a little bit of background on your education.

A. Sure.

So I have a bachelor's of science in biology from Cal Poly San Luis Obispo. And then I have a master's of science in human nutrition from Columbia University.

Q. How did you come to work at Regeneron?

A. So at the end -- as part of my master's program, I was required to complete thesis research. And I did that research at St. Luke's Roosevelt Hospital in New York City and was exposed to clinical research and clinical trials there. They had an obesity clinical research unit.

And so I knew, coming out of my graduate program, that I was interested in clinical research. I actually moved back to California and was subsequently hired at Sequus Pharmaceuticals as a clinical trial assistant.

Q. And where did you go from Sequus?

A. So from Sequus I subsequently worked for Purdue Pharma as a regulatory compliance or clinical quality assurance associate.

Q. And what was your next stop?

A. After that I went to a CRO, or a contract research organization, called Barton & Polansky. And there I was a clinical project manager helping to oversee the conduct of

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Phase IIIB clinical trials in HIV.

Q. So still doing clinical trial work at that point?

A. Absolutely.

Q. And from there what was the next stop in your career path?

A. So after Barton & Polansky I was hired by GenVec. They were a small gene therapy company based in Gaithersburg, Maryland. And they did a lot of work in New York City with their scientific founder at Cornell.

Q. What kind of diseases or disorders was GenVec looking to treat?

A. So we had gene therapy products for both oncology indications as well as a product that we were testing in ophthalmology indications, specifically AMD at the time.

Q. And why did you ultimately leave GenVec?

A. So I was at GenVec for over four years. And towards the end of my time there, there were some changes in the gene therapy field that made it more difficult for the company to stay funded. And we -- the company had to make some hard decisions and laid off a number of people.

At that time I was not laid off, but it certainly didn't portend for a positive future for the company. So I started looking around for other opportunities at that time.

Q. Is that how you ultimately arrived at Regeneron?

A. Exactly. So I knew about Regeneron from mostly the

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oncology field, because at that time anti-VEGFs were presenting brand-new data and were very much seen as a revolutionary treatment. And so I knew that Regeneron had an anti-VEGF product that they were developing as well as the fact that they happened to be in New York, which was convenient.

Q. And just so we can put this kind of in time, what year was it when you started with Regeneron?

A. I started with Regeneron in 2003.

Q. And what was your title at that point?

A. I was hired as a clinical trial manager.

Q. And what was your role at that point in 2003 when you first started?

A. So primarily I was brought in to help implement and execute the clinical trials. At that time we had mostly early phase clinical trials. And having had experience in both oncology and ophthalmology, I was a very good fit for the team at the time. But my role quickly pivoted to being very much focused on ophthalmology.

Q. And can you describe for the Court kind of how your responsibilities at Regeneron have changed over the last two decades in your time with the company.

A. Sure. So I've certainly -- my entire career at Regeneron has been in ophthalmology. And, certainly, I have been part of the Eylea development program really from the time that it came from our preclinical group and entered the clinic.

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When I started at Regeneron, Regeneron was a small company. We were only about 500 employees total. And in our clinical and regulatory group, I think we were about 30 people total. So everybody wore a lot of different hats. And I had the great opportunity to be involved, really, from the very beginning in discussions around development strategy as well as had input into study designs, et cetera.

Q. Ms. Chu, do you have a medical degree or formal medical training?

A. I do not.

Q. How is it that you're able to contribute to the clinical research and development work at Regeneron without that educational background?

A. Sure. So I have over 25 years of direct experience in clinical development in various therapeutic areas but over 20 years of experience in ophthalmology and specifically in retina clinical development.

Q. So I'd first like to discuss just a little bit Regeneron's clinical development efforts for aflibercept for the treatment of wet age-related macular degeneration. Is that okay?

A. Sure.

Q. Just as some background to begin, can you remind me what stage clinical trials did Regeneron ultimately perform of aflibercept in wet AMD?

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A. So we performed Phase I, Phase II, and Phase III clinical trials in wet AMD.

Q. And what do Regeneron's Phase I clinical trials entail in ophthalmology?

A. Yeah. So typically -- so with ophthalmology clinical trials, our Phase I trials are relatively small. These are considered first in human trials; so the primary purpose is to get initial safety information.

So typically these trials would be less than 50 patients total, and we would be looking, as I said, to get initial safety but also to do dose ranging and get additional information around the kinetics of the drug and systemic exposure to the drug.

Q. And what do Regeneron's Phase II ophthalmology trials typically involve?

A. So Phase II trials are what we call proof-of-concept trials. So these are the first trials where we're really looking to get a confirmation of efficacy or biological effect. And we're -- of course, we're always looking for additional safety information. And typically Phase II trials tend to be a bit larger, somewhere between, I would say, 100 to about 300 patients at the most.

Q. And how about Regeneron's Phase III ophthalmology trials? What do those typically look like?

A. So Phase III trials are the pivotal trials that we

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plan to, if successful, hopefully submit to health authorities to support a marketing application. And so these are trials that are what we call powered for a statistical difference between treatment groups. And they can typically be very large, so on the order of hundreds to thousands of patients.

Q. Could you give us a sense of how long it typically takes Regeneron to plan and execute its Phase III ophthalmology trials?

A. So the planning for even the late phases of development really begins very, very early in product development. So even before we would bring a product into the clinic, we would be looking at -- we would be laying out what we think the clinical development plan would look like, and that would include kind of a high-level review of Phase I, Phase II, and Phase III clinical trials.

Obviously, as we conduct the clinical trials and receive more information during development, we refine our thoughts and our strategies around how we will move forward. And so from the time that we would have that Phase II or proof-of-concept data to the initiation of a Phase III protocol, it would take somewhere between 18 months to a year.

Q. And how expensive is it for Regeneron to run a Phase III ophthalmology clinical trial?

A. So our -- in my experience, our clinical trials typically cost about 150,000 to $200,000 per patient. So when

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you're talking about a trial on the order of, you know, 600 to 1200 patients, that can easily run in the hundreds of millions of dollars.

Q. In your experience, does Regeneron typically disclose publicly the details of its clinical trials or maintain those details confidentially?

A. We're always very careful about ensuring that we have confidentiality agreements in place, even when we're having discussions with external experts about aspects of planning or early, you know, decisions around indications to potentially move into, et cetera.

And during the clinical trials all of the investigators and their stuff operate under the clinical trial agreements, which include a confidentiality clause.

Q. Now, are patients in Regeneron's clinical trials subject to confidentiality agreements?

A. No, they are not.

Q. Have you ever heard of the term "investigator brochure"?

A. Yes, I'm aware of that.

Q. Could you tell us what that is in your experience.

A. Sure. So the investigator brochure is a document that summarizes all of the available data for that investigational product. So it would detail important information for an investigator to know, like the toxicology

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results, any safety information we have received from ongoing or if completed clinical trials, as well as any information from the class itself or what we know about the mechanism of the drug.

Q. And do patients or subjects in Regeneron's clinical trials get access to the investigator brochure?

A. No, they do not.

Q. Do patients in Regeneron's clinical trials know what dosing regimen or arm of the trial they're in?

A. No. So, obviously, informed consent is a major focus, and every patient who enters a clinical trial is provided adequate time to ask questions and review the informed consent form before agreeing to enter the trial. And we always strive to put sufficient information into the informed consent form so the patient understands the procedures and the design of the study.

Typically, especially in Phase III trials, the patients as well as the staff are masked to treatment assignment or blinded to treatment assignment. So the patient typically would not know what treatment assignment they were receiving.

Q. Do patients in Regeneron's clinical trials know if they're receiving -- in trials where a sham injection is employed, do patients in those trials know if they're receiving an actual injection as opposed to a sham injection?

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A. No, they do not. And the purpose of the sham procedure is really to mimic as closely as possible without actually piercing the globe, the intravitreal injection procedure. So they're prepped in the same way and the needle of the syringe -- or sorry -- the hub of the syringe is pressed against the globe so the sensation is similar.

THE COURT: Counsel, if I could interrupt, and, Ms. Chu, if this is outside your scope. So we're not talking about a placebo. We're talking about a fake injection that doesn't actually puncture the eyeball.

THE WITNESS: That's right.

THE COURT: Okay. All right.

THE WITNESS: If it helps you, I know --

THE COURT: None of this helps me. I'm still having all manner of eyeball and contact fake discomfort. But go ahead, ma'am. Sorry.

THE WITNESS: Well, I hope this will help you.

THE COURT: Thank you.

THE WITNESS: The way that these physicians complete the intravitreal injection, the patient -- they certainly don't come at the patient from right in front of their face with a needle. So you -- typically, a patient is reclined in a chair, and they prepare the injection behind the patient and they come at them from behind so the patient really never has a chance to see the syringe or the needle.

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THE COURT: Okay. Don't think that helped, ma'am, but thank you.

Counsel, go ahead.

MR. GREGORY: I have the exact same question, Your Honor.

THE COURT: The sneak attack sham injection. Understood. Go ahead, Counsel.

BY MR. GREGORY:

Q. Ms. Chu, do patients in Regeneron's clinical trials typically know the technical details of the product they're being administered?

A. No. So the investigators brochure, obviously, contains a high-level description of the product, but as we've discussed, that's typically not provided to the patient.

Q. Do patients in Regeneron's clinical trials know the formulation of the drug product they're being administered?

MS. MAZZOCHI: Objection, Your Honor. Calls for speculation as to what the patients know.

THE COURT: Sustained.

BY MR. GREGORY:

Q. Does Regeneron provide information to the patients in its clinical trials about the formulation of the drug product they're being administered?

A. No, we do not.

Q. In the informed consent that is given to the patients

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as part of their participation in the clinical trials, it does not contain that information, correct?

A. It does not.

Q. Do you recall a time frame in or around 2007 when Regeneron was engaged in planning for its prospective at that point Phase III wet AMD trials?

A. Yes. We actually began our development in DME back -- all the way back beginning in 2004.

Q. What role did senior management play in those development discussions around the Phase III trials?

A. Yeah. So as I've already mentioned, Regeneron was and in many ways is still a small company, and so our senior management has always been heavily involved in discussions around the clinical development planning and strategy as well as decisions around study design.

Q. Just for clarity, was it the -- what Phase III planning began in 2004? Was it wet AMD? Was it DME? What indications in that planning? What began then?

A. I mean, obviously, in 2004 we were already thinking about development in DME, but in 2004 we were really focused on what we felt was the initial indication or the priority indication, which was neovascular AMD.

Q. What was Dr. Yancopoulos's typical role in those discussions around Phase III wet AMD planning?

A. So Dr. Yancopoulos was heavily involved and certainly

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was part of many, many discussions related to the clinical study designs and strategy, and ultimately he was the final decision maker regarding aspects of the study design and clinical development program.

Q. I'd like you to take a look at a document for me, Ms. Chu. And you should have a binder in front of you, and we're also going to put it up on the screen. But I'd like you to take a look at PTX 0188.

Let me know when you have that in front of you.

A. Yes, I see that.

Q. And do you recognize this document?

A. Yes. This is an email from March 28, 2007, regarding decisions that need to be made to facilitate the beginning of the first AMD pivotal study.

Q. And I'd like you to take a look at item number -- just for clarity, you are a recipient of this email, right?

A. Yes, I am on this email as a recipient.

Q. It's dated March 28, 2007?

A. That's correct.

Q. And I'd like you to take a look at Item Number 2 in the body of the email.

Can you please explain to the Court what was under consideration at this time.

A. Yeah. So in this email we were planning on a four-arm study with approximately 1,200 patients with the doses

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of .5 milligrams, 2 milligrams, and potentially 4 milligrams with different intervals being considered, q4, q8, and q12.

Q. There hadn't been a decision yet on the exact dosing interval?

A. At this time we had not made a final decision.

Q. Could you please take a look at Item Letter G at the bottom of the email. Do you see that?

A. Yes, I see that.

Q. And so what is being discussed here?

A. So this was an action item for an internal meeting to be set up; so that way we could make decisions -- have discussions and make decisions about these elements that would facilitate the finalization of the -- what we call the clinical study concept document, which was the precursor to the clinical protocol.

Q. And when was that meeting set for?

A. That was set for April 13th, 2007.

Q. Could you take a look back just briefly at that.

A. Oh, sorry.

Q. Just for clarity. The first line reads, "Kathleen to set up a meeting next week, week of April 2nd."

A. Oh, sorry. The week of April 2nd.

Q. Let's look at DTX 227, which should also be in your binder, and we'll also put it up on the screen.

Do you have DTX 227 before you, Ms. Chu?

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A. Yes, I see that.
Q. Do you recognize this document?
A. So this is an email from April 2nd, 2007.
Q. And you're a recipient of this email?
A. Yes, I am.
Q. And there's a -- the first line of the body of the email reads, "Below is a summary of the decisions and actions from the AMD Phase III program meeting," right?
A. Right.
Q. Could you please take a look at the decision bullet a little bit further down the page and explain to us what decision had come out of this meeting.
A. So we had made a decision about the study design and the arms that would be included in the Phase III -- one of the Phase III AMD studies, the 0605 study, which was the VIEW 1 study. And we were planning to include a Lucentis group as a control, .5 milligrams aflibercept every four weeks, 2 milligrams every eight weeks after three initial monthly doses, and a 2-milligram-every-four-week group.
Q. Ms. Chu, do you specifically recall how that decision was made in this meeting?
A. I do not specifically recall.
Q. What was the typical practice at Regeneron for making these type of clinical trial design decisions?
A. So typically the study team would be charged with

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coming to our senior management with proposals and any supporting data or other aspects of the program that would support our proposals, and then we would have a discussion about it with senior management. And then ultimately a final decision would be made about how to move forward.

Q. What was Dr. Yancopoulos's typical role in those decisions?

A. Dr. Yancopoulos was very involved in the discussions as well as in any analysis of data. He very often would ask for additional data or additional analyses to be presented, and he was ultimately the final decision about the study -- the groups that went into the study.

Q. I want to direct your attention to the final action item, the bottom of the email. It says, "Discussed proposed development plan with Darlene Jody," and then it's Bob, George, Peter.

Who was Darlene Jody?

A. Darlene Jody was with Bayer at the time. She was a senior executive responsible for the collaboration that we had with them for Eylea.

Q. Did Bayer make the Phase III trial design decision that we just saw in the upper part of this email?

A. No, they did not. The nature of our collaboration with Bayer was such that Regeneron held the final scientific decision-making for the program. So while we would certainly

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have discussions with them and include members of their team both at the team level as well as the senior management level in our meetings and discussions about aspects of the clinical development program, ultimately Regeneron had the final say.

Q. If Bayer had come up with a decision that we were looking at in the upper part of the email, would the final action item here have been discussed, proposed development plan, with Bayer?

A. Well, they would probably have a set of minutes that said they should discuss it with us.

Q. Okay. Let's take a look -- let's turn our attention, actually, to the question of Regeneron's development of aflibercept for the treatment of diabetic macular edema. Okay?

A. Sure.

Q. And I may slip from time to time and call diabetic macular edema DME, but you'll understand what I'm talking about, right?

A. Yes.

Q. Approximately when did Regeneron begin its clinical development of aflibercept for the treatment of diabetic macular edema?

A. Yeah. So like I already said, we actually began in 2004 with a study utilizing intravenous delivery of aflibercept for the treatment of DME.

Q. And that was a Phase I study?

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A. Yes.

Q. Did you eventually also do a Phase I intravitreal study?

A. We did. So we eventually did a small study with five patients with intravitreal delivery.

Q. Did Regeneron perform Phase II studies in DME?

A. Yes. So we conducted the 0706, or DA VINCI study, which was a Phase II study in diabetic macular edema.

Q. Did Regeneron perform or conduct Phase III clinical studies in DME?

A. Yes. Our Phase III studies were called VIVID and VISTA.

Q. I want to put another document before you. I want to direct your attention to, actually, a pair of documents that go together. One is PTX 3150 and the next is PTX 3151, both of which, again, should be in your binder. And we'll put the first of them up on the screen right now.

A. Okay.

Q. Do you recognize this document, 3150?

A. Yes. So this is an email from May 2nd, 2007, with a high-level summary of a DME planning teleconference.

Q. Did you attend that DME planning teleconference?

A. Yes, I did.

Q. So I want to take a look now at the attachment to PTX 3150. This will be PTX 3151.

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Do you recognize this document?

A. Yes. So this is a summary of the discussion at that same teleconference.

Q. And I want to direct your attention up to the attendees list at the top of the document here. Could you let me know or tell me who the external doctors were who attended this teleconference.

A. Sure. So Dr. Lloyd Aiello from Harvard University, Neil Bressler from Wilmer Eye Institute, Quan Nguyen also from Wilmer Eye Institute, and Dr. Jeff Heier from Ophthalmologic Consultants of Boston.

Q. Did Regeneron have questions for those assembled doctors about the nature of diabetic macular edema?

A. Yes, we did.

Q. And I want to take a look at the first bullet here, the first item. Coming out of this call with these assembled doctors, what was your understanding about the progression and the nature of DME relative to, for example, wet AMD?

A. Yeah. So I think we understood that, first, this is a very different eye disease because it stems from, obviously, the underlying diabetes that these patients have; and we wanted to know more about exactly how these patients are diagnosed, treated, et cetera.

And out of this teleconference we had a better understanding that DME is -- can be not only a slowly

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progressive disease but also one that fluctuates much more than AMD.

So in AMD the typical course for patients was that, within the year after diagnosis with neovascular AMD, patients would precipitously lose vision and that vision could not be regained. But in DME we understood that vision is often more recoverable. And so it was a very different disease from that perspective.

THE COURT: Yes, Counsel.

MS. MAZZOCHI: Your Honor, I think now we're starting get to the point where Ms. Chu is offering the equivalent of expert testimony. She's just expounding on DME generally, not what did she know back at that time period. She's offered as a 30(b)(1).

THE COURT: Understood.

Stay within the lane of Ms. Chu's capacity as a witness here, Counsel.

MR. GREGORY: Yes, Your Honor. My question was specifically about her understanding coming out of this meeting. I'll try to keep it to that narrow lane.

THE COURT: Understood.

BY MR. GREGORY:

Q. Ms. Chu, I want to direct your attention to the third bullet on this page, and I want -- I'm asking some narrow questions here, okay, with the Court's guidance in mind.

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Did Regeneron pose to the assembled doctors on this teleconference any questions about the treatment outcomes of patients with DME?

A. Yes. So we were obviously very interested in the current treatment landscape as well as their expectations around what outcomes they could expect or anticipate with the current treatments available, including laser and steroid.

Q. And, again, I want to be narrow here. What was your understanding at the time, including coming out of this call with these doctors, about those treatment outcomes?

MS. MAZZOCHI: Your Honor, I'm just going to object as well to the relevance of this. We're all -- the questions that are before the Court relate to the validity of these patents with regard to the perspective of a person of ordinary skill in the art. And to the extent she's been offered on issues relating to conception or reduction to practice, again, we don't think that it's been established that she has knowledge on that.

But going through all this history is not really relevant to any of the issues here. I'm concerned, again, that Regeneron is trying to just -- actually, I'm not going to predict what's going on in their heads.

I'm just going to object that it's not relevant to the issues before the Court.

THE COURT: How is this line of questioning relevant,

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Counsel?

MR. GREGORY: Of course, Your Honor. While the Federal Circuit has been very, very clear that the inventor's path to the invention cannot negate the invention or prove obviousness, the Federal Circuit has also been equally clear that the inventor's efforts, the roads that they went down, the roads that they did not go down, their understanding can be relevant to, for example, the motivation to combine elements of the prior art or whether there was a reasonable expectation of success.

Ms. Chu is here talking about the clinical development. Dr. Yancopoulos's invention occurred within the context of the clinical development program. They didn't occur in a vacuum. It was in the context of this program and Regeneron's understanding of these disease states at the time and of what was going on in the world at this time, and Ms. Chu is providing some of that.

THE COURT: Understood. Overruled.

MR. GREGORY: Your Honor, I'll move on from this document quite quickly.

BY MR. GREGORY:

Q. I want to look at Item Number 1 once more along with an item from the -- I believe it's the third page of the document. We put it up on the screen here.

I want to understand if Regeneron asked the doctors

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that it assembled about the available DME treatment options at this point in time.

A. Yes. So we absolutely had a discussion about available treatments. And, you know, certainly, as I already mentioned, laser and steroid were being used as treatments for DME, and we also understood that the patient's underlying diabetic status was something that was a focus for these physicians as well.

Q. I have one more question about this document, Ms. Chu. Can you look at -- I think it's the final page, Item Number 5.

Do you see there's a question there or there's an item about competitive landscape and a reference to Lucentis? Do you see that?

A. I do see that.

Q. What is Lucentis?

A. So Lucentis is another anti-VEGF molecule that was being developed by Genentech.

Q. And was Regeneron monitoring the status of Lucentis's development?

A. Yes. We were very interested in the status as well as their decisions around development with Lucentis.

Q. I want to move to a different document. This is going to be DTX 8190, which again should be in your binder. I will also put it up on the screen.

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A. Okay.
Q. Do you have DTX 8190 before you?
A. Yes, I do.
Q. Do you recognize this document?
A. Yes. So this is a summary of the EMEA's scientific advice procedure that was requested by Bayer.
Q. And I want to look -- and Bayer was your codevelopment partner at the time?
A. Correct.
Q. I want to take a look at the third page of the document, and there's a sentence about midway down -- we have it called up right here -- the sentence that begins "based on this experience."
Do you see that sentence?
A. Yes, I do see that.
Q. First, just to be clear, whose position is being set forth here? Is this Bayer's?
A. No. So this would be the joint position between Bayer and Regeneron.
Q. And I just want to be very clear. The sentence reads, "Based on this experience, we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD."
Do you see that?

A. I do see that.

Q. To be clear, was it Bayer or Regeneron's position that they could predict the success of a dosing regimen to be employed in the Phase III trial solely on the basis of this Phase II data?

MS. MAZZOCHI: Objection, Your Honor. Again, this is attempting to elicit expert testimony. To the extent Mr. Gregory said that this was going to be relevant to anything on reasonable expectation of success, reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art. So this is not relevant to that question.

If their expert wanted to rely on it because he thought it was relevant to his opinion, he could have. He didn't. So we don't need this -- so this witness's testimony is simply not germane to that issue.

MR. GREGORY: Again, Your Honor, the inventor's path can be reflective of, in support, a lack of reasonable expectation of success and a lack of motivation to combine the elements in the prior art. This is a Regeneron -- as she just testified, a Regeneron and Bayer joint document that she saw at the time. I'm asking her to clarify the meaning of this sentence.

THE COURT: Understood. And we're going to hear from experts, Counsel, presumably on this very point. Her testimony

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is not going to be credited with that respect. This strikes me as background and factual information leading up to what we're going to hear from the experts.

Objection overruled.

BY MR. GREGORY:

Q. I'm not sure if I actually got an answer to that question; so I'm just going to repeat it.

Looking at this first sentence that reads, "Based on this experience, we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III and DME could be selected based on the results of the Phase II study in patients with wet AMD."

But you had that sentence. My question was, to be clear, was it Bayer or Regeneron's position that they could predict the success of a dosage regimen employed in the Phase III trial solely on the basis of the Phase II data?

A. So, obviously, with any scientific experiment there's the possibility of failure. And although we understood that DME, like neovascular AMD, is a disease driven by overexpression of VEGF which causes the pathological neovascularization, we also understood that DME was a very different disease.

And so typically in our interactions with health authorities, our approach is to ask questions around minimum requirements. And so this was a question intended to frame support for our proposal in the document but not one that was

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predictive of what we expected from the Phase III studies certainly.

Q. I want to now shift gears and take a look at a new set of documents. These are going to be PTX 3167 and 3168. Again, it's a paper and an attachment that go together.

Will you please let me know when you have them in front of you, Ms. Chu.

A. Yes, I have them in front of me.

Q. So do you recognize PTX 3167?

A. So 3167 is an email dated January 31st, 2008, highlighting some scenarios for a meeting that would be held the same day.

Q. And the first sentence says, "Enclosed are the DME scenarios that the team has put together for today's meeting"?

A. Right. So there was an attachment with a PowerPoint presentation intended to be presented and discussed at the meeting.

Q. There's an acronym on this page, JSC. Can you tell us what the JSC was.

A. So JSC stands for joint steering committee. And as part of our collaboration agreement with Bayer, we had several joint committees that were formed. The joint development committee was charged with overseeing all development of Eylea and included members from both Regeneron and Bayer. And the joint steering committee was the senior-level committee that

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included members from both companies.

Q. I want to now look at the attachment. So this is PTX 3168. And in particular I want to take a look at the second page -- or the second slide.

This is a slide titled "DME Target Product Profile," right?

A. Yes.

Q. What is a target product profile at Regeneron?

A. So a target product profile is a document that we typically put together early in development just highlighting at a high level what we see as the sort of minimal as well as target claims that we would like to strive for for our product to be commercially viable or commercially successful.

Q. So to be clear, these TPPs -- these are a regularly prepared type of Regeneron document?

A. Yes.

Q. And these are commercial documents?

A. Typically they're driven by commercial. Clinical obviously has input in terms of the end points and expectations, but this is typically charged -- the responsibility of our commercial group.

Q. How many monthly loading doses were set forth in the TPP at this point in time?

MS. MAZZOCHI: Again, Your Honor, she's talking about -- she's talking about Regeneron documents, Regeneron's

perspective. She's being offered in her 30(b)(1) capacity. She's testified this is a joint collaborative document between Regeneron and Bayer.

This is not relevant to any of the issues relating to the commercial success or the motivation or any of the things that Mr. Teagan identified. It's not even relevant to his inventor's path because the cover email said that Mr. Yancopoulos was not present at this meeting. So how can this be in any way, shape, or form relevant to either Dr. Yancopoulos's path or --

THE COURT: Commercial success.

MS. MAZZOCHI: -- commercial success.

THE COURT: Counsel?

MR. GREGORY: Your Honor, again, it's the path to the invention. And this invention occurred in the context of this broader clinical development program. There is no, I think, dispute about that. All right? It was part of the clinical development program that these inventions occurred in.

The path to that invention is relevant to both the motivation to combine elements of the prior art as well as reasonable expectation of success. The roads that Regeneron did go down, the roads that it did not go down, the walls they bumped their heads against, that all goes to those issues.

I'm looking at here Regeneron's path to get to five loading doses. And as we see, there's no five loading doses on

this page.

MS. MAZZOCHI: And, Your Honor, again, motivation, reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art based on the prior art that was available at the time. These are Regeneron's internal documents. That's completely irrelevant to that question.

MR. GREGORY: Your Honor, I would point the Court to *Micro Chemical v. Great Plains Chemical*, 103 F.3d 1538, which I think is clear on this point.

THE COURT: Understood. Overruled.

MR. GREGORY: We can set this document aside.

BY MR. GREGORY:

Q. We've talked a little about Regeneron's planning for its own clinical trials. I think you mentioned previously that Regeneron was also monitoring the clinical trial work being performed by the folks who were developing Lucentis.

Do you recall that?

A. Yes.

Q. And those companies that was Genentech and Novartis, right?

A. Right. So Genentech had rights to Lucentis in the United States and Novartis outside of the United States.

Q. Did Genentech and -- or let's frame it like this: Was Lucentis approved for treatment of diabetic macular edema

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in 2010?

A. No. I believe they received their approval for DME in 2012.

Q. And were they approved for -- was Lucentis approved for the treatment of diabetic retinopathy in 2010?

A. No. That came subsequent to their DME approval.

Q. Was Lucentis being explored in clinical trials for the treatment of DME in 2010?

MS. MAZZOCHI: Again, Your Honor --

THE COURT: Stop saying "again." What's the objection?

MS. MAZZOCHI: I object that he hasn't established this is her own personal knowledge. Again, she --

THE COURT: Understood. Sustained.

BY MR. GREGORY:

Q. Ms. Chu --

MR. GREGORY: May I try to lay a foundation, Your Honor?

THE COURT: I would encourage you to do so if you want an answer to that question ultimately, yes, sir.

MR. GREGORY: Thank you.

BY MR. GREGORY:

Q. Ms. Chu, were you monitoring -- you personally monitoring the status of Lucentis's clinical development in mid-2010?

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A. Yes. It was part of my role to understand what the competitive landscape was.

Q. Did you have an understanding of -- I'm asking a narrow question right now.

Did you have an understanding of what clinical trials were -- of any clinical trials that were being performed with Lucentis in 2010?

A. So the Phase III RISE and RIDE trials were ongoing as well as, during that period of time, Novartis had a couple of studies called the RESOLVE and RESTORE trials.

Q. And did you personally have knowledge of what the dosing regimens were that were being tested in those trials in 2010?

A. So in RISE and RIDE, it was both .3 and .5 milligram monthly compared to sham. And in the RESOLVE and RESTORE trials -- in RESOLVE it was .3 and .5 milligrams with three initial monthly doses with the ability to double the dose at month one followed by prn dosing. And RESTORE was .5 milligrams with three initial monthly doses followed by prn .5 milligrams, three initial monthly doses followed by prn plus laser photocoagulation. And the control in that group was laser photocoagulation.

Q. Okay. I want to talk about what Regeneron was doing at this same point in time. In mid-2010 what was Regeneron's -- let me reframe the question.

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In mid-2010 was there a Regeneron Phase II trial ongoing?

A. Yes. So the 0706, or DA VINCI, trial was ongoing in 2010.

Q. And in mid-2010 had Regeneron received any results from the DA VINCI Phase II DME trial?

MS. MAZZOCHI: Again, Your Honor, can she please not speak on behalf of Regeneron but on her own personal knowledge.

THE COURT: Sustained.

MR. GREGORY: Your Honor, I'm asking if the company received it. I can reframe the question if defense counsel would like.

THE COURT: Please.

BY MR. GREGORY:

Q. Ms. Chu, were you aware of any preliminary results from the Phase II DA VINCI trial as of mid-2010?

A. So the DA VINCI trial was a year-long trial with a week 24 primary end point. So at the beginning of 2010 we had received data from the Week 24 primary end point, but the study was ongoing through 52 weeks, or one year.

Q. Had you, personally, Ms. Chu, seen by mid-2010 mean visual acuity gain data for the DA VINCI trial up through Week 24?

A. Yes. So typically when we execute clinical trials, once the patient has completed the final visit of interest and

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the data has been entered into the database, there's a process we go through to clean the data and, quote/unquote, lock the database, which is the initiation of the statistical analysis.

And then the output from the statistical analysis is provided to the clinical group, where we review the detailed data and typically summarize it in PowerPoint presentation format.

Q. I want to skip ahead a little bit, then, from mid-2010 to the fall. Let's look at PTX 3131 and PTX 3133.

Do you recognize this document -- or these documents, Ms. Chu?

A. Yes. So this is an email dated October 6th, 2010, circulating PowerPoint slides related to an upcoming program strategy meeting for VEGF Trap-Eye, or aflibercept.

Q. And I want to take a look, then, at the attachment, the slide deck. So this is PTX 3133. Can you please direct your attention to page 11 of that deck.

A. Okay.

Q. Do you have an understanding at this point in the -- in October of 2010 as to what the planning was as to the design of Regeneron's Phase III DME trial?

A. So at this time we were planning on a three-arm study, 2 milligrams aflibercept every four weeks, 2 milligrams every eight weeks after three initial monthly doses, compared to macular laser photocoagulation.

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Q. Okay. And to be clear, your understanding at this point in time was that Regeneron was not planning for a five-loading-dose study?

A. That's correct.

MS. MAZZOCHI: Objection. She can't speak to what Regeneron was thinking; she can only speak to her own personal knowledge.

THE COURT: Sustained.

BY MR. GREGORY:

Q. Ms. Chu, I want to phrase this question very narrowly. I want you to listen to my question. Okay?

Did you have an understanding -- you personally have an understanding of what the planning was as of October 2010 as to the number of loading doses in Regeneron's Phase III clinical trial?

A. Yes. At this time we were still considering three initial monthly doses followed by every eight weeks as one of the dosing arms for the clinical trial.

Q. Ms. Chu, again, to reiterate, at this point in time in October of 2010, how long had you had the Week 24 DA VINCI data? Was that nine months at that point?

A. I believe we had received it in January of that year; so we had had it for nine or ten months.

Q. Let's take a look next at PTX 3188.

Do you recognize this document, Ms. Chu?

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A. Yes. So this is a slide presentation from the joint development committee to the joint steering committee.

Q. And I just forget if you provided this elaboration already. So I apologize. I think you've told us what the joint steering committee was.

What is the joint development committee?

A. Yeah. So, again, that's the joint committee between Bayer and Regeneron responsible for the development decisions for aflibercept.

Q. I want to take a look at -- let's just skip ahead here to -- skip ahead here to page 4. There's a reference on this page to the EMA. Do you know what the EMA is?

A. So that's the European Medicines Agency.

Q. And there's a -- the title here is "EMA - Outcome and Consequences." I guess the title of the slide is "Health Authority Feedback."

Do you see that?

A. Yes, I do see that.

Q. Okay. What was your understanding of what was being discussed here?

A. Yeah. So at this time we were seeking health authority feedback about our plans for DME development. And the EMA had pointed out that they did not feel that our AMD safety data could be extrapolated completely to the diabetic macular edema population.

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Q. Let's jump to page 19 of this same deck.

And do you see the reference there again in the middle of the page to the safety data?

A. Give me one minute.

Yes, I do.

Q. What was your understanding at this time as to EMA's position on that?

A. So their position was that the diabetic population was distinct from the neovascular AMD population, that this is -- while a younger -- somewhat younger population, that they also had several comorbidities and an increased -- so, for instance, diabetics are more frequently hypertensive as well as they have an increased risk of what we would term thromboembolic events; so things like stroke and heart attack.

And we knew that VEGF inhibitors like aflibercept had certain class effects, especially when delivered systemically, that included increased blood pressure as well as an increased risk for thromboembolic events. So this was a population that we felt could be particularly vulnerable to systemic exposure.

Q. Let's next look at PTX 1028C. Let's put the first page of this up on the screen for you here.

MS. MAZZOCHI: Your Honor, that last part of her answer where she started off from diabetic hypertension through what they thought, that's either getting into what Regeneron thought or it's expert testimony.

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THE COURT: Understood. Motion to strike denied, though.

Go ahead, Counsel.

MR. GREGORY: Thank you, Your Honor.

BY MR. GREGORY:

Q. PTX 1028C, which is up on the screen and also should be in the binder, do you recognize this document?

A. Yes. So this a PowerPoint presentation of the one-year data from DA VINCI.

Q. DA VINCI again, that's the Phase II DME trial?

A. That's right.

Q. And how would a document like this -- I think you may have already talked a little bit on this subject, but how would a document like this typically be prepared at Regeneron in your experience?

A. Yeah. So as I mentioned -- so the process is typically that once the last patient completes their -- that last visit of interest, there's a process where the data is entered into the database and any questions about the data are resolved.

Once we lock the database, our statisticians then begin their process of analysis. And from that comes a detailed set of what we call tables, figures, and listings, which really is the -- the raw data from the study as well as any aggregate data or analyses that are performed.

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And so the clinical group would be charged with reviewing those tables, figures, and listings and summarizing that in this kind of PowerPoint presentation for disclosure and discussion with management.

Q. And so it gets rolled up, then -- the initial set of data gets rolled up through a series of steps into this type of deck?

A. That's correct.

Q. What becomes of that broader underlying set of data?

A. The tables, figures, and listings become the basis for the clinical study report which is eventually provided to health authorities.

Q. And what, if anything, does senior management do with that broader set of data at Regeneron typically?

A. So I think I already mentioned that our senior management has always been heavily involved in the discussions and decisions. And certainly when we would review this kind of PowerPoint presentation with them, there would often be questions that would require we would pull up raw data. They certainly would have access to the tables, figures, and listings. And frequently they would ask for additional analyses, et cetera. So it was always a very lively discussion.

MR. GREGORY: Your Honor, permission to approach.

THE COURT: Granted.

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BY MR. GREGORY:

Q. Ms. Chu, I've just handed you a sizable document marked PTX 1170.

Do you recognize that?

A. So this appears to be tables, figures, and listings from the DA VINCI study, the 0706 study.

Q. Do you recall when a decision was made about the treatment arms to evaluate in Regeneron's eventual Phase III DME trial?

A. I don't recall the specific date that a decision was made.

Q. Do you recall the general time frame?

A. Yes, I do. It would have been the end of 2010 or early -- very early 2011.

Q. And in the meeting that we were just looking at where this deck -- the deck we were just looking at, do you remember exactly when that meeting occurred?

A. I believe it was the beginning of December.

Q. Do you remember who ultimately made the decision about the dosing regimens to be explored in the Phase III DME clinical trial?

A. So it was ultimately George's decision to move forward with the five initial monthly doses followed by q8.

Q. And George, that's George Yancopoulos?

A. Yes. Sorry. That's Dr. Yancopoulos.

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Q. Why do you remember that?

A. So part of the landscape in diabetic macular edema is that these are patients that are not only more susceptible to some of what we knew were the potential class effects of anti-VEGF from a safety perspective, but they were also patients that are at working age and have a high burden of healthcare in general.

So the pressure was really to minimize the number of doses. Especially in an investigational arm in a trial, we were really seeking to minimize the treatment burden for these patients. And members of the team disagreed with Dr. Yancopoulos' decision, but it -- ultimately it was his decision based on what he felt would optimize outcomes for patients.

Q. Did the Phase III trials at Regeneron ultimately conducted in DME, did those have names?

A. Yes. So they were called the VIVID and VISTA trials.

Q. And just for clarity, what treatment arms were explored in those trials?

A. So both studies included a 2-milligram monthly treatment group, a 2-milligram every-eight-week treatment group after five initial monthly doses, and the control group was laser photocoagulation.

Q. I want to talk very briefly about Regeneron's development efforts around diabetic retinopathy if that's okay.

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A. Sure.

Q. Can we take a look at PTX 3332.

Do you recognize this document?

A. Yes. So this is a section from our supplementary BLA, or biologics licensing application, for diabetic retinopathy in DME.

Q. And there's a reference on -- actually, why don't we go down to page 3 first. That's probably the easiest place to look.

Do you see there's this heading "Summary of the Requests for Breakthrough Therapy Designations"?

A. Yes, I see that.

Q. What's your understanding of what a breakthrough therapy designation is?

A. So a breakthrough therapy designation is a relatively new designation that the FDA allows for products that have shown -- that are indicated for a severe disease and have shown preliminary evidence of significant effect over standard of care or available treatments.

And it allows many aspects of what we call fast-track designation, which essentially facilitates more frequent and more informal interactions with the FDA during your development.

Q. What breakthrough therapy designation -- or what indication did Regeneron seek a breakthrough therapy

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designation at this time?

MS. MAZZOCHI: Again, Your Honor, objection. In her personal capacity, not on behalf of Regeneron.

THE COURT: Understood. But given her position and testimony she's offered, I do believe this witness would have personal knowledge about that. Overruled.

MR. GREGORY: Your Honor, I'll just -- we're coming up to the end here. I have three questions left, I think.

THE COURT: Understood.

BY MR. GREGORY:

Q. For what indication did Regeneron seek breakthrough therapy designation for aflibercept?

A. We were seeking a breakthrough therapy designation for diabetic retinopathy broadly.

Q. Can you turn to page 43 of this document.

And embedded within this document we just have this email here from Jennifer Woo.

Do you see that?

A. I do see that.

Q. And could you explain to us what's being discussed here.

MS. MAZZOCHI: Objection, Your Honor. Foundation. She's not on this email.

THE COURT: Sustained.

BY MR. GREGORY:

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Q. For clarity, Ms. Chu, let's look back to the first page of the document.

Could you explain what this document is broadly speaking.

A. Yes. So this is a section of the SBLA that would summarize our interactions with the FDA leading up to the filing.

Q. Did you review this document at the time?

A. Yes, I did.

Q. You're familiar with this document?

A. I am.

Q. The email that we were just talking about, that's not a standalone email; it's an email that's included within this section of the supplemental BLA, correct?

A. That's correct. So that was a communication between our regulatory group and the FDA that was included as part of this summary or interactions with the FDA.

MR. GREGORY: Your Honor, with your permission, I'd like to examine her about that.

THE COURT: You may proceed, Counsel.

BY MR. GREGORY:

Q. Ms. Chu, could you look at page 43 again.

A. Sure.

Q. Could you explain to us what's being discussed here.

A. So this is in regards to a teleconference that we had

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to the -- with the FDA on August 21st, 2014, to discuss our breakthrough application.

Q. And what did FDA do with your breakthrough therapy designation application for the treatment of DR, diabetic retinopathy?

A. They did not grant our breakthrough designation for DR.

Q. And what was your understanding at the time as to the rationale for that?

A. My understanding was that they did not consider the evidence we had provided of patients achieving a two-or-more-step improvement in diabetic retinopathy severity in the VIVID and VISTA trials, which enrolled patients with DME, as representative of the broader DR population.

Q. Did Regeneron ultimately pursue or forgo approval in DR alone?

A. Yes, we did. We subsequently conducted an additional Phase III trial called the PANORAMA trial in patients with diabetic retinopathy without DME.

Q. And what treatment regimens did Regeneron test in that trial?

A. In the PANORAMA trial we included 2 milligrams dosed every eight weeks after five initial monthly doses, 2 milligrams dosed every 16 weeks after three initial monthly doses and 1q8 interval, and the control group in that study was

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sham or observation.

Q. And so those are not exactly the same dosage regimens that you tested in the Phase III DME trials, right?

A. The group that received five initial monthly doses, then every-eight-week dosing, that was the same group as had been used in the VIVID and VISTA studies.

Q. Was there an additional arm, though?

A. Yes. So there was the additional treatment arm with the q16 dosing after the three initial monthly doses and 1q8 interval.

Q. What was your understanding of the basis for including that additional treatment arm?

A. The basis was that again -- so patients with DME have underlying diabetic retinopathy, but patients can have even severe diabetic retinopathy and not have DME, and those patients can have very good vision.

So again, the focus was really on minimizing the treatment burden as well as minimizing the risk, especially for the diabetic retinopathy patients that did not have immediate vision loss.

MR. GREGORY: Thank you, Ms. Chu. I have no further questions at this time, Your Honor. I may have some exhibits to move into evidence before the witness leaves the stand, but I'll wait till the end of cross-examination.

THE COURT: Understood.

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Counsel, you may proceed with cross.

MS. MAZZOCHI: Thank you, Your Honor.

May I proceed, Your Honor?

THE COURT: You may.

CROSS-EXAMINATION

BY MS. MAZZOCHI:

Q. Ms. Chu, I'm going to show you DTX 5385, exhibit page 1.

MS. MAZZOCHI: I'm sorry, Your Honor. May we do the ritual distribution of the binders?

THE COURT: Please.

BY MS. MAZZOCHI:

Q. Ms. Chu, I'm going to show you DTX 5385, exhibit page 1, which is titled the "JDC Update to the JSC Clinical Plan" dated January 26, 2011.

And you participated in that discussion, right?

A. I don't remember the specific meeting, but this is the type of meeting that I would participate in.

Q. Let's go to the second page of the exhibit.

You can confirm that the JSC did include Bayer employees, right?

A. Correct.

Q. And the JDC, which included Regeneron and Bayer employees, endorsed running Study B?

A. Yes, I see that here.

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Q. Let me take you to the seventh page of DTX 5385. This confirms that the choice of five loading doses for the DME indication was a compromise of the joint development committee, right?

A. Well, this indicates that it was a suggested compromise.

Q. And it says five loading doses was the suggested compromise for DME?

A. It does suggest that, but again, the caveat here is that the -- this included commercial and market access perspective as well.

Q. Okay. But whatever the case may be, five loading doses was the compromise position with the JDC, right?

A. It was suggested, yes.

Q. Okay. And it says in parenthesis after five loading doses, "equals one additional dose," right?

A. I see where it says that, yes.

Q. And your understanding that this five loading dose compromise from the JDC meant just adding in one additional dose at the 12-week mark, right?

A. So, again, the proposal that had been being discussed was the same as what we had utilized in the AMD Phase III trials, which was three initial monthly doses, so -- followed by every eight weeks. So this did represent, at least in the first year, an additional dose.

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Q. Right. And that additional dose was going to come at the 12-week mark, right?

A. Correct.

Q. And one of the reasons why this was viewed as an attractive compromise is because it would not have involved changing the primary end point, which would have required a substantial protocol amendment, true?

A. That's actually not true. So the primary end point in these studies was a discussion point from the very beginning because there were -- the EMA accepted a one-year primary end point in Phase III studies with diabetic macular edema while at this time the FDA required a two-year primary end point.

Q. Let's take a look at page 21 in the exhibit where it's talking about Study B and loading doses. If we look at the second dash under the heading "Operational aspects of a potential change of number of loading doses," can you read what it says, please.

A. So sorry. Do you just want me to read this?

Q. Yeah.

A. So the second main bullet is "Operational aspects of a potential change of number of loading doses," subbullet, "Protocol amendment required," subbullet, "Four or six loading doses would result in a shift of the primary end point visit to maintain the paradigm that efficacy should be determined four weeks after the last injection in the 2q8 arm (equals

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substantial protocol amendment)."

Q. So we can agree, then, that one of the benefits of the five loading doses as compared to four or six is that it would not require a shift of the primary end point visits to maintain the paradigm that efficacy should be determined four weeks after the last injection in the 2q8 arm, which would have been a substantial protocol amendment?

A. Well, these were design considerations, yes.

Q. Okay. Ms. Chu, let's take a look at PTX 3332, exhibit page 16, the breakthrough therapy application that Regeneron submitted to the FDA, dated July 14th, 2014, which you discussed on your direct examination. And I'd like to direct you to the last paragraph heading "Overall Summary of Study Results."

Do you have that on screen?

A. Sorry. What page is this on?

Q. Exhibit page 16. Well, it will say 12 of 30 on the bottom, but it's PTX exhibit page 16. It's on the screen in front of you as well.

A. Yes, I see that section.

Q. The data that Regeneron relied on as the basis for this application was the Phase III VIVID and VISTA studies, right?

A. Correct.

Q. But neither the clinical trial protocol for the

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Phase III VIVID or VISTA studies are set forth in the '572 or '601 patents that are at issue here, right?

A. I would have to look at the patents to be able to answer that sufficiently.

Q. Do you recall being asked at your deposition, "If you can take a look at the '601 patent, is the clinical trial protocol for the Phase III VIVID or VISTA studies set forth in any of the patent examples?"

You gave that same answer. And then after your review you said, "So in my review of Patent '601, I do not see a description of the VIVID or VISTA trials given as an example."

Does that help to refresh your recollection?

A. Okay.

Q. Let me call up DTX 19, exhibit page 2.

You're a named inventor on this patent, true?

A. Sorry. Give me a minute.

Yes, I am a named inventor on this patent.

Q. So this is U.S. Patent Number 10,973,879?

A. Is that a question?

Q. Yes.

A. Yes, 973,879.

Q. Dr. Yancopoulos is not listed as a named inventor on this patent, right?

A. No, he is not.

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Q. Let's go to DTX 19 at exhibit page 38, right-hand column 2, lines 48 to 67. We've got that on the screen in front of you.

A. Okay.

Q. Ms. Chu, can you confirm that in your patent, DTX 19, lines 48 to 49, you stated that "The present invention provides a method for treating diabetic retinopathy," right?

A. So our process at Regeneron is that we, as clinicians and scientists, provide information to our intellectual property attorneys for the purpose of patent applications and documents.

Q. Ms. Chu, I'm going to say my question again.

In your patent, DTX 19, lines 48 to 49, you stated, "The present invention provides a method for treating diabetic retinopathy," right?

A. That is what the patent states.

Q. Okay. And if we go down a few more lines to the description of the dosing regimen you consider to be part of the present invention, can you confirm that dosing regimen (ii) is listed as "3 or 4 or 5 monthly doses followed by one or more secondary doses every 8 weeks, wherein the secondary doses initiate 8 weeks after the final of the 3 or 4 or 5 monthly doses and continues with a dose given every 8 weeks thereafter"?

Do you see that?

A. I do see that.

Q. And that's something that your '879 patent, DTX 19, said was your invention, right?

A. That's correct.

Q. Okay. Let's go to the sixth exhibit page of DTX 19. Do you have a Figure 1 there?

A. Sorry. What page?

Q. The 19th -- I'm sorry. It's the sixth page of the exhibit, DTX 19.006, where Figure 1 appears.

A. Yes, I do see that figure.

Q. Does Figure 1 display a dosing regimen with what could be called three monthly doses followed by doses every eight weeks where the eight-week doses initiate after the final of the three monthly loading doses and continue with a dose given every eight weeks thereafter?

A. Sorry. Could you just restate your question.

Q. Sure. Looking at Figure 1, does that figure show a dosing regimen with three monthly doses, or what could be called three monthly doses, followed by doses every eight weeks where the eight-week doses initiate after the final of the three monthly loading doses and continue with a dose given every eight weeks thereafter?

A. Yes. So my understanding of this figure is that there's an initial dose given at baseline, followed by secondary doses at -- it appears to be four and eight weeks,

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followed by a tertiary doses, I think, every eight weeks apart.

Q. And if we were to put an arrow at the 12-week mark in your patent's Figure 1, that would be a dosing regimen that would correspond to what we could call five monthly loading doses followed by one or more doses every eight weeks, wherein the eight-week dosing is initiated after the final of the fifth monthly loading dose is given, right?

A. Yes. That would be a graphical representation of that dosing regimen.

Q. You, at your deposition, did not identify George Yancopoulos as the person who first came up with the idea of a five-loading-dose regimen for diabetic retinopathy that we see in Claim 18 of the '601 patent, right?

A. So as I mentioned previously, our process was that the team was charged with bringing proposals for discussion and decision-making by senior management; so I don't know who first came up with that idea.

Q. But Dr. Yancopoulos did not have any input into the particular methodology for the PANORAMA study, for example, right?

A. He definitely did have input into the methodology for the PANORAMA study.

Q. Let me bring -- let me have you take a look at DTX 7212, exhibit page 0024, your deposition testimony. And just to give you context, we'll start at line 17 of page 91 and

we'll go over to page 92, line 6.

Starting at line 25, referring to Dr. Yancopoulos --

A. Sorry. I don't have a page 92.

Q. No. It'll be transcript page 92. So it's exhibit page 24.

THE COURT: Ma'am, if you'll see, there's actually four pages on each page. The upper right-hand corner will be the second page number that counsel's referring to.

BY MS. MAZZOCHI:

Q. And we'll call it up on the screen for you as well.

The question was, referring to George Yancopoulos, "And did he have any input into what this particular methodology in the PANORAMA study was going to look like?"

And did you give the answer, "I don't recall the specific meeting, but we most certainly would have discussed it with him."

A. Yes. I think that's consistent also with our process that I just described.

Q. But the day-to-day involvement was really more with the clinical team, yourself and Dr. Vitti, right?

A. And Dr. Berliner, who is also on the patent.

Yes. I mean, as a clinical team, we're obviously responsible for providing proposals around future development and development strategies.

Q. You mentioned something about filing patent

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applications.

Was it your understanding that patent applications would be filed on all of the methods that were going to be tested by Regeneron in human Phase III clinical trials?

A. That was not my understanding. So, typically, we would have discussions with our intellectual property attorneys about the programs and planning and the decisions around what patent applications were to be filed or made by them.

Q. Again, let me pull up your deposition testimony, DTX 7212, page 34. Your testimony at lines 31:12 to 22.

Were you asked the question, "Was it Regeneron's custom and practice to file patent applications on all of the methods that it was going to test in human Phase III clinical trials?"

And did you give the answer, "It's my understanding that Regeneron always seeks to patent any novel inventive aspects of both our -- of any aspect of our development process."

Was that the question you asked and the answer you gave?

A. That's the answer that I gave, but I don't think that's inconsistent with the idea that there's a decision made about what aspects of our development program is inventive and possible to patent.

Q. But we can agree that Regeneron put a five monthly

loading dose regimen followed by every-eight-week dosing for diabetic retinopathy in both your '879 patent, saying it was your invention, as well as in the '601 patent's Claim 18 and 19, right?

A. I understand that regimen appears in both patents.

Q. Okay. Ms. Chu, during your time at Regeneron, did you also become aware of the Protocol T study that was conducted by the Diabetic Retinopathy Clinical Research Network?

A. Yes, I'm aware of that study.

Q. But that Protocol T regimen was not Regeneron's idea, was it?

A. Well, the Protocol T study was conducted by the DRCR, which is a collaborative group funded by the National Eye Institute, and Regeneron did have input into the study design and provided drug for the conduct of the study.

Q. Well, let's take a look at what I will designate as DTX 9002 and exhibit page 1.

Can you confirm this is an email forwarding Protocol T color handouts to Regeneron dated Saturday, March 31st, 2012?

A. So I can see this is an email dated March 31st, 2012, regarding Protocol T color handouts to Regeneron.

Q. Do you know based on -- given your capacity and your involvement in clinical trials, whether Regeneron had ever

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given any input into the Protocol T protocol prior to this date?

A. I'm not on this email, and I don't recall specifically what date we had input into the Protocol T protocol.

Q. Well, let's go to the eighth page of the exhibit. And there is a slide that's titled "Visit/Treatment Schedule Year 1, the 4:2:7 Guide."

Do you see that?

A. I see.

Q. Is this Protocol T regimen consistent with your recollection?

A. With the Protocol T study design?

Q. Yes.

A. Yes. So I understand this to be the Protocol T dosing regimens.

Q. And so here for aflibercept, they proposed a mandatory four loading doses every four weeks at the start of the regimen for Protocol T, right?

A. Yes. So this was a comparative study with three different anti-VEGF molecules, and all three dosing groups received four initial monthly injections.

Q. And then on weeks -- those monthly loading doses were to be given on weeks 0, 4, 8, and 12, right?

A. That was the proposed schedule, yes.

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Q. Then Protocol T allowed for two required injections if the patient hadn't reached success; but if they had, they could skip a dose at their next four-week visit, right?

A. That was the dosing regimen outlined in the protocol.

Q. And, likewise, in the weeks after that, when the patient showed up at their next four-week office visit, if they had not reached success, they were dosed; if they had reached success, they would skip and come back in four weeks, right?

A. Yes, that's correct. So they were essentially dosed as needed during that period of time, but the visits were still every four weeks.

Q. And that regimen would include an eight-week interval then, right?

A. Well, not necessarily. I mean, obviously, each individual patient was dosed based on the criteria outlined in the protocol.

Q. Right. But this regimen permitted an eight-week dosing regimen dosing interval, right?

A. Potentially. But, again, it wasn't specifically stated that that was the intent.

Q. But -- and, likewise, this Protocol T could permit for five monthly doses before any extended dosing interval, right? Just depended on the characteristics of the patient, to your understanding?

A. It could. But, again, it would be based on the

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individual patient status.

Q. And this Protocol T is the only dosing regimen you're aware of where aflibercept was tested head-to-head with ranibizumab and performed better, right?

A. Yes, that's correct.

Q. But this isn't the dosing regimen in the FDA-approved labeling for Eylea, is it?

A. No, it is not. It's not the approved regimen for ranibizumab either.

Q. Ms. Chu, let's put DTX 216 before you.

Can you confirm this is a March 21st, 2006, email from Jesse Cedarbaum to you and others?

A. Yes, I see that this is an email dated March 21st, 2006, from Jesse Cedarbaum and I'm one of the recipients.

Q. And according to the email, the attachment is the final version of the 0502 Part A abstract for the American Society of Retinal Specialists, ASRS, meeting in the fall, yes?

A. Actually, the email states that this is the 0508 Part A abstract for ASRS.

Q. Well, if you take a look at the attachments line, does it say 0502A ASRS attachments -- ASRS abstract?

A. Yes. The attachment was titled "0502A ASRS Abstract."

Q. If you take a look at the second page of DTX 216, does this confirm that you were an author on the abstract to

present the results of the Phase I study of intravitreous VEGF Trap in 2006?

A. Yes. So I was an author on this abstract of the Phase I study in neovascular AMD.

Q. Right. And based on this description here of this being the CLEAR-IT 1 study, this was the 0502 protocol, right?

A. Right.

Q. Not 0508?

A. Correct.

Q. And this CLEAR-IT 1 study is where Regeneron first dosed aflibercept in humans intravitreally, right?

A. Right. So this is summarizing the dose escalation portion of this study, which is where we dosed a small number of patients across a range of doses.

Q. And Dr. Yancopoulos is not listed as a coauthor on this study, is he?

A. He is not on this particular abstract, no.

Q. But you understand this study is found in Example 1 of the '572 and '601 patents?

A. Again, I'd have to review the patent to be sure.

Q. Well, maybe we can shortcut it. I'm happy to call up your deposition testimony, page 169, lines 14 to -- actually we'll do lines 13 to 17.

So this is exhibit page 43.

THE COURT: What page of the deposition again,

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Counsel?

MS. MAZZOCHI: It's deposition page 169.

THE COURT: Thank you.

BY MS. MAZZOCHI:

Q. And, Ms. Chu, did you confirm -- "So the study in Example 1 was referred to as the CLEAR-IT 1 study. The study in Example 2 was the CLEAR-IT 2 study."

Was that the testimony you gave?

A. Yes, but I had -- I was provided with the patents as an exhibit at that time. So I'd be happy to look at the patents now. Are they in my binder?

Q. Was that true testimony you gave at your prior deposition?

A. Again, if I had the patents in front of me, I'd be happy to take a look and confirm this.

Q. Well, let's go ahead and put up the '601 patent, PTX 1, exhibit page 14, the '601 patent at Column 8, lines 3 to 27, which corresponds to Example 1.

Do you have that there on the screen?

A. I see it on the screen. Just give me a minute to find it in the document.

Sorry. What page would it be on?

Q. Exhibit page 14.

A. Okay.

Q. So this is the CLEAR-IT 1 study, right?

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A. So Example 1 appears to be the CLEAR-IT 1 study, the Phase I study in neovascular AMD, yes.

Q. And looking at the dose listed here in Example 1, what was the volume injected into the eye in your 2005 CLEAR-IT 1 study? Was it 0.05 or 0.1 milliliters?

A. So at this time we were using 100 microliters or .1 milliliters.

Q. At least the 4-milligram dose concentrations that were administered in the study were formed at a 40 mg/mL concentration, correct?

A. In this study, yes.

Q. Regeneron put exactly what amounts it was dosing in its Phase I protocol documents, right?

A. Well, we certainly outlined the doses and dose volume intended.

Q. Okay. Let me take a look at what I've marked as DTX 9005.

Can you confirm that this is an April 5th, 2005, email to -- that you were cc'd on from Sri Vuthoori?

A. Sorry. Did you say DTX 9005?

Q. Yes.

A. I don't have that in my binder.

Q. You should. It should be right before PTX 1.

A. Okay. I see it now. Sorry.

Q. Can you confirm that this is an email to you and

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others dated April 5th, 2005, from Ms. Vuthoori?

A. Yes. So this is an email from Sri Vuthoori, dated April 5th, 2005, and I am a recipient of this email.

Q. If we look at the email attachment, can you confirm that this is Regeneron's April 5th, 2005, protocol for the intravitreal Phase I study, protocol VGFT OD 0502?

A. So this is what at the time we called a pass document, which was basically a synopsis intended to be the basis for the final protocol.

Q. But you're familiar with this document?

A. Yes. This is the type of document that we would have written, again, to lead into the writing of the final protocol.

Q. Let's go to the 23rd page of the exhibit that describes the clinical drug supply profile.

Do you have that on screen?

A. Yes, I see that.

Q. All right. And, again, this confirms that the 4-milligram doses were given at a concentration of 40 mg/mL in the CLEAR-IT 1 clinical trial that you published in your abstract in or about 2006?

A. Yes, in the 100 microliter volume.

Q. And Regeneron, according to this document, also proposed having a percent overage in the vials of 30 percent, right?

A. That appears to be in this document, yes.

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Q. And the total fill size was 1.2 milliliters with a max withdrawable volume of 1 milliliter, right?

A. That's what's specified in this document, but I'm not the manufacturing expert. So if you're asking me to confirm that that's what was actually in the trial, I would defer that to the expert.

Q. Well, this is what you were using to prepare the protocol, right?

A. These were assumptions that were being used to prepare the protocol, yes.

Q. Now, we've talked about the ASRS meeting in 2006, but Regeneron also presented your CLEAR-IT 1 study at the ARVO meeting in Ft. Lauderdale, right?

A. I don't recall, but that's typically one of the meetings where we would seek to present data.

Q. And were you a named author on the abstract that was presented at the 2006 ARVO meeting?

A. I don't recall specifically.

Q. Well, let's take a look at DTX 9003.

This is titled "Results of a Phase I, dose-escalation, safety, tolerability, and bioactivity study of intravitreous VEGF Trap in patients with neovascular age-related macular degeneration."

Do you have that?

A. Yes, I see that.

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Q. All right. And you're a named author on that one?
A. Yes, I am.
Q. And this is referring to the CLEAR-IT 1 study?
A. Yes, this would have been the CLEAR-IT 1 study.
Q. And that ARVO meeting where CLEAR-IT 1 was presented was held between April 30th and May 4, 2006, right?
A. I don't remember the exact dates, but that's the time of year where it's typically held.
Q. Okay. Well, just to tie it up because I don't want you to have to take my word for it, let me give you a document. It should be in your binder. And I apologize. I think it's the very last one that's entered in there. It's got the designation DTX 9006.

I'll go to exhibit page 12, citation Number 56.

And is that referring to your abstract results of the Phase I dose-escalation, safety, tolerability, and bioactivity study of intravitreous VEGF Trap in patients with neovascular age-related macular degeneration as something presented at the annual meeting of the -- of ARVO between April 30th to May 4th, Fort Lauderdale, 2006?
A. Yes. This appears to be a reference to that abstract.
Q. Now, Ms. Chu, you indicated that Regeneron was keeping some things secret, but I'd like you to -- when it came to its clinical trial work, but I'd like you to take a look at

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DTX 4957.

Do you see that this is Regeneron's Form 10-K for the prior year 2005?

A. I see that this is a Regeneron Form 10-K, yes.

Q. I'd like to direct your attention to this exhibit page 5 in DTX 4957 and specifically under the heading "VEGF Trap - Eye Diseases."

And we'll pull that up for you on the screen.

Do you see that?

A. Yes, I see that.

Q. All right. And do you see in the second paragraph it says, "In February 2006, Regeneron announced positive preliminary results from an ongoing Phase I dose-escalation study of VEGF Trap-Eye"?

That was your ASRS abstract, right?

A. So I actually don't know exactly which meeting this is referring to. February -- ASRS is typically held later in the summer. But it has moved around over the years; so it could be referring to the ASRS abstract.

Q. All right. Well, can we at least agree that your CLEAR-IT 1 0502 protocol Phase I test results we just looked at in DTX 9002, that Regeneron believed they had announced that -- those results at least as early as February 2006?

A. So in this 10-K it indicates that we announced positive preliminary results from the ongoing Phase I

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dose-escalation study, which I understand to be the CLEAR-IT 1 study.

Q. And you also -- it was also reported that VEGF Trap-Eye was delivered by intravitreal injection into the eye, right?

A. Yes.

Q. And Regeneron reported in its 10-K that the patients in your CLEAR-IT 1 study where you coauthored the abstract received a high dose of VEGF Trap-Eye of up to 4 milligrams?

A. Right. So the design of the study was to test across a range of doses, those -- some very low and some higher; but yes.

Q. And that 4-milligram formulation was dosed as a 40 mg/mL formulation?

A. So I don't see that as part of this document.

Q. Right. But you know that it was?

A. The concentration used to dose the 4-milligram dose in these studies was 40 mg/mL.

Q. And Regeneron described that dose as well tolerated in its SEC 10-K filing, right?

A. We did describe it as well tolerated in this small, early phase study.

Q. Right. And that was consistent with what you had seen in that study, right?

A. Yes.

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Q. And if we take a look at the 51st page of the exhibit, it indicates that this document had been signed off on by your CEO, Len Schleifer, right?

A. Yes. I see that it indicates that Len Schleifer had signed this document.

Q. Dated February 28th, 2006?

A. That's what it appears to be, yes.

MS. MAZZOCHI: Your Honor, I'm about to go into a different set of topics. Would this be a good time for our lunch break?

THE COURT: It probably is. Why don't we go -- let's take a half hour. Let's pick back up at 12:45.

Ms. Chu, ma'am, because you're midstream on your testimony, no one can talk with you about what you've said or anything else. So you'll see folks flee from you in the hallways. They're not being rude or discourteous; they're just following the rules. But I wanted to make sure you understand that.

They are permitted to feed you, however, and they are required to feed you. But, otherwise, they can't interact with you. But, ma'am, you can go ahead and step down, and we'll resume with your testimony at 12:45.

So we'll see everyone at that point.

(A recess was taken from 12:18 p.m. to 12:58 p.m.)

THE COURT: Ms. Mazzochi, you may resume.

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MS. MAZZOCHI: Thank you, Your Honor.

BY MS. MAZZOCHI:

Q. Ms. Chu, Mr. Gregory took you to PTX 188 on your direct examination, which was previously your deposition Exhibit 225, to talk about that meeting referenced -- supposedly referenced in the email from April 2nd.

If you slide down just a little bit on the exhibit, we'll put it in front of you, Item G, but let's keep all of Item 2 up on the screen.

Who decided to put the q8 interval on the table for this meeting?

A. I don't recall who specifically put the q8 interval on the table for the meeting.

Q. Mr. Gregory also asked you about DTX 227, where you indicated that some type of decision was made, but you don't actually recall this specific meeting, right?

A. I don't recall this specific meeting.

Q. And you don't recall who actually assembled that particular regimen with 2 milligrams q8 weeks with PIER lead-in, dosed monthly for first three months, as one of the arms to consider for the VIEW 1 Phase III clinical trial, right?

A. I don't recall who specifically proposed that first, but the final decision about the study design would have been made by George.

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Q. Ms. Chu, unequivocally, you don't recall specifically who proposed that dosing regimen, right?

A. I don't recall who first proposed it.

Q. Ms. Chu, are you aware that this document, DTX 227, was not identified as a document that Regeneron thought related to conception or reduction to practice for the '572 and '601 patent and Regeneron's discovery response?

THE COURT: Yes, Counsel?

MR. GREGORY: Objection, Your Honor. That's a misrepresentation of our discovery responses.

THE COURT: Overruled. You can address it on redirect.

Repeat your question, please, Counsel.

BY MS. MAZZOCHI:

Q. Ms. Chu, are you aware that this document, DTX 227, was not identified as a document relating to conception and reduction to practice for the '572 and '601 patent in Regeneron's discovery responses?

A. I'm not an attorney; so I don't think I can adequately answer your question.

Q. Do you know if you ever assisted in the preparation of those responses?

A. Sorry. Which responses are you referring to?

Q. Sure. I'll put it up on the screen for you, DTX 7001. And we've also got some hard copies, I believe, that

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we can pass out.

A. Sorry. Is this in your binder or --

Q. No. We're going to hand you a copy if we can.

MS. MAZZOCHI: Your Honor, may we approach?

THE COURT: You may.

MS. MAZZOCHI: Thank you.

THE COURT: They're fresh. They're still nice and warm.

BY MS. MAZZOCHI:

Q. Ms. Chu, do you see this is titled "Regeneron Pharmaceutical Inc.'s Objections and Responses to Defendants' First Set of Interrogatories (1 to 17)" as DTX 7001?

A. I see that this document has that title, yes.

Q. Okay. And if you can turn to page DTX 7001, exhibit pages 37 to 38.

A. Okay.

Q. Do you see there's a long list of documents there that have numbers that say RGN-EYLEA-MYLAN and then followed by a more specific number?

A. Yes, I see that beginning on page 37 and continuing on page 38.

Q. All right. Will you accept my representation that a document ending with the number -- with the Bates Number RGN-EYLEA-MYLAN-00631182 is not found on that list?

A. Unless the Court wants me to take the time to review

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this whole list, I'll accept your representation.

THE COURT: And I do not, ma'am. The Court will likewise accept that representation.

MS. MAZZOCHI: Thank you.

BY MS. MAZZOCHI:

Q. You describe this document, DTX 228, as the one where Dr. Yancopoulos conveyed to Bayer the optimal designs for the VIEW 1 and VIEW 2 trials, right?

A. I did not. I actually indicated that Dr. Yancopoulos would have spoken with Darlene Jody about the plans.

Q. Let's go to your deposition transcript. It's transcript page 287. I believe it's going to be DTX 7272. Here, we've got it up on the screen for you.

And were you asked about DTX 228, the April 4th, 2007, email from George Yancopoulos to Darlene Jody -- strike that. Let me start over.

Were you asked, "Sure. In your capacity as Regeneron's 30(b)(6) witness, what's the significance of this April 4th, 2007, email from George Yancopoulos to Darlene Jody?"

And did you give the answer, "So this email from George to Darlene Jody, who is a senior executive responsible for the Bayer collaboration with us, is communicating the Regeneron proposal and decisions around the optimal designs for the VIEW 1 and VIEW 2 trials"?

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Is that the testimony you gave?

A. Yes.

Q. Okay. And also at your deposition, this document, DTX 228, the April 4th, 2007, email from George Yancopoulos to Darlene Jody, that document was identified by your legal counsel to prepare you for your deposition, right?

A. I don't recall if this specific document was provided to me in preparation for my deposition.

Q. That's fine. I know some time has passed. So let's go back to your deposition transcript, then, DTX 7212. This is exhibit page 73.

And starting around line 13, were you shown this -- were you asked the question, "This is an email dated Wednesday, April 4th, 2007, from George Yancopoulos to Darlene Jody. Do you have that?"

"A Yes. So I have Exhibit 228 dated Wednesday, April 4th, 2007, with the subject 'Summary of Issues for Call, AMD P3 Planning' from George Yancopoulos to Darlene Jody.

"Q Now, earlier in the deposition today you referred to an email that you recalled seeing that you discussed with George Yancopoulos. Was this one of the emails?

"A Yes. This was the email I reviewed in preparation for this deposition."

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Was that the testimony you gave?

A. Yes. It appears to be my testimony.

Q. Ms. Chu, let's go to PTX 3167, exhibit page 1, that your counsel took you to. And according to the second-to-last sentence in the top paragraph, the sentence that starts out, "Unfortunately," do you see that on the screen?

A. Sorry. Can I just -- this is in the original binder, right, not in your binder?

Q. Yes. So PTX 3167, exhibit page 1.

A. Okay.

Q. And while you have DME scenarios the team had put together, you did note that, "Unfortunately, George, Len, and Neil are unavailable today, but we can send them the final recommendations after today's meeting."

Is that what's written in the email?

A. That's what's written in the email. It's also consistent with our process of having team discussions before presentation and discussion with senior management.

Q. But these ideas of using no more than three to six monthly doses, if there was any decision made as to choose one amongst them, that was not generated at that meeting attended by -- it would not have been -- if it was generated at that meeting, it was not one attended by Dr. Yancopoulos, right?

A. Again, it was the role of the team to prepare proposals for discussion and decision by senior management.

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But Dr. Yancopoulos was, according to this email, not in attendance at this meeting.

Q. Ms. Chu, I believe you also indicated on your direct examination that you believe George Yancopoulos was responsible for the five-loading-dose regimen. And I believe you pointed to PTX 1028 and PTX 1170, that big, thick exhibit, as support for that.

Do you recall that?

A. Yes.

Q. Do you also recall me asking you at your deposition if your theory that George Yancopoulos made the decision about the five loading doses was documented anywhere?

A. I don't recall that specific question.

Q. That's fine.

Let's pull up DTX 7212, exhibit page 21, which is your deposition transcript pages 80 to 81. And feel free to look at your prior answer just to get the context that we were talking about, five loading doses, but I'd like to focus on the question that starts at line 16.

Were you asked the question, "Right. Who decided that the dosing was going to be for the first five injections as opposed to three or four"?

"A My recollection is that George Yancopoulos made that decision.

"Q Is that documented anywhere?

"A I don't recall if there is specific documentation of that."

Was that the testimony you gave?

A. Yes.

MS. MAZZOCHI: Your Honor, there's several other places where I believe Ms. Chu testified inconsistently with her prior deposition; but because you heard that yesterday, to move things along, we'll save that for the posttrial findings if that's all right.

THE COURT: Understood.

MS. MAZZOCHI: Thank you very much, Your Honor.

With that, I'll pass the witness.

THE COURT: Redirect, Counsel?

MR. GREGORY: Briefly, Your Honor.

REDIRECT EXAMINATION

BY MR. GREGORY:

Q. Hello again, Ms. Chu.

A. Hi.

Q. Defense counsel showed you DTX 7001. I think it was a somewhat lengthy document. It's kind of collected together with a binder clip. Do you have that in front of you?

A. Yes, I do.

Q. And this is Regeneron Pharmaceutical Inc.'s objections and responses to defendants' first set of interrogatories.

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Do you see that?

A. Yes. This document has that title.

Q. Now, defense counsel showed you the response to Interrogatory Number 10 set forth on pages 37 and 38.

Do you recall that?

A. Yes.

Q. And do you recall her asking you whether a particular document was within the list of the approximately 50 documents identified on those pages?

A. I remember her asking me to agree with her assertion, and I agreed.

Q. Defense counsel did not show you the interrogatory itself, did she?

A. No.

Q. I want to direct your attention to page 36. And that Interrogatory Number 10 at the bottom of page says, "For each claim of each of the initial patents, identify (a) the date that the claimed subject matter was first conceived and the date it was reduced to practice, and the diligence leading to such reduction to practice, and for each such date and diligence, identify with particularity the documentary evidence supporting that date or diligence and at least three persons with any knowledge relating to that date and diligence."

Do you see that?

A. I see that.

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Q. I read that correctly?
A. Yes.
Q. You can set that aside.
Defense counsel asked you some questions about DTX 228.
Do you recall those questions?
A. Let me just find the exhibit first.
Okay. Yes, I have that.
Q. Was DTX 228 the only email you reviewed to prepare for your deposition in this case?
A. No, it was not. I reviewed several emails in preparation for my deposition.
MR. GREGORY: No further questions, Your Honor.
THE COURT: Recross?
MS. MAZZOCHI: Nope. It's all in the record, Your Honor. Thank you.
THE COURT: Ms. Chu, thank you so much. You can step down.
MR. GREGORY: Your Honor --
THE COURT: Oh, no, no. You may not step down.
MR. GREGORY: We have just a few exhibits I think we would move into evidence at this point.
THE COURT: Thank you, Counsel. I forgot about that. Go right ahead. Slowly, please.
MR. GREGORY: Of course. And I'll ask defense

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counsel as well to make sure that I'm not reading any that are already in evidence. I think I've done that filtration process myself.

We would move PTX 3131, PTX 3133, PTX 3332, PTX 0188, DTX 227, PTX 3150, PTX 3151, PTX 3167, and PTX 3168. We would move those into evidence.

I believe additional documents we discussed were DTX 8190, PTX 3188, and PTX 1028C, all of which I believe are already in evidence.

THE COURT: Any objection or disagreement with that?

MS. MAZZOCHI: I would like to object to PTX 3151. And the reason for that, Your Honor, is because this is the lengthy list of -- they're basically hearsay statements from a DME expert teleconference. So, again, I had no problem with Ms. Chu discussing something that was in her personal knowledge, but because, again, these are proffering supposed expert opinions, I don't want to see them later on as being proffered as this is what the experts thought or something along those lines.

THE COURT: What is the purpose of offering 3151?

MR. GREGORY: Yes, Your Honor. It's PTX 3151. It's not for the truth of the matter asserted; it's the Regeneron and Ms. Chu's state of mind.

THE COURT: Understood. Objection overruled.

Any other objections other than 3151?

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MS. MAZZOCHI: I believe that's the only one, Your Honor.

THE COURT: All right. Subject to that -- I'm sorry, Counsel.

MS. MAZZOCHI: You did not do --

MR. GREGORY: I don't believe I showed those to Ms. Chu.

MS. MAZZOCHI: Yes. Then we're good, Your Honor.

THE COURT: All right. Subject to that ruling on the objection of 3151, each of those identified by counsel are hereby admitted.

(PTX 3131, PTX 3133, PTX 3332, PTX 0188, DTX 227, PTX 3150, PTX 3151, PTX 3167, and PTX 3168 were admitted.)

THE COURT: Any from the defense?

MS. MAZZOCHI: Yes, Your Honor. We have DTX 19, DTX 216, DTX 4957, DTX 5385, DTX 9002, DTX 9005, DTX 9006, DTX 7001, and PTX 3332.

I'm sorry, Your Honor. Hang on.

I might be -- told I might have gotten one of the 9000 numbers wrong.

9006, which was the drugs of the future article.

THE COURT: Any others, Counsel?

MS. MAZZOCHI: Nope. That's it.

THE COURT: Any objection to any of those from plaintiff?

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MR. GREGORY: Your Honor, if you give me just a moment to consult with my cocounsel?

THE COURT: Certainly.

MR. GREGORY: No objection, Your Honor.

THE COURT: Without objection, each of those will be admitted.

(DTX 19, DTX 216, DTX 4957, DTX 5385, DTX 9002, DTX 9005, DTX 9006, DTX 7001, and PTX 3332 were admitted.)

THE COURT: Anything further we require of this witness, then?

MS. MAZZOCHI: Nothing from us, Your Honor.

MR. GREGORY: Nor from us, Your Honor. Thank you.

THE COURT: I now reextend my invitation to step down, ma'am. Thank you very much. You can leave whatever there. We will tidy up. Thank you.

MR. GREGORY: May I approach to remove the binders?

THE COURT: You may, yes. It's Ms. Chu's chance to escape.

Regeneron may call its next witness.

MR. TRASK: Your Honor, Regeneron calls Dr. Kenneth Graham.

THE COURT: Dr. Graham, sir, if you wouldn't mind making your way all the way to the front of the courtroom.

You're going to pause here with Madam Clerk so she can swear you in, then we'll ask you to take the witness stand

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over here to your left.

KENNETH S. GRAHAM, PhD, PLAINTIFF'S WITNESS, SWORN

THE COURT: Anticipating a request to approach and distribute, so granted.

MR. TRASK: Thank you, Your Honor.

MR. RAKOCZY: William Rakoczy from Mylan and Biocon. I'd like to get an objection on the record before this witness begins, if I may.

THE COURT: Why don't we distribute materials, and then when it's a little calmer and quieter, Mr. Rakoczy, the floor will be yours again.

Mr. Rakoczy, sir.

MR. RAKOCZY: Yes, Your Honor. We object to any testimony or proffered exhibits from this witness on invention date. This goes back to our motion in limine.

THE COURT: Good thing I waited for calm and still, Mr. Rakoczy.

MR. RAKOCZY: We object to any testimony or proffered exhibits from this witness on invention date. This goes back to our Motion in Limine Number 5, which I believe is in the compilation of documents at Docket Number 449. This also goes back to our interrogatories to Regeneron.

Interrogatory Number 10 asks for detailed information on the alleged conception and reduction to practice of the invention. We asked for Regeneron to identify with

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particularity all documents they would rely on and for knowledgeable witnesses. We received a three-line response to that. They cited no witnesses and cited one page of one document.

And for the record, the interrogatory is at DTX 900 at page 36, and the response is at DTX 900 and page 37. So this --

THE COURT: May I have a copy of that?

MR. RAKOCZY: Yes, Judge.

THE COURT: I don't believe I have that. If I do, I apologize.

Mr. Rakoczy, you said that was Interrogatory Number 10?

MR. RAKOCZY: Interrogatory Number 10, which is at the bottom of page 36, and the response on the '865 patent is in the middle of the page on DTX 900 at page 37, where it says "with respect to the '865 patent" and it begins, talks about the inventors conceived, and then it gives a Bates number RGN-EYLEA-MYLAN-00475679. There is no witness identified. There are no documents except, again, one page of one document.

Now, two nights ago, Your Honor --

THE COURT: What is that document, 475679?

MR. RAKOCZY: Your Honor, I believe that is DTX 3580, also PTX 2275. It is a several-page document.

The other night I received a list of exhibits that

they intended to go through with this witness which is -- I don't know -- a couple feet high, two large binders, a lot more than is cited in that interrogatory answer, and obviously, Dr. Graham is not named in that interrogatory answer at all.

And this is exactly what we had feared and why we filed Motion in Limine Number 5. So at the very least, Your Honor, I want to put that objection on the record and also would like to orally renew Motion in Limine Number 5 as well for the very same reasons.

THE COURT: Understood.

What is Dr. Graham purportedly going to tell us, Counsel?

MR. TRASK: Yes, Your Honor. So Dr. Graham is one of the inventors on the '865 patent, and he's here to describe, in large part, the work that he did leading to the inventions described in the '865 patent.

This is, obviously, information about which he has personal knowledge, experience himself.

THE COURT: He's been disclosed as a witness presumably, correct?

MR. TRASK: Absolutely, Your Honor.

The point Mr. Rakoczy made about the Interog 10 conception date, it's important to remember in context there were other interrogatories that were propounded by Mylan which -- to which Regeneron provided responsive information.

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Interrogatory 2 asked for documents regarding the development efforts that led to the present formulation of aflibercept. There's a range of documents disclosed in response to that interrogatory.

Interrogatory 7 asks for documents underlying the examples in the patent. There's a long list of documents disclosed at page 27 of this interrogatory response.

So these are all -- all of the documents about which Dr. Graham will be testifying today are documents that were disclosed to counsel for Mylan and Biocon from essentially day one of this case. They've been aware that Dr. Graham was an inventor of this patent from day one of this case. They took the deposition of Dr. Graham. They asked him about some of these documents. They didn't ask him about other of these documents. And it is routine in patent cases for inventors to testify on the stand about the work they did leading to their inventions.

THE COURT: Yes, Mr. Rakoczy.

MR. RAKOCZY: Your Honor, it is not routine to testify about an invention date when you didn't respond to the interrogatory on an invention date and you gave a three-line answer citing one document and not identifying that witness as someone who would testify about invention date. That is a problem, and again, it's not routine.

We had no reason to believe Dr. Graham would testify

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about the invention date or earlier invention date because his interrogatory doesn't identify him, and it certainly doesn't identify all the documents that they've disclosed.

MR. TRASK: If I may, Your Honor.

THE COURT: Go ahead.

MR. TRASK: With respect to the invention date question in particular, so the invention date, of course, is keyed off of defendants' invalidity case. They bear the burden of showing invalidity. And the prior art reference that they've been relying on principally is this Dix reference. That was filed in March -- on March 22, 2006.

And so responding to that case, we took the position in this interrogatory response that the invention was conceived no later than March 21, 2006. This is a responsive answer to their asserted prior art.

Now, the facts you'll see, if Dr. Graham testifies, are that work was done prior to that date, and he wants to describe the work that he did leading to the invention.

But the position we took here was directly responsive to the prior art that they've raised, and so Regeneron had no need to prove up a priority date any earlier than the prior art date on which Mylan and Biocon rely.

THE COURT: Understood.

Last word, Mr. Rakoczy. Go ahead.

MR. RAKOCZY: Your Honor, we could not have asked a

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clearer or more unambiguous interrogatory: Identify the date of conception and reduction to practice; identify with particularity the documents you will rely on; identify the witnesses with knowledge you will rely on. And they answered with none of that.

THE COURT: I agree. I'm going to hold the objection in abeyance at this point given the totality of the interrogatory responses, the fact that Dr. Graham's disclosed as a witness. Defendants obviously had an opportunity to depose him.

I do understand and appreciate the concerns, Mr. Rakoczy, you raised with respect to the response provided in Interrogatory Number 10 and the response thereto, but I'm going to hold it in abeyance at this point finding, at least at this point, there's not sufficient prejudice to preclude the doctor from testifying about it. But I would certainly expect and encourage that to be addressed in posttrial submissions at this point with the distinctive prospect the Court not accepting any of that testimony for the reasons you've articulated.

MR. RAKOCZY: Thank you, Judge. And would Your Honor prefer if I objected to each and every document?

THE COURT: As a matter of fact, I would not, sir. I'll -- the subject area is noted and, I think, defined by our conversation here, and we are certainly aware of it and mindful

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of it, addressing it in posttrial proceedings.

MR. RAKOCZY: Thank you, Judge. I just want to make sure the objection is preserved. And I'll just assume I have a continuing objection to all of these exhibits.

THE COURT: No, I understood. And I will certainly -- that certainly works for me.

MR. RAKOCZY: Thank you, Your Honor.

MR. TRASK: Thank you, Your Honor.

THE COURT: Thank you, Counsel. You may proceed.

MR. TRASK: Thank you.

May I proceed, Your Honor?

THE COURT: You may.

MR. TRASK: Thank you.

DIRECT EXAMINATION

BY MR. TRASK:

Q. Dr. Graham, how are you?

A. I'm all right. How are you doing?

Q. Fine. Thank you.

Would you please introduce yourself to the Court.

A. My name is Kenneth Graham. Right now I live in Pleasant Valley, New York. I've been an employee of Regeneron Pharmaceuticals for 22 years and some months at this point in time.

Q. What is your role at Regeneron, Dr. Graham?

A. So now I am a senior director in charge of one of the

teams in formulation development; so we manage a suite of products.

Q. And where are you from originally?

A. Well, I was born smack dab in the middle of Pennsylvania in a little town called Bellefonte.

Q. Where did you do your undergraduate degree?

A. Actually, right down the road at Penn State University, State College, Pennsylvania.

Q. What was your major?

A. Animal bioscience.

Q. And why did you study animal bioscience?

A. Well, my family has a farm in Schuylkill County. So I grew up with animals and kind of was looking to be a large animal veterinarian, and I read the James Herriot books and was thinking I want to be a veterinarian and go that route.

Q. Did you continue there for a master's degree?

A. I did.

Q. What was your focus?

A. So my focus was actually -- the master's degree was in veterinary science. What I was studying was a number of diseases related to selenium and vitamin D. There's a disease in sheep called white muscle disease, and when lambs are deficient in selenium, they basically lose their ability to walk, become paralyzed.

Q. After getting your master's degree at Penn State, did

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you go on to do a PhD?

A. I did.

Q. Where was that?

A. That's at the California Institute of Technology, Caltech.

Q. What was your PhD thesis in?

A. So I was studying the way in which a specific class of proteins bind DNA. So my thesis had a couple of parts. One was what aspects of the protein molecule determine which sequence in the DNA will bind. Another aspect was developing what I refer to as a synthetic enzyme. So I was able to take a part of a human serum al binding -- human serum albumin copper binding domain and attach it to this protein that binds the DNA, gamma-delta resolve. It's the binding agent from that. And then in the presence of nickel and an oxidizing agent, site specifically cut the DNA in much the same way a restriction enzyme does. And I also characterized that reaction doing some kinetic isotope effects studies as well.

Q. And did you graduate with your PhD?

A. I did.

Q. And what did you do after you graduated?

A. So immediately after I graduated from my doctoral degree, I went to work at a place called the Beckman Research Institute - City of Hope. It's a private cancer institute that was in Duarte, California, that has a research institute that's

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endowed by Beckman Institute. It's an arm of Beckman.

Q. How long did you remain at the Beckman Research Institute?

A. About ten years.

Q. Where did you go after that?

A. After that I joined Regeneron.

Q. What was your first role at Regeneron, Dr. Graham?

A. So I was hired in to manage or supervise the bioanalytical testing lab that was part of our pilot manufacturing facility in Tarrytown, New York.

Q. And what was the first product you worked on at Regeneron?

A. So the first product I worked on was something we referred to as IL-1 Trap. It's now marketed as a compound called Arcalyst.

Q. And what is that product used for?

A. So Arcalyst is a IL-1 inhibitor. It is used to treat a disease called FCAS. It is basically an ultra-orphan or orphan indication. There's maybe a thousand people in the world that have this disease. And it works out to be an allergy to the cold.

So people that have this disease, if they would walk into an air-conditioned room like this courthouse, mild form, they break out in hives; more severe, they break out in hives, have joint pain; most severe, you know, they start having their

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hands and knees get twisted like you do with rheumatoid arthritis. Quite a horrible, actually, disease.

I actually met a woman -- I don't know whether I can call it fortunate or not, but my wife and I were waiting to go see a movie, and we were talking and she made some comment about Regeneron. And the woman a couple people behind us said, "Oh, you work for Regeneron." And I said yes. And she proceeded to tell me her story.

And she had the disease, both her kids had the disease. And the way she described it, she said, "Prior to your drug, I didn't have a life." Literally, that was her quote. And, basically, she couldn't go out in the summer and go into a theater or anyplace, had problems going outside in the winter just because of the response to the cold.

Q. When did you first work on aflibercept, what is now known as the active ingredient in Eylea?

A. So at the end of my first year at Regeneron in 2002, the pilot manufacturing facility changed over from IL-1 track, and we set up to work on our new molecule which we were calling VEGF Trap at the time.

Q. And what was your contribution at that time to the aflibercept project?

A. So in the bioanalytical lab we do in-process testing of the product as it goes through the purification steps. We also monitor some aspects of the product during bioreactor

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production.

So I set up methods that would be able to follow the product through the purification strain and to ensure the ultimate material that we got out of the bioreactor was of suitable quality.

Q. And can you explain, Dr. Graham, how the aflibercept material that you worked on was being purified within your facility was first made?

A. Well -- so when you make a protein with CHO cells, Chinese hamster ovary cells, in some ways -- this is going to sound a little weird -- but it's like brewing beer. So you have a big stainless steel vat. You put a bunch of things in that the protein or the yeast -- or the cells or the yeast need to grow.

You grow it up for a period of time. And when it's ready, you take the material out of the vat. And in the case of the aflibercept molecules, the cells are expressing the protein into the solution. And you have a solution of aflibercept, just like you have beer with a bunch of cells floating in it like a cloudy IPA.

Then you take this through a series of purification steps, and you remove the cell debris. You remove all the unwanted stuff. And you end up with something that's a clear solution and probably looks like more Coors Light.

THE COURT: Finally, something I understand. Thank

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you, Doctor.

MR. TRASK: Happy hour.

BY MR. TRASK:

Q. So just to be clear, the aflibercept that you were saying is made by these cells, is it in solution from the very beginning?

A. Yes.

Q. Okay. When you were doing this work on the purification of aflibercept, were you in the formulation development group at the time?

A. No. I was in pilot manufacturing.

Q. Did you join the formulation development group at some point after that?

A. I did. In 2005 Regeneron was having some financial problems. We started off by eliminating redundant functions, one of which was the pilot manufacturing facility. And ultimately they laid off more people beyond that. But I was fortunate enough to be able to transfer into preclinical development and formulation development at that time.

Q. And after joining the formulation development group, when did you start working on formulations of aflibercept?

A. Probably within the first two, three months, tops.

Q. And what was your first project on aflibercept when joining the formulation and development group at Regeneron?

A. So we had a formulation that was being tested for

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ophthalmic purposes. And that formulation in our formal stability group, which is where our QC group monitors the GNP product that is used for people, they started seeing particles in the formulation.

And this is kind of a very serious thing. So I was tasked with what -- why are we seeing these particles? What's going on here? You know, this became an all-hands-on effort, and everybody in the group focused in on this.

Q. Who were you reporting to at the time in the formulation development group?

A. Dan Dix.

Q. And who did Dan report to?

A. Eric Furfine.

Q. Okay. And did you also work with someone named Kelly Frye?

A. Yes. She was one of my colleagues.

Q. Are those the four people, including yourself, who are named as inventors on the '865 patent?

A. They are.

Q. When you joined the formulation development group, did you become aware of work that was previously done as part of that group on formulating aflibercept?

A. So when I joined the group, there were several years of research that had been conducted prior to arriving there. I wanted to -- wanted to -- needed to go back, look at what was

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done so I could understand the types of things that had been tested, what the results were. So I went through and reviewed the previous stability studies and things that we had conducted and in formulation development.

Q. Were all of the prior aflibercept formulations intravitreal formulations?

A. No.

Q. What were some of the others used for?

A. So aflibercept was originally developed to treat cancer. So it was -- the idea was it would stop tumors from growing. So we had looked at IV, maybe some subcu routes, but the predominant work was focused on IV.

Q. And when you were tasked with developing an intravitreal formulation of aflibercept, did you consider using the prior formulation for cancer for that purpose?

A. No. So the cancer formulation was designed to be a concentrate that you would put into an IV bag, dilute out, and give to a patient through an IV. So it had a really high osmolality, like 1100, 1160 milliosmoles. It had a lot of sucrose in it, 20 percent sucrose. And there was concerns that sucrose can be toxic to the eye. Different buffer system.

Q. Now, when was it that you first attempted to develop an improved intravitreal formulation of aflibercept?

A. Well, the improved version came after our first version started to fail. And this was -- I'm sorry. I was

going to say oh, crap, you know, now what do we do? because everything is falling apart.

And it was pretty much, all right, we have to have this trial -- these clinical trials to keep running. We have to be able to dose the patients. What do we do?

So we started looking at the cause of what was happening with the first formulation. We figured out -- or I figured out that exposure to the shear stress going through the tiny needle that's used for intravitreal injections was likely causing the particles to form. And we began working on that, really, mid of 2005, May time frame, I would say.

Q. Now, when you set out to develop an improved intravitreal formulation of aflibercept, did you have any objectives in mind relating to the stability of the formulation?

A. So we wanted to ensure that the product had a minimum two-year shelf life. We were looking to make the most stable product possible; so we were concerned about having very pure aflibercept to start with. That was a focus in the pilot manufacturing, and then we wanted to sustain that.

Q. Did you have any objectives in mind regarding the concentration of aflibercept in the intravitreal formulation?

A. So the desire was to have a -- I'm going to use the words "high-concentration formulation." And we tested a range of concentrations, but we didn't have a specific one in mind at

that point.

Q. Were the objectives of having a formulation that was -- had high stability and a high concentration, were those compatible or in contention with one another?

A. Well, to put it simply, they're like opposites. So if you have a lower concentration formulation, they tend to be more stable. As you make the concentration higher, the stability goes down. And this is because, at least with aflibercept, the primary degradation pathway is molecules coming together.

So it's just -- the more concentrated, the more molecules, the greater the chance that they'll come together and aggregate. You know, if you want to put it in an equation, it goes up as the square of the concentration. So, you know, you double the concentration, you go from 10 to 20, it's the difference between a rate of 100 and a rate of 400 if I can still do math.

Q. Why was it that you were aiming to develop a formulation with a high concentration of aflibercept?

A. So this is for an injection into the eye. Based on my experience when my mother was treated for AMD, an injection into the eye is really traumatic. You know, even if you go once a month, it takes a couple days out of the person's life. There's a lot of risk associated with it. A lot of bad things can happen. And we wanted to be able to have as long an

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efficacious range as possible.

Q. Now, if the goal was to get more drug into the patient's eye, why couldn't we just use a lower concentration formulation and inject more of it?

A. Well, the eye is a closed thing. It's kind of like -- I don't know -- a ping-pong ball. You just have that much volume in there. And when you go to inject it, you run the risk of increasing the pressure. So you can't put a lot of volume in it.

Based on what I understand to be the limits, you know, you certainly don't want to inject more than 100 microliters. You know, 50 microliters is considered to be an optimal injection.

MR. RAKOCZY: Objection, Your Honor. This witness has not been qualified as an expert in ophthalmology or intravitreal injections.

THE COURT: Understood. Sustained.

But you can continue. I recognize it's background information.

MR. TRASK: Thank you, Your Honor.

BY MR. TRASK:

Q. So about -- can you just give the Court a sense for how much is the volume that we're talking about here in these formulations that would be injected.

A. So I don't know if you've ever played with the

old-school glass eyedroppers in, like, elementary school or high school chemistry. It's like one or two drops from one of them.

Q. And did the fact that the formulation you were developing would be injected intravitreally pose any challenges to you from a formulation standpoint?

A. Okay. Yes. It did.

Q. What was that?

A. So we knew we had limited volume. We knew that it was going to have to go through a very small needle. You know, the small needle causes what's called shear stress or shear on the drug. And that can be destabilizing to the drug. It can cause the drug to, in the case of aflibercept, precipitate.

Q. What was the gauge of the needle that you understood these formulations would be injected through?

A. 30-gauge.

Q. Did you bring demonstratives with you today to illustrate these needles?

A. Yeah. We have a couple examples.

MR. TRASK: May I approach with those, Your Honor?

THE COURT: You may.

MR. TRASK: I'm going to hand up what has been marked for identification as PDX 7.001. This is the 30-gauge needle. And PDX 7.002, this is the 22-gauge needle. I'm going to be very careful with these.

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THE COURT: I was going to say marshal services isn't in here. Usually you don't get this close with a sharp object.

THE WITNESS: Well, it would take a lot of effort for me to do any appreciable damage.

THE COURT: I'm pretty soft. I'd probably crumble pretty quick.

THE WITNESS: I don't know. You don't look that soft to me.

BY MR. TRASK:

Q. Dr. Graham, where did these demonstratives come from?

A. Actually, they came out of my lab.

Q. And can you explain to the Court what these are.

A. All right. So I grabbed the one that was labeled 02 out of the baggie. So this is a 22-gauge needle. So this is the typical needle that is used -- or a typical gauge that this is used to do an IV infusion is 22.

The other one -- I probably should have pulled both of these out first so I don't stab anybody -- is a 30-gauge. And the 30-gauge is what's typically used to inject somebody in the eye. I don't know if you want to take a look at these.

THE COURT: I might as well.

MR. TRASK: For the record, there's nothing but water in those needles, Your Honor.

THE WITNESS: Please don't stick yourself.

THE COURT: I promise I will not.

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All right. Thank you so much, Doctor. I'm going to hand those back to you. Thank you, sir.

BY MR. TRASK:

Q. I'll let you put the caps back on those so we don't have any inadvertent accidents.

A. That would be a good thing.

Q. And why was the size of the needle through which the formulation would be injected relevant to your work as a formulator, Dr. Graham?

A. All right. So I think I said that you encounter something called shear when you go through the needle. What shear is, it's basically like you run down a three-lane highway and you slam into one lane. So everything kind of comes together and bounces up on the walls as well. So the narrower the needle gauge, the greater the amount of shear.

Q. Let's take a look at PTX 3327.

What is this document, Dr. Graham?

A. This is a presentation that I prepared some years ago.

Q. Okay. And this document itself isn't dated. But if we can take a quick look at PTX 3326, what is this document?

A. It's an email that I sent to Eric Furfine back in April of 2006.

Q. And what is the first attachment indicated on this email that you sent?

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A. KSG PCD talk, March of 2006.

Q. Okay. And which presentation is that?

A. The previous document you had up on the screen.

Q. Let's then turn back to 3327.

You said you yourself prepared this slide deck as part of your work on --

A. Yes.

Q. -- Eylea -- rather, aflibercept intravitreal injections?

A. I did.

Q. Let's look at page 44 of this document.

Did you prepare this slide, Dr. Graham?

A. I did.

Q. What does this slide show?

A. So what I did is I went back and did some calculations to estimate the shear rate that the formulation would experience when it went through different needle sizes.

Q. And if we look at the row labeled "One Second" under "Time to Inject," what did the data show that you calculated for a 22-gauge needle and a 30-gauge needle?

A. So for the 22-gauge needle, you've got about 16,000 reciprocal centimeters' worth of shear -- or not reciprocal centimeters, reciprocal seconds. So shear is like a frequency. It's seconds to the minus 1.

And then when you narrowed that needle gauge -- so

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you went down to the 30-gauge -- if you're going at the same rate, that number jumps up to 370,000, about 20, 22 times more.

Q. So when comparing the amount of shear experienced by a formulation through a 22-gauge needle versus the amount of shear experienced when passing through a 30-gauge needle, about how much higher is the shear with the 30-gauge needle used for intravitreal injection?

A. Massively. I think I said 22 times, but it's a huge difference.

Q. And how does that compare to the shear that's experienced by the formulation during normal manufacturing processes?

A. So one of the most shear-intensive or stressful parts of the manufacturing process is when you take the formulation through a diafiltration step. At that point you're pushing the formulation up against a membrane with a great deal of force. And that's only about 3,000 reciprocal seconds.

Q. So if a formulation is being manufactured and then administered through a 30-gauge needle, what's the point in time at which the formulation experiences the highest shear rate?

A. Going through the 30-gauge needle.

Q. Now, can changes to the formulation lead to higher shear stress?

A. Yes, they can.

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Q. How so?

A. So as the formulation protein concentration goes up, the solutions become a little bit more viscous and you increase the viscosity. That will increase the shear stress.

Q. What is viscosity, Dr. Graham?

A. All right. So this is -- the definition is the resistance of a solution to flow. What that means --

THE COURT: To what, Doctor? I'm sorry.

THE WITNESS: To flow.

So what it means is if you take, like, a bottle of water, you go to pour it. Water is 1 centipoise. It starts immediately. You stop; it stops immediately. Take honey, go to pour it, it takes a little while for the honey to start going. Go to stop it, it takes a little while for the honey to stop. Low viscosity/high viscosity.

BY MR. TRASK:

Q. Why is shear an issue when it comes to the handling of formulations?

A. In the case of aflibercept, work that I did identified that shear stress or shear caused the formulation to form particles.

Q. And what's the process by which particles are formed?

A. So this is one of those things that it's kind of like a spectrum of what you deal with. You have the individual molecules in solution. You know, sometimes a couple slam

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together. Sometimes a couple more slam together. When you get to the point you get enough of them stuck together, it falls out of solution and you get a visible particle.

Q. Is this related to the concept of aggregation?

A. It is.

Q. And so what happens when proteins aggregate?

A. So if I'm talking about aflibercept, aflibercept exists as what we call a native dimer. It's two of the same protein strands that are hooked together. So if you take two of those native dimers and they come together, that starts to form aggregates or high molecular weight species.

Usually what happens first is you'll get to maybe four or eight of these things come together. They stay in solution. And then if it gets bigger, you know, you'll start getting some of these things that show up as turbidity. So if you look at smoke, smoke is particles. Do you see individual smoke particles? No. You see the mass of them, but you can't see one. So turbidity is the whole bunch of these little things that are coming out now that you can't see individually but you see as a group.

And then the next step -- or the next step can be these things come together. And then it falls out of solution and becomes something that you can see by your naked eye.

Q. From your perspective as a formulator, was the formation of particles in an intravitreal formulation a bad

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thing?

A. It was an exceptionally bad thing. It's bad in any formulation; but for the eye, it's very bad.

Q. Can you explain why that is.

A. So I think the eye being a closed system, whatever you put in tends to stay in. You know, one aspect is there's a drain in the back of the eye called the trabecular network. And these particles have a chance to, if they move into that area, plug the drain.

What happens when you plug the drain in the back of the eye is you raise the pressure. And this is what happens in glaucoma. So you can cause blindness.

MR. RAKOCZY: Objection, Your Honor. Again, the witness has not been qualified as an expert in this area.

THE COURT: Understood. Sustained. The Court will disregard that testimony.

Next question, Counsel.

BY MR. TRASK:

Q. I think you touched on this a moment ago, but was the possibility of particle formation in an aflibercept formulation just a theoretical concern to you?

A. No.

Q. Why not?

A. So we had gotten -- I don't know -- a year, year and a half in to a clinical trial. And all of a sudden our

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clinical supplies were falling out of solution, forming particles.

Q. If particles are forming in a formulation, what does that mean about the formulation's stability?

A. That's bad.

Q. Now, you mentioned that there was a prior oncology formulation for cancer.

A. Yes.

Q. What was the concentration in that formulation?

A. It was 25 mg/mL.

Q. Okay. So if Regeneron had already developed a stable 25 mg/mL aflibercept formulation, weren't you sure that you could make a stable 40 mg/mL formulation as well?

A. No.

Q. Why not?

A. So increasing concentration leads to decreasing stability. The challenges with aggregation or particle formation, however you want to describe it, go up as the square of the concentration.

Q. And when you set out to develop a 40 mg/mL aflibercept formulation for intravitreal use, were you reasonably sure that you could achieve such a formulation with acceptable chemical and physical stability?

A. Certainly not when I'm sitting there staring at vials of IVT1 with particles in it.

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Q. I'd like to now switch gears just a bit to some of the analytical techniques that you used in your laboratory to assess the stability of the formulations you were working on.

So first if we could take a look at the '865 patent. This is PTX 2.

Is this your '865 patent, Dr. Graham?

A. Yes, it is.

Q. And you're the Kenneth Graham named on the face of it?

A. I am.

Q. Let's look at Table 3 of this patent. What's shown in Table 3?

A. So this is data from a stability study. The study is VGFT-SS207.

Q. Okay. And I'd like to ask you about the headings of the different rows here. Are these -- do these reflect different analytical data on the formulation?

A. They do.

Q. Let's cover each of these just briefly. What is the visual appearance analysis that was done here?

A. So visual appearance is simply how does the formulation look in its container. You're looking to see if you've got particles in it. Has it discolored? You know, what does it look like?

Q. You mentioned turbidity a moment ago. Can you just

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briefly remind us about turbidity analysis.

A. All right. So turbidity, we use a machine to measure that. And what we do is we look for a decrease in the amount of light that goes through the sample. As the amount of light drops, the signal goes up. You'll see we're at 00 here. This is a -- not an absolute measure; this is corrected for the first time we make the formulation. So we make it, we test it immediately. And then after time we look at it again and see if it's changing. So we subtract that zero value from the value at the month where we measure it again.

Q. What is the pH analysis reported here?

A. It tells you the alkalinity or acidity of the formulation. We look for no change.

Q. And the last two columns, percent VEGF Trap recovered and percent VEGF Trap native configuration, what analytical technique is used for those measurements?

A. Size-exclusion chromatography.

Q. Okay. And what does size-exclusion chromatography measure?

A. So it's a sieving method, basically. So you have a column. And it separates things -- the material in the column separates things based on their size. Big stuff comes out first, intermediate stuff kind of hangs around for a while, and the small stuff comes out last.

Q. Now, over the course of your career at Regeneron,

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roughly how many size-exclusion chromatography analyses have you run on aflibercept?

A. I don't know. 100,000. Tens of thousands. More than I can count.

Q. And what does SEC tell you -- if I use SEC to refer to size-exclusion chromatography, you'll understand that?

A. Yes.

Q. What does that technique tell you?

A. So SEC gives you an indication of the molecule in its native state. So it tells you what percentage of the molecules in that solution are hanging out as they're individuals. It also tells you when the molecules start coming together and have -- and form the soluble aggregates that I described earlier.

Q. And now beyond the ones that we've just discussed here from the example in the patent, did Regeneron use other techniques for analyzing the formation of insoluble particulates in formulations?

A. Yes, we did.

Q. Why did you need so many different analytical techniques to understand aggregation and particle formation in formulations?

A. Well, first off, they cover a range of sizes. So you have techniques that are dialed in for each size of particle.

Secondly, the formation of particles in a formulation

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is very bad. You know, we talk about the stability of the formulation. The problem is with these particles or aggregates, it can cause the drug to become either inactive or worse. In some cases it can lead to, you know, autoimmune responses or immune responses to the drug.

MR. RAKOCZY: Objection, Your Honor. Again, he's not qualified as an expert in that area.

THE COURT: Understood. Sustained. I'll disregard that last portion of the testimony.

BY MR. TRASK:

Q. Let me just ask, Doctor, in the course of your duties at Regeneron, do you meet with ophthalmologists to understand their concerns regarding aflibercept formulations?

A. Yes, I have.

Q. And do you take into account the information you learn from ophthalmologists in designing the formulations that you've done as part of your invention and on other molecules as well?

A. Yes, absolutely.

Q. Do you analyze particle formation using a technique called HIAC, H-I-A-C?

A. We did, yes.

Q. Let's return to Exhibit 3327. And I'd like to look at page 34 of this document now.

What is this page of the presentation, Doctor?

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A. So this is a -- kind of a section divider. So I was talking about one topic and then I switched over to talk about HIAC.

Q. Okay. And did you prepare this section of the presentation as well?

A. Yes, I did.

Q. At the time you prepared these slides, who was the in-house specialist in Regeneron's formulation development group on the HIAC analysis?

A. That would be me.

Q. And did you actually perform the HIAC analysis in this section of the slide deck?

A. Yes.

Q. Let's take a look at page 46 of the same exhibit, 3327. What's shown on this slide, Doctor?

A. So this is a summary table taking account the impact of needle shear on a number of different protein formulations and --

Q. And what -- I'm sorry.

A. Go ahead.

Q. What's shown -- the first row of the table is highlighted in blue. What does that show?

A. So the one that's highlighted in blue is the clinical oncology formulation that we had at the time. You'll note there's a note on the backside of it that says 22-gauge needle.

So what we did is we took the oncology formulation, pushed it through the 22-gauge needle four times, and looked to see how many particles we had when we began and after we did it. And we showed that there were really no difference. You know, it only went up a small amount.

Q. And what about the fourth line down that's highlighted in red? What does that convey?

A. So the IVT1 formulation that we were looking at that was forming particles, this is that formulation four times through a 30-gauge needle. So in that case we got about a tenfold increase in particles.

Q. And what about all of the rows below the fourth row labeled "Formulations" numbered 2 through Number 9. What is the information conveyed there?

A. So those are a series of different formulations that we made seeking to come up with an improved ITV formulation. What that data shows is our improved versions were all better than the original. Some of them are better than each other. But said that yes, we had demonstrated something that works better.

Q. And let's turn to page 60 of this slide deck.

Are these some of the conclusions you drew from the data we just looked at?

A. Yes.

Q. Can you explain what's conveyed in the first bullet

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point.

A. Well, the first one's pretty straightforward. The small 30-gauge needle caused more shear than the bigger needle and more particles.

Q. What about the third bullet point highlighted on the screen?

A. So what that is is we had the improved IVT formulations, those 9s that you were talking about. And basically it showed that, compared to our original formulation, we were at least three times better with the worst ones that we were dealing with.

Q. And the fourth bullet point?

A. So it said that when we added polysorbate, we had more resistance than when we added PEG.

Q. Okay.

We can take that down, please.

I'd now like to look at your '865 patent, again, PTX 2.

Can we look at the provisional application date on the face of the patent.

Doctor, what was the filing date of the provisional application for your '865 patent?

A. June 16th, 2006.

Q. And were you involved in the preparation of that provisional application?

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A. Yes, I was.

Q. What was your involvement?

A. So I supplied data and data tables to the attorney who drafted the document.

Q. Were those the same data tables that appear in the '865 patent itself?

A. The data is the same that appears in the patent, yes.

Q. And did you also review the provisional application before it was filed on June 16th, 2006?

A. Yes, I did.

Q. And you're familiar with the contents of that provisional application?

A. Yes, I am.

Q. All right. I'd like to ask you about some of the internal work you did at Regeneron leading and relating to your invention.

So first let's take a look at PTX 2293.

What is this document, Dr. Graham?

A. It's one of Regeneron's laboratory notebooks. It looks like it belonged to Kelly Frye.

Q. And remind us. Who's Kelly Frye?

A. So she was one you of my colleagues. She worked in the lab alongside of me.

Q. Does she have a PhD as well?

A. She does.

Q. And she's your coinventor on the '865 patent?
A. Yes, she is.
Q. Did you review this lab notebook, PTX 2293, as part of your role in Regeneron's formulation development group?
A. Yes, I did.
Q. You're familiar with its contents?
A. Yes.
Q. Let's turn to page 58 of this document. What's shown on this page of the laboratory notebook?
A. So this is a protocol for a stability study. This is Protocol Number 195.
Q. What is a stability study, Dr. Graham?
A. So a stability study is a collection of tests and formulations or formulations containers and tests that we assemble and conduct to look at the stability of a formulation. The protocol's kind of like a contract in that it tells you what you're going to test, what tests you're going to do, and when you're going to do them.
Q. And what other types of documentation would be associated with a stability study?
A. So typically we create what's called a pull schedule. And the pull schedule outlines when we're going to do specific thermal tests. So thermal tests basically put the formulation in a refrigerator or a freezer, an oven. And, you know, you say I'm going to come back three days, one month, six months,

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and check how it is.

Q. So if we look at the second paragraph shown on this page of the exhibit, can you make out what's written there highlighted in yellow?

A. It's getting to be a stretch; but yes, it says, "There is a problem with the physical stability of VEGF Trap in the current IVT formulation above 10 mg/mL, VEGF Trap. Specifically, particulate is seen after high-concentration formulations are pulled into a syringe and ejected into vials or into a vial. Therefore, a more stable ITV formulation is essential."

Q. Does this help explain why your group was researching more stable intravitreal formulations of aflibercept?

A. Yes.

Q. What are the types of stress conditions that were used in the stability studies your group ran?

A. It was dependent on the study. But, typically, we would look at agitation stress. Agitation stress is you take the container of the formulation and you put it on a lab scale vortexer, which is like a paint shaker. And it just shakes it up.

We would do thermal stress. So we would look at it at a range of temperatures. Sometimes we would just use accelerate and stress temperatures like 25, 37, and 45 to kind of get an early read on what's going on.

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We'd also do freeze/thaw, is another one that we would use.

Q. Let's take a look at the formulations that you tested in this SS195 stability study. This is under the heading "Procedure" on page 58 of PTX 2293.

Doctor, how many different formulations did you test in this study?

A. There were five.

Q. And can you make out what is the makeup of the Formulation Number 2 in the study?

A. Okay. So what we would do is we had a base formulation which was common to all the formulations that are being tested in the study. That's in the little snippet out above. And that says that we used 10 millimolar phosphate, .03 percent polysorbate 20, 40 mg/mL of VEGF Trap, and the pH was 6.25.

In addition, that formulation also contained 40-millimolar sodium chloride and 5 percent sucrose.

Q. And does that Formulation Number 2 stand out to you today, Dr. Graham?

A. It does.

Q. Why is that?

A. It's what ultimately became the commercial Eylea formulation.

Q. And does this laboratory notebook also indicate when

that formulation was first made?

A. Yes, it does.

Q. Let's turn to page 60 of PTX 2293.

What's shown here, Dr. Graham?

A. So this is the compounding record; so the mixing of the formulation. And it's for Formulation Number 2 with a specific lot number. And it was conducted on September 30th of 2005.

Q. To your knowledge, is this the very first time that the formulation was made that is known today as the Eylea formulation?

A. I believe it is, yes.

Q. And who made this formulation?

A. This was done by Kelly.

Q. Okay. And what was the date?

A. September 30th, 2005.

Q. Did your group test the stability of this formulation that was run as part of Stability Study SS195?

A. Yes, we did.

Q. And what did you find?

A. We found it to be a very good stable formulation.

Q. Is there stability data for this same composition in the '865 patent?

A. For the same composition in terms of the excipients, yes, there is. It's for a different lot of material.

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Q. Do you recall which example in the '865 patent this is?

A. So it's Stability Study 207, and I think it is Example 3.

Q. And so as of September 30th, 2005, had you and your coinventors made and tested the stability of the formulation that eventually became the commercial Eylea formulation?

A. Yes, we did.

Q. Let's look at Example 1 of the '865 patent. You see that on the screen, Doctor?

A. Yes, I do.

Q. Do you see that the formulation in Example 1 is highlighted in yellow?

A. Yes, I do.

Q. What's the term VGFT-SS065 that's shown as part of Example 1?

A. So that's our stability study number. The VGFT identified the product. 065 is it's the 65th study we put up.

Q. Was there a protocol associated with this stability study?

A. Yes, there was.

Q. Let's look at PTX 2292.

What's this document, Doctor?

A. It's one of Kelly Frye's notebooks.

Q. And are you familiar with that document?

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A. Yes, I am.

Q. How is it that you're familiar with this notebook?

A. I reviewed its contents when I joined the VEGF Trap team.

Q. Let's turn to page 34 of the notebook.

What's shown on this page, Dr. Graham?

A. It says that the protocol for stability VEGF Trap 065.

Q. And is there a date on this stability study protocol?

A. Yes, there is.

Q. Can you make out the date?

A. It was signed by Kelly on December 4th of 2003. I can't make out the other signature.

Q. That's okay.

Let's look at the procedures section of this protocol on page 34. What types of things were varied with respect to the formulations studied in this stability study?

A. So a couple things. There were different buffers used. We changed the concentration of sodium chloride. We tested 50 and 100 millimolar. We tested polysorbate. We tested PEG. We tested a couple of different concentrations of sucrose.

Q. And what is Formulation Number 2 in this study?

A. Formulation Number 2 was a 50 mg/mL VEGF Trap formulation with 10-millimolar phosphate, 50-millimolar sodium

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chloride, .1 percent polysorbate 20, and 5 percent sucrose.

Q. Let's compare this formulation, Formulation Number 2 in Stability Study SS065, with the formulation in Example 1 of the '865 patent.

Do you see those both on the screen?

A. Yes, I do.

Q. Can you confirm whether or not the same formulation is used in both of these documents?

A. They're identical.

Q. Does this formulation have a buffer?

A. Yes, it does.

Q. What's that?

A. 10-millimolar phosphate.

Q. Does it have an organic cosolvent?

A. Yes, it does.

Q. What's that?

A. Polysorbate 20.

Q. Can that also be called a stabilizer?

A. Yes, it can.

Q. Does it also have a stabilizing agent?

A. That would be 5 percent sucrose.

Q. Is the VEGF Trap referenced here in these formulations aflibercept?

A. It is.

Q. And what's the concentration of VEGF Trap in this

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formulation?

A. 50 mg/mL.

Q. Did you do size-exclusion chromatography analysis on this study?

A. Yes, we did.

Q. Let's look at PTX 1921.

Is this the SEC data for SS065?

A. Yes, it is.

Q. For Formulation Number 2 stored at 5 degrees C, what was the starting percent native VEGF Trap percent?

A. It was 98.8 percent.

Q. And what was the value at three months stored at 5C?

A. 98.7 percent.

Q. And what about at six months?

A. 98.3 percent.

Q. What does that tell you about the percent native conformation of this sample at two months at 5 degrees Celsius?

A. I would expect it to be greater than 98.7 percent.

Q. Why is that?

A. So when a protein aggregates, it's like rolling a ball downhill. It goes -- the level of purity goes down. It doesn't roll back up.

Q. Let's look at the bottom of this spreadsheet, PTX 1921. Does this information tell you when the six-month pull sample in Stability Study 065 was analyzed by SEC?

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A. Yes, it does. It says it was May 24th, 2004.

Q. Let's look back up at the Formulation Number 2 in this spreadsheet. Now, you've said that this formulation involved aflibercept at 50 mg/mL, right?

A. Yes, it does.

Q. What did this tell you about the percent native conformation of 40 mg/mL formulation of aflibercept stored at 5 degrees Celsius for two months?

MR. RAKOCZY: Objection, Your Honor. Again, the witness has not been qualified as an expert.

MR. TRASK: Your Honor, if I may, this is data from his group that he would -- he testified he routinely relied upon in performing the studies that led to the claimed invention, and he testified that he's run over 100,000 size-exclusion chromatography analyses during his time at Regeneron. He has personal knowledge of this data and relied upon it in the course of developing the inventions.

THE COURT: Understood.

Counsel.

MR. RAKOCZY: Your Honor, that didn't have anything to do with my objection. My objection is -- let me back up.

I'm not objecting that this formulation tested a 50 mg/mL. That's the whole point. That's what this is. The question was asking for an opinion on how does that bear on a 40 mg/mL, a different formulation. That's asking for an expert

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opinion.

THE COURT: It is, Counsel. You need to reword that question, please.

BY MR. TRASK:

Q. Okay. Doctor, what did you understand the percent native conformation at 50 mg/mL reported in this table would tell you about the percent native conformation of a 40 mg/mL formulation of aflibercept at 5C for two months?

MR. RAKOCZY: Objection, Your Honor. It's the exact same question.

THE COURT: It's not exact. It's close.

But I assume, Counsel, this is part of the work in developing the ultimate formulation that results in the patent at issue, correct?

MR. TRASK: Absolutely, Your Honor.

THE COURT: With that understanding, objection overruled. Would you repeat your question, Counsel.

BY MR. TRASK:

Q. Dr. Graham, for the third time, I suppose, what did you understand the percent native conformation at 50 mg/mL, as reported in this data sheet, tell you about the percent native conformation of a 40 mg/mL formulation of aflibercept stored at 5 degrees Celsius for two months?

A. Okay. So as the concentration of a formulation increases -- at least as the concentration of aflibercept

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formulation increases, generally the rate of -- the rate of aggregation goes up. So it's more concentrated, more crowded, faster aggregation.

If you got a rate at 50 mg/mL, you can predict reliably that the rate at 40 mg/mL is going to be less in the same formulation.

MR. RAKOCZY: Objection, Your Honor. Again, that's pure expert opinion predicting what would and would not happen. That's for the experts.

MR. TRASK: I disagree, Your Honor. He's a scientist talking about the work he did leading to the inventions claimed in that patent being asserted in the suit. This is routine testimony at patent trials.

THE COURT: I don't believe the word "routine" shows up in the rules of evidence, but I understand the background involved here. Objection overruled.

BY MR. TRASK:

Q. Did you view the results of this study as promising, Dr. Graham?

A. Yes.

Q. Let's turn to Example 3 of your '865 patent, Doctor. You see Example 3 on the screen?

A. I do.

Q. You see the formulation used in this study is highlighted in yellow?

A. Yes, it is.
Q. What is the term there, VGFT-SS207?
A. That is Stability Study 207, 207th study.
Q. That's another stability study you performed?
A. Yes.
Q. Let's look at PTX 1825, and I want to see page 85 of this document.

Now, is this the protocol for Stability Study VGFT-SS207?

A. Yes.
Q. This stability study is part of a larger document that was produced in this case, all of which appeared to relate to SS207.

Is this how the documentation for stability studies was kept in the ordinary course of Regeneron's business?

A. So yes, it was. We kept what was called a study file, and that collected all the paper. We also kept lab notebooks as well.
Q. Okay. Let's turn to page 92 of this exhibit. Is this the approval page for the stability study we just discussed?
A. Yes, it is.
Q. Is that your signature on the page, Doctor?
A. It is.
Q. What does this page indicate your role was with

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respect to SS207?

A. It says that I was the study director.

Q. And what does the role of study director entail?

A. Well, that meant I was the responsible party. So I had to ensure pulls were done as scheduled, make sure there was staff assigned to do the analysis, do some of the analysis myself, summarize the data, interpret the data, give readouts to management in terms of what we had, prepare presentations. Pretty much name it.

Q. And when did you sign this protocol, Dr. Graham?

A. On the 16th of January 2006.

Q. And so had you made the formulation that was tested in SS207 prior to January 2006?

A. Yes. It actually was made the previous year, I think in October of 2005.

Q. I'd like you to compare the formulation identified in the study protocol for SS207 -- that's PTX 1825, page 85 -- with the formulation in Example 3 of the '865 patent. That's PTX 2, page 8, Column 9.

Do you see those on the screen?

A. I do.

Q. Is the formulation that you studied in Stability Study 207 the same as the one disclosed in Example 3 of the '865 patent?

A. They're identical, yes.

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Q. Does this formulation have a buffer?
A. Yes.
Q. What's that?
A. 10-millimolar phosphate.
Q. Does it have an organic cosolvent?
A. Yes, it does.
Q. What's that?
A. .03 percent polysorbate 20.
Q. Is there a stabilizing agent?
A. Yes, there is.
Q. What's that?
A. 5 percent sucrose.
Q. And the VEGF Trap here is aflibercept?
A. Yes, it is.
Q. And what's the concentration?
A. 40 mg/mL.
Q. Let's turn to Table 1 of the SS207 protocol. This is PTX 1825 at page 86.

You see that table on the screen?

A. I do, yes.
Q. Did this study involve testing the formulation stability in different containers?
A. It did.
Q. Was a glass vial one of those containers?
A. So the glass vial was what's listed as Device

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Number 7.

Q. Okay. Was there a pull schedule for this stability study as well?

A. Absolutely.

Q. Let's look at that. Page 172 of PTX 1825.

Is this the pull schedule for SS207?

A. Yes, it is.

Q. What was the two-month pull date for this study?

A. March 21st of 2006.

Q. And so what does that mean? What happened on that date?

A. So this is for a 5-degree C condition. That meant on the 21st analysts went in, removed the samples from the 5-degree, and began performing the tests that were outlined in the protocol.

Q. And was size-exclusion chromatography one of the tests performed on these samples?

A. Yes, it was.

Q. Let's look at PTX 2277 at page 15. This is a spreadsheet produced in native format.

Does the spreadsheet shown in this document report the SEC data for the glass vial Device Number 7?

A. It does.

Q. What did the SEC data show after two months' storage at 5C?

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A. It showed that the percent native VEGF Trap is 99.18 percent or -- which rounds to 99.2 percent.

Q. What did that tell you about this formulation's stability?

A. That it had good stability, yes.

Q. Let's look at the bottom of the same document.

Does this tell you when the size-exclusion chromatography data was obtained for this sample at two months, 5 degrees Celsius in a glass vial?

A. Yes, it does.

Q. When was that?

A. So this is a different date format than what we had been using earlier. We transitioned to going year-month-date; so we had the whole list of things in the computer you could find by year.

So 06 is 2006, 03 is March, and 20 is the 20th of March.

Q. Was this the first time you'd made an aflibercept formulation achieving at least 98 percent native conformation after two months at 5C?

A. No, it wasn't.

Q. Had you done that sooner?

A. Yes.

Q. Did you analyze the stability in SS207 by more than just size-exclusion chromatography?

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A. We did.

Q. Let's look at PTX 2278, page 9.

What type of data do we have here, Doctor?

A. This is turbidity or OD at 405.

Q. Does the column on the right report when the turbidity analysis was performed for the 5C two-month sample in a glass vial?

A. The two-month samples were analyzed on March 21st of 2006.

Q. And what were the results reported here?

A. So for the glass vial, the value was -- is negative .003, which is reported as 0.00.

Q. And what did that tell you about this formulation's stability?

A. It was stable. It was not changing from the initial state.

Q. Did you analyze the pH of the samples in this study as well?

A. We did.

Q. Let's look at page 10 of this document, again, PTX 2278. Is this pH data?

A. Yes, it is.

Q. Can you tell when the pH was measured at the two-month time point for the sample stored at 5 degrees Celsius in a glass vial?

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A. March 21st of 2006.

Q. And is the pH result reported here a good one?

A. Yes, it is.

Q. What did it indicate to you about the stability of the sample?

A. That the sample was stable.

Q. Let's turn back to the size-exclusion chromatography data spreadsheet at PTX 2272. Now, you testified that there was a two-month pull and a sample was analyzed at that time?

A. Yes.

Q. Was that the end of the study?

A. Oh, no.

Q. What happened?

A. So we wanted to understand how the formulation performed at 5 degrees C over a number of years. So we continued to pull samples monthly through six months. So we had a three-, four-, five-, and six-month pull.

After that we pulled samples every three months, which was 9, 12, 15, and 18. And then after 18 months, we went every six months, which worked out to 24, about 31 months, and then 36 months.

Q. And why were you testing the stability of this sample at so many different time points?

A. So we were making decisions pretty much on the fly. We had a lot of pressure to come up with what is going to go

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into the clinic, go into the patient. We were getting early reads, and we were trying to confirm that yes, our projections are right. And if by some quirk of fate something went wrong, we would know it immediately and be able to course correct.

Q. Thank you, Doctor. And just for the record, I think I may have misspoken. If I said PTX 2272, I meant to say PTX 2277, the exhibit we're looking at with this data.

Turning now, Doctor, to Example 5 of your '865 patent, do you see that on the screen?

A. I do.

Q. And do you see the formulation that was tested in this example?

A. Yes, I do.

Q. And there's a term here "VGFT-SS203." Is that another stability study you ran?

A. That was the 203rd stability study.

Q. Let's look at that one. This is PTX 1860. Is this the protocol for SS203?

A. It looks like it's a pull schedule, actually.

Q. I'm sorry. It's a pull schedule. Thank you.

If we turn to page 122 of this document, is this the stability study protocol for this study?

A. That's the first page of the stability study protocol.

Q. And this again was produced as part of a larger

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collection of documents relating to Stability Study 203. Is this also how these documents were kept in the ordinary course?

A. Yes.

Q. Now, I'd like to -- I'd like for you to compare, if you could, Doctor, the formulation investigated here in SS203, page 122, of PTX 1860, with the formulation in Example 5 of the '865 patent, PTX 2, page 8, Column 10.

Do you see those both on the screen?

A. I do.

Q. Are these the same formulations?

A. Yes, they are.

Q. Let's go back to the protocol, SS203. This is PTX 1860, page 129. Is this the approvals page for the SS203 protocol?

A. Yes, it is.

Q. Is that your signature next to -- above study director?

A. It is.

Q. Were you the study director for this?

A. Yes, I was.

Q. And when was this protocol approved?

A. The 19th of January 2006.

Q. All right. Let's turn back to the first page of the protocol. This is page 122 of PTX 1860. What was the -- let's turn to page 123, actually, with the Table 1 displayed.

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Was this a study that involved testing the formulation in different containers?

A. It did.

Q. And were glass vials tested in this study?

A. Yes.

Q. Which device is that?

A. So it's Number 6.

Q. And if we look at page 8 of PTX 1860, what is this document?

A. So this is the pull schedule for that study.

Q. And what does it tell you about the two-month 5C sample pull date?

A. So it was scheduled to be pulled on the 12th of February; and it actually was pulled on the 13th of February.

Q. Okay. And did you do size-exclusion chromatography analysis in this study as well?

A. Yes, we did.

Q. Let's look at a spreadsheet marked as PTX 2238, page 14. Is this the SEC data for the formulation in SS203 sorted 5C in a glass vial at different time points?

A. Yes, it is.

Q. What was the native conformation you found for the vial at two months?

A. 99.2 percent.

Q. That's greater than 98 percent, of course?

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A. Yes, it is.

Q. What did that tell you about the formulation's stability?

A. That it had good stability.

Q. Let's look at the bottom of this page. Does this document also tell you when the size-exclusion chromatography test was run?

A. Yes, it does.

Q. What does it say?

A. So 06, year, so 2006; 02, February; 14, 14th.

Q. If we could turn to page 156 of PTX 1860, is this more data from the Stability Study SS203?

A. Yes, it is.

Q. What's shown here?

A. So it's the osmolality of the formulation.

Q. And what osmolality is reported here, Doctor?

A. 287.

Q. And what units are those?

A. Milliosmoles.

Q. And so is the formulation that was analyzed in SS203 an isotonic formulation?

A. No, it's not.

Q. What's your understanding of what's isotonic?

A. 300, 320, that range.

Q. And you said earlier that the formulation in SS203 is

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the same as the formulation reported in Example 5 of the '865 patent. Was that right?

A. Yes, it is.

Q. So what does that mean about the tonicity of the formulation disclosed in Example 5 of the '865 patent?

A. So it's hypertonic, below iso-osmolar.

Q. Did you say hypo, H-Y-P-O?

A. H-Y-P-O.

Q. Now, I next would like to look at the disclosure of your '865 patent, Dr. Graham. And I'd like to see if you can confirm whether the data for the native conformation for the stability studies we just reviewed are the same as the native conformation data disclosed in the examples of your patent. Okay?

A. Okay.

Q. Let's start by comparing the size-exclusion chromatography data in Table 1 of your '865 patent -- this is PTX 2, page 7, Column 8 -- with the SEC data from study SS065 for Formulation Number 2 at 5 degrees Celsius. This is PTX 1921.

Do you see both of those on the screen?

A. I do.

Q. Do the SEC data in these two tables match?

A. They do.

Q. Next let's compare the SEC data in Table 3 of your

'865 patent -- this is PTX 2, page 8, Column 9 -- with the SEC data from your SS207 study for the glass vial stored at 5C.

Do you see those?

This is PTX 2277, page 15.

A. I see it.

Q. Do you see those on the screen?

A. Yes, I do.

Q. So the SEC data in these two tables match?

A. They do when you appropriately round the values in the spreadsheet.

Q. And can you explain how the rounding works.

A. Yeah. It's very straightforward. If it's .5, it goes up; if it's .4, it goes down. So -- or .5 or greater, .4 or less. So if it's 98.49, that becomes 98.5.

Q. And next I would like to compare the size-exclusion chromatography data from Table 5 of your '865 patent, PTX 2, page 8, Column 10, with the SEC data from the SS203 study for the glass vial at 5C. This is PTX 2238, page 14.

Do you see those on the screen?

A. Yes, I do.

Q. Do the SEC data in these two tables match?

A. Yes, they do.

Q. Okay.

Let's take that down, please.

Now, we've been looking at your issued '865 patent up

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till now, right, Doctor?

A. Yes, we have.

Q. Were there earlier related patent filings that preceded the '865 patent?

A. Yes, there were.

Q. And when did you first disclose the data in the '865 patent to the U.S. Patent Office?

A. We filed a provisional patent.

Q. And you testified earlier that you were involved in the preparation of that provisional patent?

A. Yes.

Q. Is the data in the examples of your provisional patent application the same as the data in the examples of the '865 patent?

A. Yes, they are.

Q. Let's take a brief look at that.

Let's look at PTX 3249.

Do you recognize this document, Doctor?

A. This is the -- it looks like the title page for the provisional filing.

Q. Okay. And let's compare a few of the examples and data in your provisional application with the corresponding examples and data in your '865 patent.

And before we do that, can we just zoom in on the date on which this is filed on the bottom right.

Does this show when the provisional application was filed, Doctor?

A. June 16th of 2006.

Q. Okay. Let's first look at Example 1 from your provisional application, PTX 3249 at page 17, with Example 1 from your '865 patent. This is PTX 2, page 7, Column 8.

Do you see both of those on the screen?

A. Yes, I do.

Q. How do those examples and data compare?

A. They're identical.

Q. Next let's compare Example 3 from your provisional application, PTX 3249, pages 18 to 19, with Example 3 of your '865 patent, PTX 2, page 8, Column 9.

You've reviewed both of these previously, Doctor?

A. I have.

Q. How do these examples and data compare?

A. They're identical.

Q. Next let's look at Example 5 of your provisional application, PTX 3249, pages 19 to 20, with Example 5 of your '865 patent, PTX 2, page 8, Column 9.

You've reviewed both of these previously?

A. Yes, I have.

Q. How do these examples and data compare?

A. They're identical.

Q. So to sum up on this point, then, are the data in

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examples -- in Examples 1, 3, and 5 of your '865 patent and your provisional application the same as one another?

A. Yes, they are.

Q. And are those data also the same as the data that was originally collected from your laboratory at Regeneron?

A. Yes, it is.

Q. Let's take a look at -- again at PTX 1825, page 172.

This is the pull schedule for Stability Study 207, Doctor.

A. Okay.

Q. What is the two-month pull date for the 5C storage condition?

A. March 21st, 2006.

Q. Of the various stability studies that you've addressed during your testimony today, were any of the two-month pull dates after March 21, 2006?

A. No.

Q. And so, Dr. Graham, in your view, had you conceived of the inventions claimed in your '865 patent no later than March 21, 2006?

A. Well, we first made it in September of 2005; but yes, no later than March of 2006.

Q. Let's --

MR. RAKOCZY: Your Honor, I'd just again renew my objection to make sure it's preserved.

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THE COURT: No. Understood. Preserved from my perspective, certainly, Counsel, and will be addressed presumably in posttrial submissions and in the Court's final order.

MR. RAKOCZY: Thank you, Your Honor.

MR. TRASK: And just to note, Your Honor, that's the same date that was in our interrogatory response, March 2006.

THE COURT: Yes. Thank you.

BY MR. TRASK:

Q. Let's look at the examples in your '865 patent. So here we've tried to show on the screen many of the examples from your '865 patent. I know it's a little too small to read. But we've been discussing Examples 1, 3, and 5 up to this point, right?

A. Yes.

Q. Are all of those liquid formulations in vials in Examples 1, 3, and 5?

A. 1, 3, and 5 are all liquid formulations in vials, yes.

Q. Are there also examples in your patent that involve prefilled syringes and lyophilized formulations?

A. Yes, there are.

Q. So for purposes of your invention involving liquid formulations in vials, what's more relevant, the examples involving prefilled syringes and lyophilization or Examples 1,

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3, and 5?

A. So the most relevant is the examples in the vial.

Q. I'd also like you to compare, Doctor, the passage in your '865 patent, PTX 2, at page 4, Column 2, lines 39 to 57, with the passage in your provisional application at paragraphs 7 and 8. This is PTX 3249 at page 11.

Do you see those two passages side by side on the screen?

A. I do.

Q. Have you reviewed these passages previously?

A. Yes, I have.

Q. Can you confirm whether or not these two passages convey the same information?

A. They do.

Q. All right. Let's turn back to your '865 patent once more. Have you reviewed the section of your patent titled "Related U.S. Application Data" on the face of the patent?

A. Yes, I did.

Q. Let's take a look at that in PTX 2.

Now, you are aware, of course, Doctor, that after your provisional application was filed but before your '865 patent issued, there were nine intervening related patent applications filed and issued naming you as an inventor?

A. Yes, I am.

Q. Have you reviewed each of those?

A. Yes. I did.

Q. Did you determine in your review of those documents whether or not each of those patents contains the same disclosure as in your '865 patent at Column 2, lines 39 to 57, and Examples 1, 3, and 5?

A. All of them contain the same examples, the exact same data. Those paragraphs, although they appear on different pages sometimes in slightly different formatting, are all identical with respect to the words.

Q. Thank you, Doctor.

Now, were the aflibercept formulations that are reported in your '865 patent the only ones that you tested for stability?

A. No.

Q. Okay. How many did you make and test, just ballpark?

A. 40.

Q. I'd like to look at just a couple of those.

First, when you varied the ingredients in your formulations, did you ever try stabilizing agents other than sucrose?

A. Yes.

Q. What did you try?

A. We tried -- mannitol was one.

Q. Okay. Let's look at your '865 patent, PTX 2, at Column 2, lines 45 or thereabouts. What does this passage of

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the patent convey in part?

A. It says that you might want to use mannitol as a stabilizing agent.

Q. And did you, in fact, do a stability study on a formulation with mannitol as the stabilizing agent?

A. We did.

Q. Okay. Let's look at PTX 2281 at page 1. What is this document, Doctor?

A. This is the 208th stability study protocol.

Q. And did you run this study?

A. I did.

Q. Let's turn to page 2 of this document. This is the mannitol-containing formulation you just referenced?

A. Yes, it is.

Q. And on page 2, does this indicate whether or not a glass vial was tested as the container?

A. Container Number 7 was a glass vial, yes.

Q. Let's compare the formulation of Example 3 from your '865 patent, PTX 2, Column 9, with the formulation of SS208, which is PTX 2281, page 1.

Do you see these on the screen?

A. I do.

Q. How do these two formulations compare?

A. They're identical.

Q. Is the stabilizing agent identical?

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A. No. So the formulations are identical with respect to every other component except one has sucrose and the other has mannitol.

Q. Did this study involve testing the mannitol-containing formulation by SEC?

A. Yes, it did.

Q. Let's look at PTX 2282 at page 14. Is this spreadsheet the SEC data for SS208?

A. Yes, it is.

Q. And this is the glass vial at 5C?

A. Yes, it is.

Q. What was the percent native conformation as measured by size-exclusion chromatography at 5C, two months' storage in a glass vial?

A. 99.05.

Q. And is that -- that's greater than 98 percent?

A. Yes, it is.

Q. Did you do turbidity on this formulation as well?

A. Yes, we did.

Q. Let's look at PTX 2283, page 12.

What is this document?

A. So this is the data that was collected for turbidity or optical density at 405.

Q. And what does it show for the turbidity of the mannitol-containing formulation following storage at 5C for two

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months in a glass vial?

A. It shows that it was unchanged from the initial measurement; so it's good stability.

Q. Now, in the course of your stability study work on aflibercept formulations, did you also vary the amounts of polysorbate 20?

A. We did.

Q. Let's look at PTX 2265, page 1.

What is this document, Dr. Graham?

A. This is the 205th stability study protocol.

Q. And what amount of polysorbate did you test here?

A. 0.06 percent.

Q. And if we look at page 2, Table 1, of PTX 2265, was a glass vial tested in this study as well?

A. Yes, it was.

Q. Was that Device 7?

A. Yes, it is.

Q. Let's compare the formulation of the SS205 protocol that we just looked at with the formulation of Example 5 of the '865 patent, PTX 2, page 8, Column 10. How do these two formulations compare, Dr. Graham?

A. So they have the same components. The difference is that there is .03 percent polysorbate in Example 5 and .06 percent polysorbate in Study 205.

Q. Did you look at these -- this .06 percent

polysorbate 20 formulation by size-exclusion chromatography?

A. Yes, we did.

Q. Let's look at PTX 2266, page 15. Is this the SEC data for the glass vial at 5 degrees C?

A. Yes, it is.

Q. And what was the percent native conformation as measured by SEC following storage in a glass vial for two months at 5C for this formulation?

A. 99.0 percent.

Q. Did you run turbidity analysis here as well?

A. Yes, we did.

Q. Let's look at PTX 2267, page 17.

THE COURT: Counsel, once we go through this table, if we're at a spot to take our afternoon break.

MR. TRASK: Absolutely, Your Honor.

BY MR. TRASK:

Q. Is this the turbidity data for the SS205 study?

A. Yes, it is.

Q. And what was the turbidity at 5 degrees Celsius for two months in a glass vial?

A. It was unchanged from the initial measurement.

Q. Is that a good result?

A. Yes.

MR. TRASK: Okay. Happy to break at this point, Your Honor, if you'd like.

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THE COURT: Why don't we go ahead and do that, then. We're going to take ten minutes. We'll resume at 3:00, a couple minutes after that.

Doctor, you haven't been in the courtroom; so this may be a new speech for you. Because you're midstream on your testimony, no one can speak with you in particular about your testimony. So everyone would run the other way as opposed to greeting you.

THE WITNESS: Sounds good.

THE COURT: You're welcome.

I just didn't want you to think that anyone was being rude or discourteous to you. But you can go ahead and step down, sir. But you're a man without a country for the next ten minutes or so.

We'll see everyone in a few. Thank you.

(A recess was taken from 2:54 p.m. to 3:15 p.m.)

THE COURT: Apologies. That break ran over. We had a cataclysmic user error with the Keurig coffee machine. That was my user error. Don't worry. We're getting new carpet as part of the great asbestos project. That's what we're telling ourselves.

Counsel, you may proceed.

MR. TRASK: It doesn't show on the black robe.

THE COURT: That's the beauty of the black robe.

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Thank you, sir. Go right ahead.

MR. TRASK: Thank you.

BY MR. TRASK:

Q. If we could turn back to Stability Study 207 briefly, Dr. Graham.

A. Sure.

Q. And if we look at PTX 2275. And, actually, this one is not in your binder; so I'm going to hand up copies of this.

MR. TRASK: With the Court's permission?

THE COURT: You may.

BY MR. TRASK:

Q. Doctor, do you have PTX 2275 in front of you?

A. Yes.

Q. Okay.

And for the record, this is Bates-stamped RGN-EYLEA-MYLAN-00475679. And it's a native Excel file printed as a PDF.

Doctor, we previously discussed the two-month 5C-degree pull date in exhibit -- in Stability Study SS207. Does this exhibit, PTX 2275, show the same pull date at two months, 5 degrees C, that we discussed in connection with PTX 1825 for Stability Study 207?

A. Yes, I believe it does.

Q. And for the record, what is the pull date at two months, 5C, in Stability Study SS207?

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A. 21 March 2006.

Q. Okay. I'd also -- we can put that aside for the moment.

I'd also like to discuss or revisit briefly in connection with SS207, PTX 2277, page 15. And this -- actually, this is -- if we could look at the bottom of this Excel spreadsheet.

So, Doctor, I think you testified about the date at the bottom of this Excel spreadsheet, SS207, indicating when the two months' SEC data was run?

A. Yes.

Q. Can you explain the date it was run and the connection to the date shown at the bottom of this spreadsheet.

A. Okay. So this is a sequence number. What we do is we start the sequence and we assign a date code to it. So 06 is 2006, 03 is March, 20 is the 20th of March. The F is the system number or system identifier that we used.

So this sequence actually was started the day before the samples were pulled. And we did that because we were running standards and systems suitability, and we wanted to ensure that we got all the standard system suitability, all that done, and then allowed -- had a system that's all set, ready to go, you walk in in the morning, you pull out your samples, you put them on, and you run them that day. We didn't want things drifting later and later. We just wanted to be set

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and primed and ready to go.

Q. Okay. So what was the date that you were getting the size-exclusion chromatography analysis machine ready?

A. So the date we were getting it ready was the 20th, which was the date before the pull.

Q. And that's March 20th, 2006?

A. Yes.

Q. And then what's the date on which you actually ran the sample for 5 degrees C, two months?

A. They would have gone up on the 21st, the day they were pulled.

Q. And that's March 21, 2006?

A. Yes.

Q. Okay.

We can take that down.

Thank you, Doctor.

Doctor, did you sit for a deposition in this case?

A. Yes, I did.

Q. Do you recall during your deposition counsel for defendants showed you some internal Regeneron documents where polysorbate was referred to as a stabilizing agent?

A. Yes, I did.

Q. During your work involving formulations of aflibercept, did you sometimes call polysorbate 20 a stabilizer or a stabilizing agent?

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A. Yes, I did.

Q. Did you also refer to polysorbate 20 as an organic cosolvent in connection with that work?

A. Yes, I did.

Q. And did you also call polysorbate 20 at times a surfactant?

A. Yes.

Q. Can you explain why you were using these different labels?

A. So surfactant is kind of self-explanatory. It's the chemical structure of the polysorbate.

Cosolvent is, you know, what we were using it for within the formulation. And a cosolvent stabilizes the formulation; so hence stabilizer or stabilizing agent.

Q. So would I be mistaken if I called polysorbate 20 a stabilizing agent?

A. No, you would not be.

MR. RAKOCZY: Your Honor, I'm going to object. Again, expert testimony. Also, he's offering opinions on construction of claims. He didn't offer any of that before. We're hearing this for the first time.

THE COURT: Counsel?

MR. TRASK: This is not in connection with the claim, Your Honor. I'm referring to the documents that he prepared in the course of his development of the invention.

THE COURT: Well, let's stick to those actual documents as opposed to what's his interpretation thereof.

Otherwise, sustained.

MR. TRASK: Thank you, Your Honor.

BY MR. TRASK:

Q. Let's look at PTX 672.

What is this document, Doctor?

A. So this is the pharmaceutical development section that I wrote for Eylea.

Q. Section of what?

A. The BLA.

Q. Is this the Eylea BLA?

A. Yes.

Q. Okay. And you're familiar with this document?

A. Yes.

Q. It's a long document, 483 pages. What was your specific involvement with this document?

A. I wrote it.

Q. The whole thing?

A. Yes.

Q. Okay. If we turn to page --

A. Sorry.

THE COURT: Understood, Doctor.

BY MR. TRASK:

Q. If we turn to page 26 of this document, Dr. Graham,

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did you write this section of the document as well?

A. I did.

Q. And what is this section of the document?

A. It is describing the choice of organic cosolvent and the selection of the concentration for the formulation.

Q. If we look at the last paragraph on page 26 of Exhibit PTX 672, do you see where it says polysorbate 20 was selected as the organic cosolvent?

A. Yes. It says polysorbate 20 was selected as the organic cosolvent because a lower concentration was required to stabilize the VEGF Trap when subjected to agitation stress.

Q. Why did you call polysorbate 20 an organic cosolvent in this document?

A. Because that's what I was using it for in the formulation.

Q. And you understood, when you wrote this document, that it would be submitted to the FDA?

A. Yes.

Q. And was it, in fact, submitted to the FDA?

A. Yes, it was.

Q. And this is an accurate statement?

A. Yes, it is.

Q. Okay.

We can take that down.

Now, when you were working to develop more stable

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intravitreal formulations of aflibercept, were you aware of public information about other existing protein formulations?

A. Some, yes.

Q. And in the course of your work, did you ever consider taking the aflibercept and just plugging it into a formulation that had been used to stabilize a different protein?

A. No.

Q. Why not?

A. All right. So proteins are individuals. No two proteins really behave exactly the same. They have different likes and dislikes. So a formulation that works well for one protein may not work well for another one. Things like pH are critical. Choice of stabilizer can be critical.

MR. RAKOCZY: Again, objection, Your Honor. Again, that's expert opinion testimony. He can testify about his personal experience with aflibercept, but now he's venturing into other proteins and what would and would not work.

THE COURT: That's sustained.

BY MR. TRASK:

Q. Moving on, when developing your invention, was tonicity a consideration for you, Doctor?

A. To a degree.

Q. Okay. Can you explain that?

A. So we knew that we -- or thought that we did not want to inject something that was 1,000 milliosmoles. We thought

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that could potentially be bad. But we weren't necessarily concerned that we had to be exactly isotonic with the environment. We figured we had wiggle room.

Q. And you testified earlier that Example 5 of your '865 patent was not an isotonic formulation; is that right?

A. That is correct.

Q. Did you nonetheless consider the formulation of Example 5 to be a candidate formulation for intravitreal injection?

A. Yes.

Q. Now, does -- the '865 patent on which you're named as an inventor, does that identify which of the formulations it discloses is the one that corresponds to Regeneron's Eylea formulation?

A. No, it does not.

Q. Does it indicate anything about whether Regeneron preferred one of those formulations over another?

A. Not that I've seen in the document, no.

Q. Were you permitted as a Regeneron employee to publicly identify the formulation for Eylea before the Eylea product was released onto the market?

A. I was not.

Q. And to your knowledge, prior to Eylea's launch, was the formulation that you invented that eventually became the commercial Eylea formulation ever publicly identified as

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Regeneron's commercial formulation?

A. Not to my knowledge, no.

Q. Now, you invented formulations of aflibercept that have greater than 98 percent native conformation following storage?

A. Yes.

Q. To your understanding at the time, did the FDA require some degree of stability in the products that it approves?

A. Yes.

Q. To your understanding at the time, did the FDA require at least 98 percent native conformation for an approved intravitreal product?

MR. RAKOCZY: Your Honor, I'm going to object to the extent he's asking what the FDA did or didn't think, did or didn't require.

MR. TRASK: He just testified that he wrote part of the BLA --

THE COURT: Understood, but let's focus on his understanding as to why or why not certain things might or might not be included in there.

Overruled with that caveat.

BY MR. TRASK:

Q. Okay. Dr. Graham, when you were developing your aflibercept formulations, did you understand that you needed to

achieve at least 98 percent native conformation in order for the product to be approved?

A. That would not have been an obligate requirement. We needed a stable formulation. A stable formulation is supported based on what your clinical experience is. We wanted the 98 percent or -- as pure as we could possibly get it because we wanted the best possible product, you know, for the patient. That was our goal.

Q. Now, is aflibercept a fusion protein, Doctor?

A. Yes, it is.

Q. Is aflibercept an antibody?

A. No.

Q. Are fusion proteins and antibodies the same thing?

A. No, they are not.

MR. RAKOCZY: Objection, Your Honor. Again, expert testimony.

THE COURT: Sustained.

BY MR. TRASK:

Q. Okay. So one brief point to wrap up, Doctor.

You've been working as a scientific researcher for about how long?

A. Well, 22 years at Regeneron, ten years at the City of Hope, and then -- god -- since probably -- what? -- '81 at Penn State. So what? 42 years, give or take.

Q. And of all the scientific work you've done over the

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course of your career, where did the inventions of the '865 patent rank?

A. Well, that's probably at the top of the heap.

Q. Why is that?

A. Well, I have a very personal story with respect to Eylea. My mother suffered from wet AMD. I knew that my grandmother, her mom, had gone blind. I didn't know why. Now, my mom was a very, very private person. She never revealed what was going on with her. She had basically gone blind in one eye from the disease, and we didn't know this. And then she started complaining about her eyesight. And then we realized or learned, she finally fessed up, that she had the disease in the other eye.

You know, she was getting regular doses of Lucentis every month, but her vision was getting worse. My wife and I were, like, trying to find every opportunity so she could see my daughter, you know, get to see her at swim meets and get to see her and spend time with her while she still could see her.

And by the time or before -- shortly before Eylea was approved, her vision had gotten to 21/20, 21/40. She wasn't driving anymore. You know, she was somebody that always liked to do crossword puzzles and word things, couldn't see to do those. So it was kind of very dire.

Eylea got approved. I had seen the clinical data and thought, well, this looks better. I started having

conversations with her ophthalmologist, which she didn't like much, but I kind of was I'm not going to sit there and let you go blind; I want to see if there's something we can do. I suggested Eylea. I got back oh, these things are all the same.

I finally, in March of 2011, got to the point where I stood and looked at him and said, okay, why are you sentencing my mother to blindness? What we're doing right now is not working. It's just getting worse. Can we just try something better or different? If it doesn't work, we're no worse off.

And he agreed at that point to order the drug in. She did her three loading doses. Her vision improved. She got to the point where she was seeing 20/40. With eyeglasses, she was driving again. She got to see Kendra grow up. And it maintained her vision up until the last few months of her life.

You know, what can you do better than save your mother's sight?

MR. TRASK: Thanks so much, Doctor.

Nothing further at this time.

THE COURT: Understood.

Cross?

MR. RAKOCZY: May we approach with some binders, Your Honor.

THE COURT: You may.

MR. RAKOCZY: Good afternoon, Your Honor. William Rakoczy for Mylan and Biocon.

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THE COURT: You may proceed, sir.

CROSS-EXAMINATION

BY MR. RAKOCZY:

Q. Good afternoon, Dr. Graham.

A. Good afternoon.

Q. Nice to meet you.

Dr. Graham, I'd like to start with DTX 722. And we'll pull it up on screen, and it's also in your binder that hopefully you were just handed.

A. Yes.

Q. I'd like you to look at page 1. You see this is an email dated March 21st, 2006, correct?

A. Yes, I do.

Q. And it's from Kathleen DeWald to you?

A. Yes.

Q. Is that right?

And I'd like to go to the attachment at page 2. And here you see a product composition, correct?

A. I do.

Q. It contains phosphate -- strike that.

And the formulation, under the "Product Composition" heading, contains phosphate, NaCl, polysorbate 20, sucrose, and 40 mg/mL VEGF Trap, correct?

A. I do.

Q. And I'd like to focus on the first sentence of the

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paragraph above it. It states, "This is an unstable formulation for VEGF Trap since there are minimal excipients for intravitreal delivery and the formulation contains a high concentration of VEGF Trap."

Is that right?

A. That is correct.

Q. Now, below that it actually goes on to caution that the drug product should -- being held or stored at 25 degrees C should be kept to a minimum during the manufacturing process, correct?

A. Yes. I see those words on the page.

Q. And at temperatures above 25 degrees C -- strike that.

Temperatures above 25C must be avoided, correct?

A. That's correct.

Q. And that this drug product should be held or stored at less than minus 20 degrees C, correct?

A. I see that, yes.

Q. Now, I'd like to look at the table just below that. And in this table we see polysorbate 20 identified as a stabilizer as its function, correct?

A. Yes.

Q. It's not identified as a solvent, correct?

A. The description on the page says stabilizer.

Q. And the solvent in this formulation is the water or

the water for injection, correct?

A. That is the description for water for injection on the page.

Q. Now, let's take a look at one of your signed memos on your ITV formulation.

Let's pull up DTX 737.

And here we see a signed memo from you dated April 6th, 2006, correct?

A. Hang on. I'm trying to follow you.

Q. DTX 737. And I have it on the screen as well. We'll go to page 2.

A. Yes, I see page 2.

Q. And you see your signature dated April 6th, 2006, at the very top, correct?

A. Yes, I do.

Q. And this is entitled "40 mg/mL VEGF Trap for ITV in a sucrose- and polysorbate-containing formulation," correct?

A. That is correct.

Q. Now, we see just below that the same cautionary statements on storing the drug product.

Do you see that?

A. There are cautionary statements. They're not exactly the same, though, no.

Q. It says the drug substance, formulated drug substance, or drug product, the time it's held or stored at 25

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degrees C should be kept to a minimum during the manufacturing process, correct?

A. That's the words on the page, that's correct.

Q. And, again, it cautions that temperatures above 25 degrees C must be avoided for this formulation, correct?

A. That is correct.

Q. And it says that this drug product formulation should be held or stored at 2 to 8 degrees C, correct?

A. Well, yes, it says 2 to 8 degrees C on this page, correct.

Q. Now, let's go down to the table below this as well. And here again, we see that water is identified as the function in the formulation -- or as the solvent in the formulation, correct?

A. Well, WFI is identified as the solvent, yes.

Q. And that's water for injection; is that right?

A. That is correct.

Q. And the polysorbate 20, its function is identified as stabilizer, correct?

A. Yes, it is.

Q. It's not the solvent, correct?

A. It's identified as stabilizer.

Q. And it's not the solvent in this formulation, correct?

A. It's identified as a stabilizer.

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Q. My question is it is not the solvent in this formulation? Is that right or is that not right?

A. Water is identified as the solvent in the formulation.

Q. And water is the only solvent in this formulation; is that right?

A. Water is what is identified as the solvent in the formulation.

Q. Let's take a look at another one of your memos, DTX-- I believe the next one would be -- let me back up. I want to stay on this one.

This particular memo does not have any stability data for the formulation in it, correct?

A. If -- can you show me the whole screenshot of this.

Q. Yes. Can we pull up that whole page, DTX 737, page 2.

A. Okay. So this document does not have stability data associated with it. It's a recipe that was provided to the manufacturing group so that they could formulate the material. It's not -- it's not our common practice and has never been our common practice to include stability data with a recipe.

Q. My question is simple. In this document there's no stability data, no turbidity data, no native conformation data; is that right?

A. That's correct.

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Q. Let's go to DTX 736. And we have another one of your memos. Can you confirm for me on page 3 that you, in fact, signed and dated this document April 21st, 2006; is that right?

A. Well, I see that on page 1 of 2 I signed it.

Q. And that is on page 3 of the exhibit; is that correct?

A. Oh. I'm sorry. I didn't understand what you were meaning by page 3.

Q. At the bottom you should see DTX 736.0003 of the exhibit.

A. Yes, I do.

Q. And under the heading "Formulation," you see this formulation contains phosphate, NaCl, polysorbate 20, and 40 mg/mL VEGF Trap, correct?

A. Yes.

Q. And we see similar cautionary statements in this memo as well for the formulation; is that correct?

A. That is correct.

Q. The time that the drug product is held or stored at 25 degrees C should be kept to a minimum, correct?

A. During the manufacturing process, yes.

Q. And temperatures above 25 degrees C must be avoided, correct?

A. Yes.

Q. And the drug product should be held or stored at 2 to

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8 degrees C, correct?

A. That's correct.

Q. And like the prior memo, there's no stability, turbidity, or native conformation data in this particular memo; is that right?

A. No. It's a recipe.

Q. Can we go to the formulation table at the second half of this page. And here again, water for injection, or WFI, is identified as the solvent; is that right?

A. That is correct.

Q. And polysorbate 20 is identified as the stabilizer, correct?

A. Yes.

Q. Now, let's look at DTX 725 and look at the lead formulation. And I want to focus in this exhibit first on the email on page 1 which is dated May 8th, 2006, from Dr. Furfine to you.

Do you see that?

It's in the middle of the page.

A. Yes, I do.

Q. And you see Dr. Furfine addresses you. He says, "Ken, can you provide to Ellen the two formulations that we are moving into the tox study." Correct?

A. Yes.

Q. And then you then responded in the email above this

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and you provided two formulations; is that right?

A. Yes, it is.

Q. And the formulation above is entitled the lead formulation; is that right?

A. It is.

Q. That formulation contains phosphate, NaCl, polysorbate 20, and sucrose, and 5 to 4 mg/mL VEGF Trap; is that right?

A. That is what's written on the page, yes.

Q. And then there's a backup formulation as well, correct?

A. Yes.

Q. Now, this email that you forwarded with the lead and the backup formulation, you didn't provide any tox study information in the email, correct?

A. No, I did not provide any tox study information.

Q. And that's because, as of the date of this email, May 8, 2006, these are the formulations, the lead and the backup, that were going to be moved into the tox study; is that right?

A. So as of May 2006, I'm not sure if -- which tox study this is referring to. There were a number of tox studies. Looking at this and knowing Ellen's function, she's pharmacokinetics; so she does PK studies. So she would be looking at a range of these things possibly for an ongoing tox

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study. So I'm not sure what you're referring to.

Can you be more specific?

Q. Well, we can look at Dr. Furfine's email again in the middle of the page. Dr. Furfine asked you to send her the formulations --

A. Yeah.

Q. -- that you were moving into the tox study, correct?

A. Okay.

Q. All right. Let's look -- you mentioned the BLA. You worked on and drafted parts of that, right?

A. Yes.

Q. Excuse me. The Eylea BLA, correct?

A. Yes.

Q. Let's pull up PTX 1519 and go to page 5. And this is already in evidence. And here we see the description composition of the drug product from the Eylea BLA, correct?

A. That is correct.

Q. And at Table 1 again we see polysorbate 20 identified as a, quote, stabilizer agent, end quote, correct?

A. Yes. It's identified as a stabilizer agent in Table 1 and I think maybe another table or two in the document. But in the pharmaceutical development section, it was described as a cosolvent.

Q. We're going to get to the -- I promise you we'll get to the pharmaceutical development section next.

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Very quickly, though, the function here on Table 1 in the Eylea BLA is identified as stabilizing agent, correct?

A. Yes.

Q. And the BLA does not identify polysorbate 20 here in PTX 1519 as a solvent, correct?

A. Could you say that again, please.

Q. The Table 1 of the Eylea BLA here in PTX 1519 does not identify polysorbate 20 as a solvent, correct?

A. That is correct. It's not identified as a solvent.

Q. And that's because polysorbate 20 has never been considered to be a solvent, correct?

A. For our purposes, we've always used it as a cosolvent or stabilizing agent.

Q. Let's pull up your deposition. You recall being deposed in this case, correct?

A. Yes, I do.

Q. And you understand you were under oath during that deposition, correct?

A. Yes, I was.

Q. And you swore to tell the truth?

A. I did.

Q. We're going to pull it up on screen, but it's also in your binder, Dr. Graham, DTX 5103. And the exhibit is page 46 of the transcript. We're going to look at transcript page 179, lines 19 to 25.

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A. Can you give me the DTX number again, please.
Q. Yes. DTX 5103.
A. Okay.
Q. At page 46. And I also have it on screen for you.
Were you asked this question; did you give this answer?
"Q So I guess I'm not understanding why Regeneron listed here in its BLA document, Exhibit 738, that the function of polysorbate 20 is stabilizing agent and not solvent like water for injection. Can you explain this?
"A Well, polysorbate 20 has never been considered to be a solvent."
Was that the question you were asked and the answer you gave?
A. Yes, they are.
Q. And that's a true answer, correct?
A. Yes.
Q. Now, I think you mentioned -- and I don't need to go through it again, but there are other places in the BLA that identify polysorbate 20 as a stabilizing agent, correct?
A. Yes.
Q. Well, let's pull up the pharmaceutical development portion that you drafted, which I believe you testified was at PTX 672.

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You recall that?

A. Yes.

Q. Now, you mentioned a portion of this document where you called polysorbate 20 a cosolvent. I'd like to look at a different portion of the same document you drafted. And let's go to page 108 of PTX 672. And I'm going to look at Table 63, I believe. You see Table 63, the document you drafted, is entitled "Role of excipients in the IVT2 VEGF Trap-Eye formulation," correct?

A. Yes.

Q. And we see polysorbate 20, excipient, the reason for addition is identified as "stabilizing agent," correct?

A. That's correct.

Q. And it goes on to describe it as "increases stability when agitated or subjected to freeze/thaw stress," correct?

A. That is correct, yes.

Q. I'd like to switch gears briefly and talk about one of the other excipients you mentioned, which are buffers. Your '865 patent only uses a phosphate buffer; is that right?

A. It describes a pH range. And the pH range tells anybody that works in this field that there are a series of compounds that you can use as a buffer.

Q. But it doesn't mention any other buffers by name beyond phosphate, correct?

A. The phosphate is mentioned as -- by name as an

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example of a buffer.

Q. And matter of fact, you recall your counsel showed you all those examples on the screen from your patent.

You remember that?

A. Yes.

Q. And they all used a phosphate buffer, correct?

A. All the examples used a phosphate buffer, yes.

Q. Now, in fact, you don't recall using a histidine buffer to develop an intravitreal formulation of VEGF Trap prior to the filing of your '865 patent application in 2006, correct?

A. I don't believe that we did, no.

Q. In fact, your boss, who is Dr. Dan Dix; is that correct?

A. Yes, my boss was Dan Dix.

Q. I think you know where I'm going here. Dr. Dan Dix had Dr. Dan Dix nevers, right?

A. Yes, he did.

Q. And one his nevers was -- Dan Dix nevers, I believe you said, things that you would never do, according to Dr. Dix, is that you would never have a liquid formulation with a histidine buffer; is that correct?

A. So Dan is quite a character. Unfortunately, he's suffering from Parkinson's right now, but he had a list of nevers. And one of the list of nevers he had is you would

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never use histidine in a liquid formulation. It was his preference. He had lots of preconceived notions around things.

You know, I personally have used histidine buffer in other formulations. And, actually, with one of the products I developed subsequent to Eylea actually completely got rid of all the Dan Dix nevers in one fell swoop with one approved product. So he has those.

Q. Let's talk about Dan Dix nevers for aflibercept, not other formulations.

A. Well, Dan Dix's nevers were for formulations, period. They were not specifically for aflibercept.

Q. And you never used histidine with aflibercept, correct?

A. I have used histidine with aflibercept.

Q. I believe you just told me that you never used histidine to develop an aflibercept formulation prior to the filing of your patent application.

A. Okay. You said prior to the filing of the patent application. You just said I never used.

Q. And that's correct?

A. So the question is what time frame are you talking about?

Q. Prior to your patent, you never used histidine to develop an aflibercept formulation, correct?

A. If you're going with prior to the patent validation,

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no, I did not. After it, I did.

Q. And none of your patent examples, again, use a histidine buffer?

A. That's there in black and white. Yes, that's correct.

Q. All right. I'd like to talk about some of the stability study documents, or SS documents, that you testified. Do you recall that? We saw quite a few of them.

A. Yes.

Q. Before we do that, I'd like to pull up DTX 900, pages 36 and 37, and I want to look at and show you a Regeneron discovery response and ask you a couple questions about it if I could, sir.

A. All right. Hang on a second. Let me --

Q. And we're going to put this on screen to make it easy.

A. Well, the challenge is the screen is just a little bit too far for the glasses, and this is a little bit too close; so if I can get to the written document, I think I'll be a little bit better.

Q. At the bottom of page 36, you'll see Interrogatory 10. And in the middle of page 37, you'll see a response with respect to your '865 patent.

A. And you said bottom of which page?

Q. Bottom of page 36 is Interrogatory 10.

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A. Okay.

Q. You see Interrogatory 10 asks, "For each claim of each of the initial patents, identify (a) the date that the claimed subject matter was first conceived and the date it was reduced to practice, and (b) the diligence leading to such reduction to practice, and for each such date and diligence, identify with particularity the documentary evidence supporting that date or diligence and at least three persons with any knowledge relating to that date or diligence."

You see that?

A. I see those words on the page, yes, I do.

Q. And the response in the middle of page 37 on your '865 patent says, "With respect to U.S. Patent Number 11,084,865" -- that's your patent, correct?

A. Yes.

Q. It goes on to say, "The inventors concede the inventions in the asserted claims of the '865 patent no later than March 21st, 2006, the date on which samples from Stability Study 207 were analyzed after two months' incubation."

Do you see that?

A. Yes, I do.

Q. It cites one page for the record, RGN-EYLEA-MYLAN-00475679. Do you see that?

A. Yes, I do.

Q. Have you seen this response before?

A. No, I have not.

Q. It doesn't identify you as a person to have any knowledge of the date of conception or reduction to practice, correct?

A. I don't see my name on the page, but this is getting into the realm of legal things. And if I'm not an expert on intravitreal injections after seeing my mother receive over 90 some-odd injections, I can't possibly be an expert on something that's a legal document without a law degree, I don't think.

Q. My question is much simpler.

You're not identified as a witness with knowledge in this response, correct?

A. I don't see my name there.

Q. It identifies one page in Stability Study 207, correct?

A. I see that it identifies the page. I'm not sure what's on the page, but --

Q. And it does not identify all the other stability studies you testified about, like the 065 study, the 203 study, the 205 study. Those aren't mentioned here, correct?

A. No, I don't see them.

Q. As a matter of fact, you testified about more than one page today, right? I saw dozens of documents you testified about.

A. Yeah.

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Q. All right. Let's look at one of those. Let's start with PTX 1825. And you recall this document, right?

This is the 207 study document.

A. Yes.

Q. Are you okay for short if I just go by the number, the 207 study?

A. I think we can handle that.

Q. All right. So I want to start with the first page. For the 207 study, we see Amendment 7.0 dated November 8, 2010; is that right?

A. That is correct.

Q. Now, you know Michelle Looyenga, correct?

A. Michelle? What was the last name?

Q. Looyenga, L-O-O-Y-E-N-G-A.

A. Okay. It's Looyenga.

Q. Looyenga?

A. I'm sorry. The Loo threw me.

Q. My apologies. Looyenga. Did Michelle Looyenga help make the invention in your '865 patent?

A. So Michelle was one of the members of the technical staff that we had. She did help with study analysis. I think she probably helped label some of the samples and things that were put up.

Q. So did she help invent the formulation?

A. I would say no, she did not.

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Q. Let's take a look at one of her lab notebooks. And then we'll jump back to 1825. But for a moment, let's jump to PTX 2304.

And you see this is a Michelle Looyenga lab notebook, correct?

THE COURT: Counsel, could I ask you to spell Ms. Looyenga's last name for our record, please.

MR. RAKOCZY: Michelle, last name L-O-O-Y-E-N-G-A, Looyenga.

THE COURT: Thank you. My apologies if I'm mispronouncing that.

MR. RAKOCZY: No worries.

BY MR. RAKOCZY:

Q. And you see this is a lab notebook from Ms. Looyenga dated March 9th, 2006, correct?

A. I do.

Q. Let's go to page 32 of PTX 2304. And here we see at the top this is the protocol for the 207 study, correct?

A. Okay. You're on page what number?

Q. 32.

A. Okay. I'm trying.

Okay. So 32.

Q. I just want to confirm this is the 207 stability protocol at the top, correct?

A. Okay. By page 32, you don't mean laboratory notebook

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page 32.

Q. No. I'm sorry, sir. I will always try to refer to the exhibit number.

A. I'm sorry. I'm looking at the lab notebook, and I'm going why are we talking about IV mixtures?

Q. If you look at the bottom, you see PTX 2304.0032?

A. Yes. 0032. All right. I'm getting there.

Q. Are you with me?

A. I am working on it. If my fingers would work. I'm sorry.

Okay. I see 0032, yes.

Q. You see the protocol for the 207 study at the top on the left, correct?

A. I do.

Q. And let's go to the bottom and look at the signatures. And you see this was signed by Ms. Looyenga March 3rd, 2006, correct?

A. So the laboratory notebook was signed by Michelle on March 3rd, 2006. The protocol itself is not signed, however.

Q. And then it was witnessed August 22nd, 2006, correct?

A. Yeah, by Gareth Walsh, it looks like.

Q. Now, I want to jump back. And I'm sorry to put you through that. Let's toggle back to PTX 1825. That's the very large 207 document in your binder that you testified about. Let's go to page 85.

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And you see here we have the purpose of the 207 study, correct?

A. And you said this is on page 85?

Q. Page 85 of PTX 1825, also on your screen.

A. Yes.

Q. And you see the purpose at the top is, "Determine the stability of 40 mg/mL VEGF Trap in the polysorbate 20-based intravitreal formulation when packaged in a prefilled syringe with six different component combinations," correct?

A. Yep.

Q. Now, the test article was the prefilled syringe, and the vial was the control in this study, correct?

A. So it goes on to say the stability of VEGF Trap, when filled in grass vials, will serve as a control for the study. So we were performing multiple pieces of work in one study. One, we had the formulations. We wanted to see how they perform in the vial.

The other thing is we were tasked with developing a prefilled syringe and had to contract to somebody to fill a prefilled syringe. Studies are a lot of work. So in one study we have six syringes, one vial. Yes, we called the vial as a control for the prefilled syringes because we expected, if anything, the prefilled syringes would perform worse than the vial.

Q. You understand the asserted claims in this case are

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all to a vial, right?

A. Yes.

Q. And so in this test, the 207 test, just so the record's clear, the test article was the syringe and the control was the vial, correct?

A. Yeah. The control for the syringe was the vial, yes.

Q. All right. Let's go to page 92 of the same document. I just want to look at the signature at the bottom. It looks like your boss Dan Dix signed this February 3rd, 2006, correct?

A. He signed it for the second time, yes.

Q. And this protocol was amended numerous times; is that right?

A. Over the course of three years, yes, it was amended a number of times. This, I think, if I look back at it, we identified that there were a number of minor changes that needed to be -- or the lead technician on the study felt needed to be corrected.

One of them was we put up 39 vials instead of 42 that we planned. So she initialed and dated the corrections on the 17th of January when she realized she was short items, signed it. I signed it very shortly thereafter, and then Dan signed off on the changes as well.

Q. Let's go to page 103. I just want to get the dates of some of these amendments.

On page 103 we have Amendment 4.0 dated August 21st,

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2008, correct?

A. Which page number are you on?

Q. We're on page 103, on your screen as well.

A. Okay.

Q. And that amendment is dated August 21st, 2008, correct?

A. That's the number in the upper left hand -- or right-hand corner, yes.

Q. And the first amendment -- I'm sorry -- the latest amendment, it's on the first page of the exhibit, page 1. And that was Amendment 7.0 all the way up to November 8, 2010, correct?

A. Yes.

Q. Now, let's go to page 137 and look at some of the data. On 137 at the top you see we have analysis of VEGF Trap by visual inspection, correct?

A. Hang on.

Yes.

Q. And if we look under vial under 5 degrees C, we can see at .5 months the technician wrote filamentous particle and one small particle, correct?

A. That is correct.

Q. Particles are not good, right?

A. Well -- so in this case, these were hand-filled vials in our lab. And we were used to getting extraneous particles

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from filaments and fibers. And we had a scoring system that allowed a certain number of particles to be present.

This is totally different than GNP product, which is produced in a clean room in an environment that ensures no particles from dust and whatever else is floating around in your lab that's in there.

Q. I just asked if particles are bad. And I recall you testifying --

A. Particles are bad.

Q. Particles are "kind of a serious thing" and "very bad."

That's what you said, right?

A. That's true.

Q. And there are particles in this formulation, correct?

A. Yes.

Q. Let's look at another one. Let's go to page 142 of the same exhibit at the top. And we see some more visual inspection data. You see that?

A. Uh-huh.

Q. And for 5 degrees C. And here we see in several places the technician noted small particle, filamentous particle, small particles, particles, correct?

A. Yes.

Q. Particles all over the place. That's very bad, correct?

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A. Well, so -- let's see. This is 2007. You're looking at Syringe Number 1, Syringe Number 2, Syringe Number 3, and Syringe Number 5, if I have the right page, 142. So this is syringes, and this isn't the vial.

Q. So this doesn't count? The syringe data doesn't count?

A. Well, you know, we're talking about a vial in the patent. One of the things that is a concern, when you move a formulation from a vial into a prefilled syringe, is you encounter a lot of different materials that are not in the vial. So syringes have silicone oil either sprayed or baked on the inside of them. Some syringes -- well, glass syringes have tungsten, and tungsten can cause proteins to precipitate. So it's kind of two different environments.

Q. I just want to get it straight.

You took us through a dozen studies showing us prefilled syringe data. And so I'm looking at prefilled syringe data that's got particles all over the place. And you're saying that's not relevant to the stability of the vial?

A. A vial is a very different environment.

Q. So all that syringe data we looked at would not be relevant to the stability of the vial, correct?

A. I would assess my stability with things in the vial. If it's unstable in a syringe, doesn't mean it's unstable in a vial. They're different beasts.

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Q. All right. Let's go to page 14 of this same exhibit and look at some additional data.

And the first thing I want to note on this page, here we have the 207 study data for 5 degrees C. And it's dated -- can you tell me, what's that date at the top?

A. Which page are you on?

Q. We're on page 14 of PTX 1825.

A. Okay. So on the screen here, if I'm seeing it right, it looks like the 28th of August 2008.

Q. August 28th, 2008, at the top, correct?

A. Yes.

Q. Now, there are no dates in this table on when exactly the testing was conducted, correct? At least none that I can see.

A. So that would be captured at the end with the sequence information.

Q. We'll get there. But on this table right here, this doesn't say when this testing was conducted?

A. No. I don't see it on the table at all, no.

Q. And I see a syringe column but not a vial column, correct?

A. Yes. So the reason why you see a syringe column -- everything had a syringe column, but that's Device Number 1.

Q. I'm just asking do I see a syringe column and not a vial column. That's all I'm asking. Your counsel can ask away

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whatever else he wants.

A. Okay. Well, you see a syringe column, and it's Device Number 1, which was a syringe.

Q. All right. Let's go to page 68 of the same document.

And here we see analysis of VEGF Trap by OD at 405 nanometers, correct?

A. That is correct.

Q. So I'll call this OD405 data for short. And at two months, you see the data that's been highlighted?

A. Uh-huh.

Q. And all this data, it ranges from .047 through about .0 -- 0.053, correct?

A. That is correct.

Q. And it's all been crossed out and rewritten, correct?

A. Yeah. It looks like there were two entries there.

Q. Now, let's jump to page 111 of this same document -- and let me back up.

You said that the way this document is compiled, this is the way that it was kept in the normal course of business?

A. So this is a file. It is called a study folder. It collected all the loose paper from the stability study. And things went in. Sometimes things went in in the middle; sometimes things went in the end.

Q. Because it kind of looks like a dog's breakfast, like someone threw everything in the air and then just recompiled

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it?

A. Well, I wouldn't say that they threw it in the air. It was like, I'm stuffing it in, I've got it, I'm stuffing it in, I've got it. You know, that's kind of the way it was done.

Q. All right.

A. Is it a good way to do it? Well, we have better ways now, but --

Q. Let's jump to page 111 of the same exhibit, PTX 1825. And here we see Amendment 5.0 --

A. Yeah.

Q. -- to the 207 study dated August 19th, 2008, correct?

A. That is correct.

Q. And I'd like to look at the second paragraph. And you see it states that, "Variability between HPLC systems and HPLC column lots over time may cause variability in purity results between samples run at discrete points in time."

Do you see that?

A. Yes, I do.

Q. And the next sentence continues that "This may impact the ability to confidently identify trends in data which have been processed on different systems and across a wide spectrum of time," correct?

A. That is correct.

Q. All right. I'd like to switch gears if I could.

You testified about your provisional application. Do

you recall that?

A. Yes.

Q. I want to look at just a couple quick things hopefully. Let's go to PTX 3249. I believe it's already in evidence. And this is your provisional application you were looking at during your direct testimony. And I'd like to go to page 11.

THE COURT: I'm sorry, Counsel. What page was that again?

MR. RAKOCZY: PTX 3249 at page 11.

THE COURT: Thank you.

THE WITNESS: Looks like you're having trouble with this too.

BY MR. RAKOCZY:

Q. I'd like to focus on paragraph 8 starting the third line. You see it describes an ophthalmic formulation.

Do you see that?

A. You're on which page?

Q. I'm on page 11.

A. Yeah.

Q. Paragraph 8. And the third line down describes an ophthalmic formulation comprises about 40 to 50 mg/mL of the VEGF antagonist Sequence ID Number 4.

Do you see that?

A. Yes, I do.

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Q. So that's disclosing a range of concentrations, 40 to 50 mg/mL, correct?

A. It lists a range of 40 to 50 mg/mL, yes.

Q. It's not describing 40 mg/mL, correct?

A. It's listing a range. What that plays out in the patent, I'm not an attorney; so I'm not going to try and interpret that one.

Q. Well, my question is simple. This formulation is describing a range, 40 to 50 mg/mL?

A. Yes.

Q. Not 40 mg/mL, correct?

A. That is what I see on the page. There's a range of 40 to 50 mg/mL.

Q. Now, let's look down on the same page, the next line. You see it describes a range of "0.01 to 3 percent polysorbate."

Do you see that?

A. Yes, I do.

Q. So that is not 0.03 percent polysorbate 20, correct?

A. It is a range that encompasses 0.03 percent polysorbate.

Q. So that range covers 0.03 percent. Is that what you're saying?

A. No. All I'm saying is, mathematically, 0.03 percent falls in between 0.01 and point -- and -- not .3 -- and

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3 percent. Interpreting the claim would be something that an attorney would need to do.

Q. Under that rationale, 40 mg/mL falls within 40 to 50 mg/mL aflibercept, correct?

A. Mathematically, yes, it does.

Q. Now, this range on screen, 0.01 to 3 percent polysorbate, is different from a range of 0.03 to .1 percent polysorbate 20; is that right?

A. Okay. Say that again.

Q. The range on screen, 0.01 to 3 percent polysorbate, is different from 0.03 to .1 percent polysorbate 20; is that right?

A. The ranges that are described -- in that case, the ranges are different.

Q. Now, let's go take a quick look at paragraphs 11 and 12. And these, unfortunately, bridge pages 11 and 12 of the same exhibit.

And do you see here it discloses 0.03 percent polysorbate; is that right?

A. It says 0.03 percent polysorbate, yes.

Q. And that is different from a range of 0.03 to 0.1 percent polysorbate; is that right?

A. If you're asking me within the context of the patent, that's something I would need an attorney to answer.

Q. I'm just asking about the number. The number

0.03 percent polysorbate is not 0.03 to 0.1; is that right?

A. Well, all right. If I'm not talking about a patent and I'm talking about math --

THE COURT: He's just asking about the specific document, Doctor.

THE WITNESS: About the specific document?

If this is about the document, this is a patent; so I don't feel that I'm the appropriate person to answer that.

BY MR. RAKOCZY:

Q. So you're not qualified to opine or testify about patents, correct?

A. I can tell you about my invention. I can tell you about the work that I've done. If -- and you're looking at what I believe are claims within the patent or a summary of the invention. By the time you're getting down to the very specific meaning, you know, is 0.03 to 1 the same as 0.03, I'm getting to the point where I'm sorry, I'm not an attorney.

Q. So when you were -- I'm sorry, sir.

When you were comparing with your counsel the text in the provisional application compared to your '865 application, you weren't interpreting any of that; you were just telling us whether the words were the same or not. Is that right?

A. So I was looking to see if there was drift or change in the words. I was looking to see if the data was correct. And as near as I could tell, when I laid the documents down

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beside one another and looked at them, the words were the same.

Q. But you weren't interpreting those words, correct?

A. I was looking to see if the words were the same.

Q. All right. Let's jump back to some of your stability studies. And I want to start with the 205 study which is at PTX 2265. And it's on screen.

Do you see that?

A. Okay. Yes.

Q. And the 205 study, I want to look at the formulation. And this formulation in the 205 study was phosphate, NaCl, polysorbate 20, and 40 mg/mL of VEGF Trap, correct?

A. Phosphate, NaCl, polysorbate 20, and 40 mg/mL VEGF Trap, yes.

Q. Now, there's no sucrose in this formulation, correct?

A. That is correct.

Q. There's no sugar or sugar alcohol stabilizer in this formulation, correct?

A. There is not.

Q. You're aware all asserted claims require a sugar stabilizer?

A. I'm not sure that that is the case. I don't know.

Q. You don't know whether the asserted claims require a stabilizer?

A. So that would be a question for my lawyer.

Q. Okay. Did you look at the asserted claims in

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preparation for your testimony today?

A. I read through them, yes.

Q. Did you ask anybody what the asserted claims were?

A. Actually, I don't recall specifically asking to go through the details of the asserted claims.

Q. All right. Let's look at another study. I want to very briefly touch on the 065 study.

If we could pull up PTX 3266. That may be the wrong exhibit. No, there it is.

I just want to confirm. In the 065 study, all the formulations were 50 mg/mL concentration of aflibercept; is that right?

A. That is my recollection, yes.

Q. And I think you testified earlier you understood that all the asserted claims are to 40 mg/mL aflibercept, correct?

A. I believe that I may have made a statement to that effect, yes.

Q. So I just want to be clear, then. We can consider the 40 and the 50 mg/mL concentrations equivalent in your view?

A. No. They're different.

Q. They're different. Okay.

All right. I'd like to pull up one of your slide decks, which is PTX 3314. It should be in your binder. We'll pull it up on screen as well. You see this is entitled "ITV Review and Summary," correct?

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A. Yes.

Q. And this was attached to an email at PTX 3313 from Jennifer Carrier dated March 14th, 2006. So we'll pull that up and confirm it.

If we could please see PTX 3313.

And you see the email at the top dated March 14th, 2006, from Jennifer Carrier. Do you see that?

A. Yes, I do.

Q. And she's attaching an ITV review and summary, March 14th, 2006, laptop presentation, correct?

A. Yes.

Q. All right. Let's jump back to the presentation. I want to go to page 7. And here we see at the top the title of the slide is "VEGF Trap ITV, the next steps," correct?

Do you see that?

A. Yes.

Q. And the first step or the first bullet is "a more stable ITV formulation was and is desired," correct?

A. Yes.

Q. And it says "because due to demonstration of instability to vortex in various syringe stresses," correct?

A. Yes.

Q. And then let's look at the next page, 8. Here you say that you're going to use stability analysis tools to identify superior formulations, correct?

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Do you see that?

A. Okay. I see two assays. I guess, yes, that is the meaning of what is on the page, yes.

Q. Now, I want to very briefly jump to page 22 of your presentation. And here we have some data at 5 degrees C.

Do you see that?

A. I'm working on it.

Okay. 5 degrees C, yes.

Q. And you see in the left-hand column you have the formulations, right?

A. Yes.

Q. And the F2 formulation is the 40 mg/mL VEGF Trap containing 0.03 percent polysorbate 20, correct?

A. So yes. It contains -- it's listed as having those components, yes.

Q. And then for the length of stress at 5 degrees C, we have one month and five month, correct?

A. Yes.

Q. And at one month, the native VEGF Trap was less than 98 percent, correct?

A. So at one month, the native VEGF Trap was 97.9. But I'm not sure what the full composition of this formulation is based on what I'm seeing here. I know it's from Stability Study 191, which I would need that detail to know the actual composition.

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Q. I'm just asking if Formulation 2 at the one month was below 98 percent VEGF Trap native. Correct?

A. It was. It started out below 98 percent.

Q. All right. Let's jump to PTX 3312. And I think you testified about this document, correct, the update on ITV syringe stability studies?

A. 3312?

Q. Yes.

A. No. I think I testified about a different document, but this might have been in my deposition.

Q. This is yours as well, correct? It's entitled "Update on ITV Syringe Stability Studies"?

A. It's mine and Dan's, yes.

Q. By Dr. Dix and yourself, dated March --

A. That is correct.

Q. I'm sorry. I'll start over.

This is one of your presentations along with Dr. Dix dated March 16th, 2006; is that right?

A. Yes, it is.

Q. Let's go to page 2 of your presentation. And here it says that "studies ongoing, examining the stability of the following formulations," correct?

A. That is correct.

Q. And at the bottom we see two of the formulations where the studies were ongoing are Formulations 8 and 9?

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A. Yes.

Q. And both of those are the 40 mg/mL which contains 0.03 percent polysorbate; is that right?

A. That is correct.

Q. Now, let's go to page 27 of this same exhibit. And am I correct? Does it say that the VEGF Trap in the oncology formulation is threefold more stable than the current ITV formulation? Is that right?

A. Which page are you on?

Q. On page 27.

A. Okay. I'm going to lose my mind because I keep looking at the document page and not your page number. I apologize.

Q. They're the same on this one. Slide 27 is page 27.

A. Yeah, it is. That's pretty good. I'm going wow.

So you said the oncology formulation is approximately threefold more stable than the current ITV?

Q. Yes. Is that right?

A. That's a fair statement, yes.

Q. All right. Just a couple more, Dr. Graham.

I'd like to go to PTX 3327. And I believe I was mistaken before, but I believe you did testify about this slide deck entitled "Travels through two stability-indicating assays," correct?

A. Yes, I did.

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Q. And I believe you said this was dated in March or April of 2006, correct?

A. I've seen enough dates right now, I'll take the record's word for that. But yes.

Q. I'd like to go to page -- sorry. Let's go to page 46 and look at formulations listed here.

A. Page 46?

Q. Yes.

A. At least I only have one set of page numbers this time.

Q. Are you there?

A. I am.

Q. And this one you see has total number of particles 500 nanometers or larger in 1 mL formulation; is that right?

A. That is correct.

Q. And if we look near the bottom, Formulations 8 and 9 are both 40 mg/mL concentration and they both contain 0.03 percent polysorbate.

Do you see that?

A. Yes.

Q. And unstressed, each of these particles -- strike that. Let me back up.

I apologize, Your Honor. It's getting late.

Unstressed, each of these formulations had over 60,000 particles 500 nanometers or larger, correct?

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A. Yes, they did.
Q. Particles are very serious and very bad, correct?
A. They are serious and bad, yes.
Q. And when stressed, they each contained over 300,000 particles, correct?
A. Yes. They increased, yes.
Q. I apologize. I forgot to ask about one other study, and then I promise you we're going to leave the studies.
Let's jump to PTX 1860, different exhibit.
And this is the 203 study. You remember mentioning that, correct? And I want to jump to page 130 and look at the formulation.
A. So the exhibit is?
THE COURT: You said 1860, Counsel?
THE WITNESS: I don't see that.
BY MR. RAKOCZY:
Q. PTX 1860. Oh, it's in your original binder. I apologize.
THE COURT: The other book, Doctor.
THE WITNESS: Thank you.
BY MR. RAKOCZY:
Q. I want to go to PTX 1860, page 130. And I just want to confirm the test article formulation.
A. 130.
Q. Do you see it?

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A. Okay. So --

Q. I'm looking at the test article on page 130. It's on screen.

A. So you're saying the document is PTX and the page is 0130?

Q. I believe it's page 130 of PTX 1860. It's on screen as well.

A. All right. Now I'm really confused. You said it was the other notebook. Oh, you mean not this other notebook; the other notebook.

THE COURT: Yes, Doctor. Yes.

THE WITNESS: Don't give me more than two notebooks at a time or I'm in trouble. Okay. And you are on page 130?

BY MR. RAKOCZY:

Q. Yes. And I want to confirm that the test article in this study did not contain sucrose or another sugar stabilizer; is that right?

A. Let me get to 130.

So ask your question. I'm there.

Q. I just want to confirm the test article -- and we have it on screen -- did not contain sucrose or another sugar stabilizer; is that correct?

A. There is no sucrose in the formulation.

Q. Now, you testified quite a bit today about the 40 mg/mL aflibercept concentration formulations, correct?

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A. Yes.

MR. RAKOCZY: I have a couple more exhibits, Your Honor. May I approach?

THE COURT: You may.

BY MR. RAKOCZY:

Q. I'm going to give you two more exhibits, Dr. Graham.

A. Thank you.

Q. All right, Dr. Graham. Let's start with the first one, DTX 4121. We're going to pull it up on screen as well.

Do you see this is United States Patent Application Publication Number U.S. 2006/0217311.

Do you see that?

A. I do.

Q. It's entitled "VEGF Antagonist Formulation."

Do you see that?

A. Yes.

Q. And the inventors are two of your colleagues, Dr. Dix and Dr. Frye, correct?

A. That is correct.

Q. And do you see the file date in the middle of the page, filed March 22nd, 2006, correct?

A. Yes, I do.

Q. And I want to look below that to the column where the heading "Related U.S. Application Data" -- date -- or data. I'm sorry. It's at the top right hand of the page. My fault.

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Do you see in the right "Related U.S. Application Data," correct?

A. Yes.

Q. And it says, "Provisional Application Number 60/665,125 filed on March 25th, 2005," correct?

THE COURT: Yes, Counsel?

MR. TRASK: Your Honor, objection. This is outside the scope of the direct examination. This is a document that was never shown to the doctor during his direct examination. And, in fact, it's a document that defendants didn't rely on at this point.

MR. RAKOCZY: Your Honor, he testified repeatedly about the 40 mg/mL concentration. This is a U.S. patent publication disclosing 40 mg/mL concentration that I'd like to address with the witness.

THE COURT: Overruled.

BY MR. RAKOCZY:

Q. Let's turn to exhibit page 3, paragraph 17. And I want to go to the ninth line down. And you see in the middle here the document describes "A 40 mg/mL prelyophilized solution."

Do you see that?

A. So you're on page 3?

Q. Paragraph 17.

A. And a 40 mg/mL prelyophilized solution. Yes, I see

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that.

Q. Now let's look at paragraph 36 on page --

A. So --

Q. -- 5.

A. -- you know, a prelyophilized solution is not a formulation.

Q. Sir, I was just asking whether it disclose a 40 mg/mL concentration in a prelyophilized --

A. It is a prelyophilized solution, but that's never designed to be a -- I'm sorry. I'm looking at the science. And I don't understand how a lyophilized solution or prelyophilized solution matches up with a liquid formulation at the same concentration. It's two different things.

Q. Sir, I'm just asking did your boss Dr. Dan Dix disclose a "40 mg/mL prelyophilized solution" in that paragraph?

A. That is what's in there, yes.

Q. So let's go to paragraph 36, which is on page 5. I want to look at the last sentence. And here you see Dr. Dix describes, "An example of a pharmaceutically acceptable liquid formulation comprises a VEGF-specific fusion protein antagonist in a pharmaceutically effective amount of buffer, a cosolvent, and one or more stabilizers."

Do you see that?

A. Yes. That's what's written on the page.

Q. Now, I want to compare this to the provisional application which is the second document I handed you, which is DTX 8149.

I'm sorry. I misspoke.

This document, the provisional, is DTX 8194. It's the second --

A. I think we had you. Even with the dyslexia, it was good. That one, I followed.

Q. All right. And do you see in the right-hand upper corner we have a stamp? You see that? You see the stamp says "Application 60/665,125."

Do you see that in the upper right-hand corner?

A. Yes. That's what it looks like.

Q. Now, let's go to page 10 of this document, page 34 -- paragraph 34. I'm sorry. Here we see that same heading. You see stable liquid formulations, correct?

A. So page 10?

Q. Paragraph 34. We have a paragraph entitled "Stable Liquid Formulations," right?

A. All right. I'm doing it to myself again, following the document pages, not the exhibit pages. Went too far.

Okay. Paragraph 34.

Q. And you see this -- we see the same sentence, the last sentence, starting, "An example of a pharmaceutically acceptable liquid formulation comprises a VEGF-specific fusion

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protein antagonist in a pharmaceutically effective amount, a buffer, a cosolvent, and one or more stabilizers," correct?

A. So you're saying the last sentence, correct?

Q. Yes.

A. Yes, that's what it says.

Q. I want to jump to the claims very quickly on page 12.

And can you confirm for me Claim 7 is directed to a stable liquid formulation of Claim 1 comprising 1- to 10-millimolar phosphate buffer, 1- to 10-millimolar citrate, 25- to 150-millimolar NaCl, 5 to 30 percent sucrose, 10 to 50 mg/mL of a fusion protein, at a pH of about 6 to 6.5; is that right?

A. This is Claim 7?

Q. Yes.

A. Yes, that's what's written on the page.

Q. Just a couple more quick questions, sir.

Let's go back to page 8 of the same exhibit, DTX 8194 -- I'm sorry -- page 5. I'm doing it as well.

Page 5, paragraph 8, of DTX 8194.

A. Doesn't that mean it's time to quit?

THE COURT: It's airborne contagious.

BY MR. RAKOCZY:

Q. Okay. I promise.

A. So you're going with paragraph 8?

Q. Yes.

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A. Okay.

Q. And here at paragraph 8 we see a prelyophilization formulation of the invention.

Do you see that?

A. Yes.

Q. And then it also at the end of the paragraph says the polysorbate may also be present, for example, as polysorbate 20, correct?

A. Yes.

MR. RAKOCZY: Can you give me one moment, Your Honor?

THE COURT: Certainly.

BY MR. RAKOCZY:

Q. A couple more quick items, Dr. Graham.

Let's go back to the prior exhibit. So can you switch for me again to the first one I handed you, DTX 4121. Let's go to page 5. And in the right-hand column you see Tables 1 and 2.

A. Yes.

Q. And Tables 1 and 2 in the titles, you see they reference Stability Study 65?

Do you see that?

A. Yes, I do.

Q. That's one of the stability studies that you worked on that we talked about earlier today and that you talked about on your direct, correct?

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A. Yes, it is.

Q. So you're not an inventor on this patent, correct?

A. That is correct.

Q. But that's your stability study?

A. Well, I helped it along after I joined the group, but my contributions to the patent were other things. I mean, I ran all the 200 through 207 studies, conducted the shear studies. So yeah, I'm not an inventor on that.

Q. All right. Last question, Dr. Graham. And I want to refer to the formulations in your '865 patent.

If an ophthalmologist administered the formulation from your '865 patent but without the aflibercept, would that be a safe and effective medicine for treating eye diseases?

A. Did you -- would you say that again. I'm sorry.

Q. Yes.

If a doctor administered the formulation from your '865 patent but without the aflibercept, would that be a safe and effective medication?

A. I would not expect so.

MR. RAKOCZY: All right. Pass the witness, Your Honor.

THE COURT: Thank you.

Redirect, Counsel?

MR. TRASK: Thank you, Your Honor.

THE COURT: Why don't we take five.

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You're still off limits for folks to speak with you, but you can step down. We'll take a quick five-minute break and finish the doctor's testimony.

THE WITNESS: Thank you.

(A recess was taken from 4:44 p.m. to 4:51 p.m.)

THE COURT: Counsel, you may proceed.

MR. TRASK: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. TRASK:

Q. Dr. Graham, do you have the binder in front of you that defense counsel handed up?

A. Yes.

Q. Could we turn to Exhibit DTX 900 in that binder.

I'd like to turn to page 37 of that document.

And if we could zoom in on the paragraph that starts "with respect" -- actually, "Subject to the foregoing general" and then following paragraph.

Doctor, do you see that on the screen?

A. Yes, I do.

Q. Do you remember defense counsel made a bit of a show about the fact that your name is not identified in this interrogatory response served by Regeneron?

A. Yes.

Q. Do you see that this document refers to the '865

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patent and it says the inventors conceived the inventions?

Do you see that?

A. Yes, I do.

Q. Who are the inventors of the '865 patent?

A. Well, that would be Dan Dix, Eric Furfine, Kelly Frye, and myself.

Q. Thank you, Doctor.

Do you remember you were asked on cross whether polysorbate 20 is a solvent?

A. Yes, I was.

Q. Is a solvent the same as a cosolvent?

A. No.

MR. RAKOCZY: Objection, Your Honor. Calls for expert testimony.

MR. TRASK: Your Honor, he asked this exact question and tried to impeach the witness about whether polysorbate is a solvent, and I'm just following up on what the doctor understands that to mean.

THE COURT: The examination was more what do the papers indicate. Sustained.

BY MR. TRASK:

Q. Let's turn to the same binder, PTX 2304. That's P as in plaintiff, PTX.

A. PTX, not --

Q. Correct.

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A. Okay. Yes. I see that.

Q. And if we could turn to page 32 of that document.

Are you there?

A. I'm trying to read it on the screen, but I'm going to have to struggle. What was the number again?

Q. It's okay. If you can see it on the screen, just a quick question. If you want it, it's PTX 2304.

A. 23 -- PTX 23 -- okay. Good with it on the screen.

What's your question?

Q. So the question, Doctor, is do you remember when counsel for Biocon and Mylan pointed to the signature by your colleague Michelle Looyenga in the bottom left of this page?

A. Michelle Looyenga, yes.

Q. Can we turn to the next page of this document, PTX 2304, page 33.

And do you see that there's a page at the bottom where -- it's not the signature block, but right above that there's a signature line for study director?

A. Yes, I do.

Q. Now, that's not signed, but this is Stability Study 207, right?

A. Correct.

Q. Who was the study director for Stability Study 207?

A. That would have been me.

Q. Let's look at PTX 1825, page 85.

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A. Yes, I see that.

Q. I'm sorry. Wrong page. Page 137. Sorry about that.

And do you remember -- I'll let you get there.

A. Okay. I can see this one on the screen.

Q. Do you remember when counsel for Biocon and Mylan asked you about the entry under 5C at .5 months that says, I think, clear, one filamentous particle. Do you see that?

A. Yes.

Q. Does that indicate to you that this formulation is unstable?

A. No, not necessarily.

Q. Why is that?

A. So the filamentous particle, those are typically items that come from the tech's wipes, the things that we use in the lab as part of the routine operations. If it had said one proteinaceous particle, then I might have been concerned. But the subsequent vial also showed clear, no precipitate. And having a particle is not a failure by our definitions.

Q. Thank you, Doctor.

If we could look in the same exhibit, page 111. And I'm looking at the second paragraph on this page.

A. Okay. Variability between HPLC systems and HPLC columns.

Q. Yeah. Are you there?

A. Yeah.

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Q. Do you remember you were asked questions by counsel for Biocon and Mylan about the variability regarding HPLC?

A. Yes.

Q. Is this referring to SEC or HPLC?

A. So this says HPLC in terms of what it's being described.

Q. Is that the same as SEC?

A. Not necessarily, no.

Q. Okay. With respect to SEC, size-exclusion chromatography, do you consider that to be a good assay for analyzing the stability of aflibercept formulations?

A. Okay. It is a very good assay. It's what I like to call the sentinel assay.

Q. What do you mean when you say SEC is the sentinel assay?

A. So it's the one that shows something going wrong, typically, before anything else. You know, unless we have major problems, generally we don't see particles, generally we don't see increases in turbidity; but we always do see some level of change in HPLC.

Q. So, Doctor, then, if you had only one assay by which you could analyze the stability of a formulation containing aflibercept, what assay would you choose to use?

A. I would use SEC.

Q. Let's look at PTX 3314, page 22.

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Do you remember being asked for counsel by Biocon and Mylan about the data under percent native VEGF Trap in this exhibit --

A. Yes.

Q. -- for Formulation 2?

A. Yes.

Q. And counsel pointed out that the percent native VEGF Trap at that condition was 97.9.

Do you remember that?

A. Yes.

Q. Was the starting percent data of VEGF Trap -- what was the starting percent native VEGF Trap with this material?

A. So it was 97.6.

Q. And what does that tell you about the stability of this material?

A. Well, so generally you have variation in your assay, but you don't go up in purity. So I started off at 97.6 plus or minus .1, .2, ended up at 97.9 plus or minus .2. It shows that there's really no change. It says that the stability is good. The fact that I started out below 98 percent, you know, I would never expect to -- if I start out below, I never would expect to come back up two.

Q. And so what does this data tell you as a formulation scientist? If you had started with material that was above 98 percent, what would you end up with?

MR. RAKOCZY: Objection, Your Honor. That's asking for opinion testimony and a prediction.

MR. TRASK: This is the very slide that counsel asked him about. I'm just asking him to explain the meaning of it, Your Honor.

MR. RAKOCZY: He's asking him to predict something that's not on the slide, Your Honor.

THE COURT: Understood.

Sustained.

BY MR. TRASK:

Q. Let's turn to Exhibit 3327, please.

And we'll look at page 46. Now, do you remember when counsel for Biocon and Mylan asked you about the last two rows of this table, Formulations 8 and 9?

A. Yes.

Q. And they pointed out that there was an increase in the number of -- I don't remember if it was aggregates or particles shown in this data?

A. I think they used the words "particles."

Q. How does -- can you explain how the HIAC analysis works that was done to generate this data?

A. So this is kind of an internally controlled experiment in that you start off by measuring the formulation and you look at whatever the base level is. Then you subject it to stress and you look for a change.

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The bigger the change -- you know, that -- large changes are not good. Small changes are to be expected. You know, there's more to the story that isn't necessarily entirely captured here, but what can happen is you not only get more particles but you get bigger particles.

In comparison, if we look at all these formulations and we say, okay, how do their performances compare? 8 and 9 are probably two of the top ones. I mean, 8 started out fairly low, went up a little bit. 9 started out at 100,000 and went up.

You know, really, the only formulations that are on there that start out significantly lower are ones that are lower protein concentration. There's a couple 10 mg/mL. And, you know, they're down in the 30 thousands. You know, it basically says that these are stable to the stress or more stable to the stress more directly than everything else that's on that page.

Q. Thank you. Can we turn to 3312, please, page 27.

Do you remember when counsel for Biocon and Mylan asked a question about the fourth bullet down on this slide comparing the oncology formulation stability to the "current ITV formulation"?

A. Yes.

Q. What is the current ITV formulation here?

A. So that was what we had referred to as ITV1. It was

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a formulation that contained 40 mg/mL aflibercept, 135-millimolar sodium chloride, and 0.1 percent PEG 3350.

So it was the formulation that we were seeing the issue with particulate formulation.

Q. Okay. Can we look at DTX 4121, please.

I believe this is one of the loose-leaf documents that counsel handed you. And I would like to look at page 3, paragraph 17.

Do you see that, Doctor?

A. I'm doing the wrong page number thing again; but yes, I do.

Q. So do you remember when counsel asked you a question about this statement in this document, 40 mg/mL prelyophilized solution?

A. Yes.

Q. Is a prelyophilized solution an ophthalmic formulation?

A. It is not.

Q. Why not?

A. Well, a prelyophilized solution is designed to have the drug remain stable solely --

THE COURT: One second, Doctor.

Yes, Counsel?

MR. RAKOCZY: Objection, Your Honor. This is calling for expert testimony.

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THE COURT: It is. It is. Sustained.

MR. TRASK: In that event, nothing further, Your Honor. We do have exhibits to move in unless, obviously, there's further from defense counsel.

THE COURT: Understood.

Recross?

MR. RAKOCZY: Depending on the exhibits, I may have none, Your Honor.

THE COURT: Let's take the exhibits first, then. Keep our fingers crossed.

One second, Doctor, if you'll bear with us. Just housekeeping stuff.

THE WITNESS: Okay.

THE COURT: Thank you.

Slowly counsel, but go ahead.

MR. TRASK: Thank you very much, Your Honor.

PTX 3327, PTX 3326, PTX 2293, PTX 2292, PTX 1921, PTX 1825, PTX 2277, PTX 2278, PTX 1860, PTX 2238, PTX 3249, PTX 2281, PTX 2282, PTX 2283, PTX 2265, PTX 2266, PTX 2267, PTX 2275, and PTX 672.

MR. RAKOCZY: I apologize. That was going too fast for me, Your Honor. Can I compare?

THE COURT: Please. Compare notes.

MR. RAKOCZY: Your Honor, as you can imagine, I need to preserve an objection for a lot of these. I'll try to do

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them in order.

No objection to PTX 672.

We object to PTX 1825, PTX 1860, PTX 1921, PTX 2238, PTX 2265, PTX 2266, PTX 2267, PTX 2275, PTX 2277, PTX 2278, PTX 2281, PTX 2282, PTX 2283, PTX 2292, PTX 2293, PTX 3326, PTX 3327.

And our objections are as I stated before, Your Honor, based on our motion in limine Number 5.

THE COURT: Understood. The Court will receive those conditionally, subject to addressing -- the parties have the opportunity to address those issues raised earlier in posttrial briefing. The Court will obviously address it in its findings of fact and conclusions of law.

MR. TRASK: Just for the record, Your Honor, we disagree with the objection. We think these documents were adequately disclosed during discovery and there's no basis for their objection here.

THE COURT: Understood.

MR. RAKOCZY: I have a few to move in, Your Honor.

THE COURT: One second.

Are those all from Regeneron's standpoint?

MR. TRASK: That's all, Your Honor.

THE COURT: All right. Subject to that condition, the exhibits previously identified by counsel are deemed admitted.

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(PTX 3327, PTX 3326, PTX 2293, PTX 2292, PTX 1921, PTX 1825, PTX 2277, PTX 2278, PTX 1860, PTX 2238, PTX 3249, PTX 2281, PTX 2282, PTX 2283, PTX 2265, PTX 2266, PTX 2267, PTX 2275, and PTX 672 were admitted.)

MR. RAKOCZY: And then we move to admit DTX 4121, DTX 8194, DTX 737, DTX 900.

And, Your Honor, I have several PTXs I'm not sure. They may already be in. Can I look at these overnight and then I can wrap it up in the morning?

THE COURT: Yeah. That would be fine.

MR. TRASK: Then with respect to those documents, Your Honor, I'll just note again that DTX 4121 is a document that plaintiffs had never relied on here. It wouldn't be appropriate for them to rely on that document by their experts or anyone else in this case.

But I understand that there's kind of been an agreement reached here where documents used on cross will come in. And on that basis, I understand the document will be admitted.

THE COURT: Understood.

Any other objections or concerns with the list from defendant?

MR. TRASK: No, Your Honor.

THE COURT: Those will all be deemed admitted pending closure of some PTX that may or may not have been in evidence.

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(DTX 4121, DTX 8194, DTX 737 and DTX 900 were admitted.)

THE COURT: May the good doctor step down?

MR. RAKOCZY: With that, I have nothing further for Dr. Graham. Thank you.

THE COURT: Sir, you may step down. Thank you. You can leave all the binders and whatnot there. We'll tidy up.

THE WITNESS: Do you want the syringes?

THE COURT: No. Water or not. No, never mind. I'll take the Fifth on what I was going to ask.

THE WITNESS: Don't go there. Now, these have been promised to Rene, so --

THE COURT: We receive those.

MR. TRASK: I don't think those are being received.

THE COURT: I thought they were simply demonstrative, purely demonstrative.

Thank you, sir. Those are all yours.

Counsel, any progress on looming or remaining exhibits from Dr. Stewart's examination?

No, sir. Go right ahead. I'm sorry.

MR. RAKOCZY: We'll have to get back to you in the morning about Dr. Stewart along with Dr. Graham. We'll clean that up.

THE COURT: Let's have a logistics discussion. What are we down to from Regeneron's standpoint in terms of witness

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presentation?

MR. BERL: Your Honor, we still have Dr. Csaky to call as well as Dr. Trout. In all candor, Your Honor, we're evaluating how the evidence comes in. And it's possible that we may not proceed with an additional witness. It's not clear that, in our view, we need to advance commercial success. And that last witness, Dr. Manning, was solely related to commercial success. And we are looking at the evidence. But it's quite possible that we may not, in fact, call Dr. Manning, which would end the case before that.

THE COURT: Would we finish Dr. Csaky and Dr. Trout tomorrow?

MR. BERL: I don't think that's likely.

MR. RAKOCZY: And, Your Honor, if I could just add, whether Dr. Manning comes, it makes a huge difference because we have the last witness, Dr. Hofmann. And so we -- it would be nice to know sooner rather than later for witness logistics just so we don't have him standing around here for no reason.

MR. BERL: Obviously, we are looking at that. We'll analyze the transcript. We will tell them as soon as we've made a decision. But that would end the trial presumably with Dr. Trout. Mr. Hofmann, I think is their commercial success witness who responded to Dr. Manning. So, obviously, no Dr. Manning, no Mr. Hofmann. And we would be done subject to their trying -- oh, sorry. I've just been reminded we have

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very short videos as well. I think it's no more than half an hour at most.

THE COURT: Are those the experts in dispute at this point?

MR. BERL: Yes.

THE COURT: Okay. Any other sticky notes? Okay.

All right. When is -- I'm sorry. Is it Mr. or Dr. Hofmann?

MR. RAKOCZY: Mr. Hofmann.

THE COURT: What are Mr. Hofmann's travel plans?

MR. RAKOCZY: Well, we were having him stick around to be the last witness on Friday. So depending on what happens with Dr. Manning, whether they're going to stipulate commercial success is out of the case and then we could potentially do something about Mr. Hofmann. But we'll need that information so we can evaluate what's left of his anticipated testimony, if anything.

THE COURT: Understood.

Any idea, Counsel, when the decision on Dr. Manning might be in the offing?

MR. BERL: We hope tonight, but tomorrow at the latest.

THE COURT: Okay. All right. Yeah, as soon as a decision is made on that, if you wouldn't mind communicating that so that Mr. Hofmann can make alternative arrangements if

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he's not going to take the stand.

MR. BERL: Absolutely.

THE COURT: Okay. All right. Anything else we need to take up today, then?

MR. BERL: Not from Regeneron, Your Honor.

MR. RAKOCZY: Nothing from Mylan and Biocon, Your Honor. Thank you.

THE COURT: Well, let's resume at 9:00 a.m. tomorrow with a renewed interest in being as efficient as possible.

Everyone have a wonderful evening.

(Proceedings concluded at 5:17 p.m.)

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CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 21, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 21st day of June 2023.

/s/Cindy L. Knecht
_____
Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 8

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 22, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

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Thursday morning session,

June 22, 2023, 9:00 a.m.

- - -

THE COURT: This Thursday we convene for day eight of trial. Counsel is present. The Court did see the joint stipulation the parties filed. The Court's digital signature is being affixed to that as we speak and will be entered forthwith.

Anything else we need to take up before we hear from Mylan's next witness, then?

MS. OBERWETTER: No, Your Honor. We're ready to call our next witness.

THE COURT: Okay.

From the defense standpoint, anything else?

MS. MAZZOCHI: No, not right now, Your Honor.

THE COURT: All right. Regeneron may call its next witness, then.

MS. OBERWETTER: Yes, Your Honor. Regeneron calls its next witness, Dr. Karl Csaky.

THE COURT: Hello, again, Dr. Csaky.

If you wouldn't mind repeating the drill. Come all the way to the front. We'll have you sworn in and ask you to take the witness stand. Thank you, sir.

KARL CSAKY, MD, PHD, PLAINTIFF'S WITNESS, SWORN

MS. OBERWETTER: Before we start, Your Honor, I

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believe everyone should have their advance copies of the binder and slides.

THE COURT: I believe I do. Thank you all very much.

Good morning again, Doctor. If you wouldn't mind adjusting that mic. Stay close to that for us.

Counsel, you may proceed.

DIRECT EXAMINATION

BY MS. OBERWETTER:

Q. Good morning, Dr. Csaky. Can you please reintroduce yourself to the Court.

A. Yes. My name is Karl Csaky. I'm a retina specialist from Dallas, Texas.

Q. And we're going to cover -- since you were here with us last week, we're going to cover some material today that relates some other of your opinions besides those bearing on infringement. I'd like to start first with your definition of the POSA.

If we can please pull that up onto the screen.

For the record, that's PDX 8.002.

Can you please read for us your definition of the POSA.

A. Yes. So this is the definition that I used during my opinions.

A person of ordinary skill in the art relevant to the claims is an ophthalmologist with experience in treating

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angiogenic eye disorders, including through the use of VEGF antagonists, and would have access to individuals with experience with intravitreal injection formulations.

Q. Okay. And if we take that slide down, how would you characterize the POSA's goals in the pre-2011 time period in coming up with a potential treatment regimen for treating an angiogenic eye disorder such as wet AMD or DME or diabetic retinopathy?

A. Right. So our goals back then were very similar to what our goals are today, right? First is to maximize patient's vision. That's our number one obligation.

Second would have been -- as we've seen through multiple testimonies, injections are not a good thing. And so we would have tried to reduce the number of injections that we were giving to patients to achieve that maximum vision that we could offer them.

And then of course we also wanted to reduce the burden on having them come to the office. That was another big burden that this new type of therapy was kind of challenging us. And, of course, last but not least was of course the safety, right? And we'll talk about that these were these new class of drugs that we weren't really that familiar with. And so we wanted to ensure that we were doing these in a safe way and not exposing patients to undue risks.

THE COURT: Ms. Oberwetter, I'm sorry. My machine

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just booted up, and my digital sticky note just reminded me.

For those charged with lunch arrangements and whatnot today, we're going to take a lunch break starting at 11:00. So if anyone needs to alert Panera, Subway, or whomever, my apologies. The vagaries of one of the Kleeh children's camp schedules and softball tournament schedules require us to move our lunch break up a little bit.

We'll break from 11:00 to 12:30 because we have a criminal matter we have to take up at 12:15. So for those charged with the all-important lunch arrangements, you're hereby on notice.

And, with that, I'm sorry, Ms. Oberwetter. You may resume.

MS. OBERWETTER: Thank you, Your Honor. That seems like information that should be spread far and wide.

THE COURT: Yes. I see the flurry of digital communications ensuing. And my apologies. Like I said, my digital reminder just prompted me.

But go right ahead.

MS. OBERWETTER: Thank you, Your Honor.

BY MS. OBERWETTER:

Q. Dr. Csaky, I'd like to address at a high level some of the treatment strategies for administering anti-VEGF treatments that existed before 2011. What were the strategies that were regularly in use?

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A. Right. So as we'll talk about, there really were the monthly injection strategy, right? And I think -- as we'll talk about through my opinions this morning, one thing that I think I really want to remind everyone in the court in particular that the advent of these anti-VEGF agents in ranibizumab, not only was it a novel therapy for patients, but the key was also the amazing success that we got.

I happened to be practicing in the era before anti-VEGF. And patients went blind, right? So, first of all, we wanted to achieve that maximal benefit to patients. And so monthly we knew could achieve that. So that was a -- still in use.

But, again, because of the burden of monthly injections, we had started to pivot to these individualized prn approaches. And eventually that kind of morphed into treat and extend. So those were really the ones that were practically in use for most of this period.

Q. Beyond those strategies that you just described, were there clinical trials that had attempted other approaches?

A. Right. We'll talk about that briefly. One of the easiest approaches that we first thought of in terms of the treatment burden was simply to extend the intervals. And one of those approaches of that was simply to say let's go out -- rather than every month, let's go out to every three months. And so those were multiple attempts to do that right really

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from the very beginning of approval of ranibizumab in particular.

Q. Okay. And prior to 2011, how were those efforts going?

A. Well, as we'll talk about, those were less than successful, right? And, again, I think what's critical to understand is that we were able to offer patients this ability to really dramatically improve their vision, right? It wasn't just that they were having some activity; we needed to make sure that these patients were getting -- you know, over a third of patients would get three or more lines of vision gained. That was unheard of before anti-VEGF therapies. So it was very important for us to continue those. And so these kinds of approaches were not achieving that.

Q. What was the predominant method of attempting to do extended dosing prior to 2011?

A. So again, you know, as we said, we were pivoting to these personalized approaches, right, these personalized prn, as we've heard, and treat and extend. And those were really kind of the major efforts that were ongoing.

Q. Can you remind us what prn stands for?

A. So pro re nata. It's basically a way -- you know, it's as needed. And as we'll talk about, we'll kind of indicate how that was used in the real world.

Q. Why was it that prn was the prevailing strategy?

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A. Well, part of it really was the development -- and so this is an interesting fact, that at the same time that we were doing these injections, there was technology that was becoming available called optical coherence tomography. And this was a --

THE COURT: Will you say that again, Doctor. I'm sorry?

THE WITNESS: Optical coherence tomography. We'll call it OCT for short. Okay?

THE COURT: Thank you.

THE WITNESS: And what this does is it's a noninvasive way. We shine a little bit of laser into the eye. It reflects back, and it gives us detailed structure of the retina, right?

And so suddenly now we were able in real time to look at patients and determine what degree of activity -- we would call it angiogenic activity -- we would be able to see because this OCT could show us changes in the retina that might reflect activity of disease.

BY MS. OBERWETTER:

Q. Why don't we take a look at just what an OCT scan looks like.

If we can pull up slide PDX 8.004, which is images taken from DTX 3131. Can you explain what we're looking at here?

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A. Yes. If I could just one second ask for a laser pointer that I forgot to bring up.

THE COURT: Yes, sir, you may approach.

THE WITNESS: I apologize. I should have brought that. Thank you.

So the key thing here -- and I think this is really a critical aspect of understanding where we were in this period of time. So here we have -- and this is from an article that I cited in my report.

Essentially these are images from an OCT device. And what you see here on Month 24 is what we would call normal morphology, right? So you could actually in real time start to see cross sections of the retina. And in this case there's retinal structures here. Underlying it there's some normal retinal structures. And you've heard on several testimonies this idea of a dry macula.

This is what we would call a dry macula. There's no swelling. I think this is a good example of -- if you go over here to -- on the left-hand side, you can see the difference, right? This area represents a change in OCT. Black just means, in some case, fluid.

And so all of a sudden now in real time I'm able to look at a patient and say, you know something? There's activity here because this doesn't look like that. And this has now fluid and activity. And in the concept of anti-VEGFs,

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right, we would actually call this approach a VEGF meter, meaning you would assume that, when there was activity, the VEGF levels were going up, causing fluid to reaccumulate. And when there was no fluid, we would assume that the VEGF levels were then normal, right?

THE COURT: Is this the same eye?

THE WITNESS: This is the same eye.

So this would be -- this is actually in this prn article. And this is what the attempt was. The patient would come in. If this was the appearance, you would inject, try to achieve this. The patient comes in now to the clinic looking like this. I go "don't need to treat" because I don't see any swelling.

So this was a critical technology that was integral to this development of prn, personalized, because it turned out that the rate of this fluid reaccumulation after treatment was all very individualized. Each person had their own rate, and we could now measure that rate with this OCT device.

BY MS. OBERWETTER:

Q. Dr. Csaky, the images that you took here were from an article about the PrONTO trial; is that correct?

A. Correct.

Q. What was the PrONTO trial?

A. So the PrONTO trial was really one of the first trials to try to understand if using this approach, right,

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would accomplish again these similar outcomes that we saw with monthly.

Again, this monthly was, you know, this very high bar that we were trying to achieve. And so in this case we were trying to see could I use this approach to tailor my treatments -- not treat here, only treat here -- and see in this way -- hold back injections, and in this way decide if this approach would get me some better outcomes than I did when I was trying to just simply -- extending my dosing every three months.

Q. And what did the PrONTO trial show?

A. So while the PrONTO trial was still a relatively small trial, it was very encouraging. There was -- the data suggested that the outcomes of this approach -- which, again, was very different than fixed -- that using this type of approach in a small study, we could start to achieve some of these really good outcome in patients.

And so you can well imagine how dramatic this was. I didn't have to treat this patient. I could have this patient come back next month. If the patient looked like this, I didn't have to treat. Next month, no treatment. Next month, reaccumulation, then treat.

So I could see -- you can understand this is very personalized, right? And each person would have their own individual time for when the fluid may or may not come back.

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Q. Dr. Csaky, is prn still a predominant methodology for treating patients?

A. It kind of fell -- it kind of evolved into treat and extend. And the reason why is prn required frequent visits, right? So the idea was I would see the patient back almost every month. And every month I would do this. And poor Mrs. Smith would say, "Well, Dr. Csaky, I wasted a trip. You told me nothing's going on. Yay."

But I'd have to see her back the next month and the next month. And then when she got fluid, I would treat. And so we eventually kind of figured out that these intervals that patients would demonstrate for recurrence could be not quite like the stock market, but we could be predicted to some degree. And so we would play around with these intervals, eventually getting to the point where we were trying to prevent this from happening just before it would happen.

So that was kind of the treat and extend. We would start to extend these intervals. When there was fluid, we would then back off and continue to treat on that interval.

Q. Okay.

We can take that slide down.

Dr. Csaky, is a fixed extended-dosing interval the same as a personalized approach?

A. No. It's completely different. As I said, with fixed we simply are having patients come back in on a very

regimented kind of schedule, and we just continue to inject. That was what -- ANCHOR and MARINA was the first trial to do that. And so this was a -- these -- the injections on prn and OCT, we would call conditional. You had to show some activity, change in vision plus fluid, in order to treat; whereas fixed, I go ahead and treat every time.

Q. I'd like to take a look at a slide from Dr. Albini's presentation that he referred to as extended regimens.

If we can put up PDX 8.0005, Slide 5.

You were here for Dr. Albini's testimony?

A. Yes, I was.

Q. And what was your reaction to the way he grouped this set of references as a category under extended regimens?

A. Well, what he outlined here were all these -- either based off various publications and surveys or articles was really either some type of prn or treat and extend. All right? So when I looked at the heading, I felt as if it was somewhat of an incomplete heading because, while this does allow you to have extended regimens, the key point, as I just pointed out, is these are all personalized based, right? So these are all based off individual response, individual recurrence of fluid. When do I treat on these varying intervals?

So I would have kind of added, to be a little bit more accurate, the adjective that these are personalized extended regimens.

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Q. All right.

And we can take that slide down.

I want to change topics a little bit and talk at a high level about clinical trials. If we can talk briefly about the phases of clinical trials. And you were here for Ms. Chu's testimony also, correct?

A. Correct.

Q. Before we get into clinical trials, can you remind us briefly of your experience with clinical trials in treating angiogenic eye disorders.

A. Yes. So I've had a fair amount of experience. When I worked at the NIH as a government employee, I worked closely with the FDA on end points in clinical trial designs. I've been involved with being a study chair, which I overran studies. And I've been involved in Phase I, Phase II, and Phase III trials.

Q. And very briefly, what are Phase I, Phase II, and Phase III trials?

A. Right. Well, as you heard briefly, so Phase I at least -- and this is from the POSA's perspective -- we kind of -- you know, when I'm doing a Phase I, what we're really looking for is to make sure that nothing horrible happens to the eye. So when you inject these new drugs into the eye, what you're really trying to make sure is that nothing terrible happens to the eye. And that's really the intent.

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And many times there's a dose escalation. So if a little bit of it doesn't do anything bad, you slowly, with a small number of patients, increase the dose and just ensure that there's nothing terrible happening with these early -- with the drug.

Q. And then Phase II?

A. In Phase II -- so once you have kind of a sense that there's -- at least the eyes are not going -- something terrible is not going to happen, then you start to think about, okay, how can we start to decipher a dose and some type of regimen that may or may not give us some ideas of activity.

Phase IIs typically are also underpowered to be sure of efficacy, to make sure there's a benefit, but it starts to give you some signals as to where you might want to go with your Phase III trials.

Q. And then just very briefly, Phase III?

A. Phase IIIs are the -- you know, they're the big ones. They're the hundreds and hundreds, if not thousands, of patients, very -- with very clear guidelines with a goal ultimately of -- with these large number of patients, being able to demonstrate safety and efficacy for the FDA's requirements and then submission to the FDA for approval.

Q. Do most drugs make it through the development process all the way through Phase III?

A. No. No. I mean, that's -- there's so many steps

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along the way. And, you know, having been in this for a while, we see lots of examples that animal work doesn't translate to humans. There's various issues that come up along the way. Safety is one of them, for example, that can be unpredicted. So there's lots of reasons why, again, we don't reach that bar of true efficacy and safety.

Q. I'd like to pause for a moment to talk about what have some of the failures been over time in the category of treating angiogenic eye disorders.

A. Right. Even back in that period of time, because of, you know, MARINA and ANCHOR and the fact that there was this tremendous enthusiasm, lots of companies were looking at different technologies. There was siRNA technologies, the company I worked with, trying to inhibit the production of VEGF at the RNA level, for example. That failed.

And then of course going through the history, there were other failures where -- you know, for example, trying to augment the activity of anti-VEGF. Those also failed. And of course we've had more recent failures. And many times there's even failures at the very end because of safety.

Q. Can you speak briefly about a drug called Beovu.

A. Yeah, Beovu, brolucizumab, was a -- somewhat unusual. And it too actually was derived -- it's an interesting history -- from antibodies found in camels. Camels have very small antibodies. And so the thinking was that these smaller

antibodies might be -- you can get them more concentrated. And so that was a -- brolucizumab. So the idea was that would also be an anti-VEGF agent. You could give more.

Turned out that, because it was this kind of -- again, I hate to use the word "weirdo," but it was another weirdo kind of molecule. While there was some efficacy, what eventually happened was that, in a group of patients, there was this devastating -- what we call occlusive vasculitis. That means the vessels in the retina shut off, and these patients would go blind. And so essentially it became something that many of us eventually just -- even though it was approved, most of us don't use.

Q. Okay. And I'd like to talk a little about how the POSA actually makes use of data derived from various of these categories of clinical trials. Can there be difficulties in drawing comparisons across different clinical trials?

A. Yeah. That's something that we were always taught not to do, right? Each trial has its own set of patients that come into the trial. There's various categories. We're all different, right?

So if I take a group of patients in one trial, I can't really fully compare it to a group of patients in another trial. There's regional differences. There's ethnic differences.

And so we typically are very much aware of the fact

that, while there may be a little bit of teachings going on, we rarely try to put a lot of emphasis on cross-trial comparisons.

Q. And are there limitations in making visual acuity comparisons across trials that use different numbers of loading doses?

A. Yes. So, again, this is where we have to be very careful because there's so much variabilities in these kinds of aspects. So you would be -- it would be very challenging, and you would not want to place a lot of confidence on trying to figure out manipulating -- if I had done that in this trial versus that trial, in drawing some conclusions. There's just so much variability in human disease and how we respond. That's something we don't do.

Q. I'd like to talk a little bit about the development status of some of the various anti-VEGF agents prior to 2011. Where was Eylea relative to Lucentis in clinical development prior to 2011?

A. Yeah. So it was behind, right? I mean, ANCHOR and MARINA, 2005/'6, was approved. We were using it full-on in the clinic. And so it was behind in its development.

Q. Okay. And how did the molecular structure of aflibercept compare to the structure of other anti-VEGF agents in use?

MR. McLAUGHLIN: Objection, Your Honor. This is beyond the scope of his expert report. I don't recall seeing

anything in his expert report about comparing the structure of ranibizumab to aflibercept.

MS. OBERWETTER: It is in his report, Your Honor, if we take a look at first paragraph 74.

THE COURT: Can I bum a copy from someone?

MS. OBERWETTER: Or if we can put it up on the page. Either way.

THE COURT: Oh, yeah. If we've got that available up on the screen, that will work for me.

MS. OBERWETTER: So this would be page 31, paragraph 74. If it's easier, we're happy to provide a hard copy, Your Honor.

THE COURT: Sure.

MS. OBERWETTER: Approach?

THE COURT: What page and paragraph again, Ms. Oberwetter?

MS. OBERWETTER: There's going to be two things we look at. The first will be in paragraph 74, where Dr. Csaky references his 2009 publication with Dr. Do as it relates to -- I don't want to -- we have the witness on the stand, but paragraph 74 starting at "In a 2009 publication."

THE COURT: Is this in his opening?

MS. OBERWETTER: This is in his response.

THE COURT: Response? Okay. Paragraph 74?

MS. OBERWETTER: Yes.

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THE COURT: All right. And where else?

MS. OBERWETTER: And then also at paragraph 114. If we scroll forward at the bottom of paragraph 114 on page 53, "Aflibercept was a different molecule than ranibizumab and, unlike ranibizumab, was a genetically engineered fusion protein."

THE COURT: Understood.

Objection overruled.

You may proceed.

BY MS. OBERWETTER:

Q. Dr. Csaky, how did the molecular structure of aflibercept compare to the structure of other anti-VEGF agents in use?

A. Right. So, you know, ranibizumab was a FAB fragment. It's an antibody fragment. It's something that we kind of were familiar with. We had studied immunology. We knew what antibodies were. So we knew what kind of an FAB fragment was from Lucentis. Avastin was the same as Lucentis; it just had the larger IgG tail. So those were two molecules that we were using. And we knew what they were. They were antibodies. We felt comfortable with it.

Along comes aflibercept. And to be quite honest, the colloquial term we used was it was a "weirdo protein" because it was this fusion -- a completely genetically engineered protein. And that was not something that -- the POSA, we were

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very comfortable with in terms of what the heck is that thing.

Q. I'd like to take a look at -- well, first of all, would those differences have affected the POSA's thinking as to how aflibercept might perform?

A. Yes. I mean, again, we had this experience with antibodies, right? There was this kind of intuitive sense of the body has antibodies. We kind of know that -- there were other agents in treatment that were using antibodies. And so kind of we were comfortable with that concept. But this idea of this fusion protein that was completely genetically engineered was something we were unsure about.

Q. If we take a look at an article on this subject.

If we can please pull up PTX 1027.

And, Dr. Csaky, what is PTX 1027 that we've pulled up on the screen?

A. So this is an article that Dr. Diana Do and I authored back in 2009. And we talked about the various issues right in the middle of all this stuff that was happening and these additional considerations that we needed to think about as we were going down this path of more and more anti-VEGF therapies.

Q. I'd like to take a look, if we scroll forward through the article, at page -- what we've marked as 1027.0006. And there's some paragraphs over on the right-hand side.

If we can focus in on that first paragraph for a

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moment.

If I can direct your attention to this paragraph, what were you and Dr. Do trying to convey here?

A. Yeah. So, again, I think what we were trying to convey or at least communicate was, again, that this VEGF Trap, which, again, was just kind of coming into our world -- at the beginning we were hearing about it and it was in trials -- to kind of understand that, again, it was not just this simple antibody, another antibody, as I say. It's a soluble fusion protein, and it had, you know, sequences for VEGF receptors. That was something that we didn't fully appreciate. What does that mean?

And so that was, I think, one of the first things that we highlighted is the idea that it was -- it was different and that it had, again, alternative affinities which, again, we weren't sure what that meant.

As I say, there's a lot of -- it may be something that's going to be a good thing, but I think the other thing that we wanted to highlight and -- during this period of time, and as you saw the article's name, was there were safety concerns. There was systemic safety concerns that were foremost in our minds.

And so that also, then, raised this issue of whether or not -- you know, the fact that this is this kind of unusual protein, potentially higher affinity, longer lasting in the

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eye, longer lasting in the systemic circulation, we just wanted to be really aware of the potential for, as we say in the very last phrase, greater systemic safety risks.

Q. I want to take a look down at the next couple of paragraphs of this article, if we highlight the next two. And in particular, if I can direct your attention down to the last several lines of this segment, talking about the VIEW 1 and VIEW 2 trials.

Do you see that part?

A. Yes.

Q. What were you trying to convey there?

A. Yes. So, again, this was during the time of the ongoing VIEW 1-VIEW 2 trials, and we just wanted to highlight the importance of these Phase III trials in helping the community kind of dissect what exactly VEGF Trap was going to do, both from a efficacy perspective but also from a safety perspective.

Q. We can take that down.

You recall Dr. Albini testifying in his -- testifying last week about whether the POSA would have thought there were safety issues with aflibercept?

A. Yes.

Q. And why don't we pull up some of his testimony on that point, if we take a look at PDX 8.007.

We've put up an excerpt of Dr. Albini's testimony

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from page 793 of the trial transcript.

What was your reaction when Dr. Albini provided this testimony?

A. I was a little, I want to say, incredulous because he refers to the safety that was seen in the preliminary study by Do and that that somehow would communicate to the POSA that this was a safe molecule.

And I can tell you, living through that period, there was a lot of sweating going on because this idea that these drugs could be involved with strokes and heart attacks -- VEGF is something that was -- something that was foremost in our minds for a long period of time. And so I really thought it underrepresented the enormous issue that this was in everybody's mind at the time we were in this period.

Q. All right. And we can take that down.

I want to turn next, Dr. Csaky, to talking about the diabetic macular edema and diabetic retinopathy claims in the case. And we're going to start first with diabetic macular edema, and let's start even preliminarily with the claims themselves.

If we can pull up PDX-- I believe it's number 8 that has Claim 11 of the '601 patent and Claim 25 of the '572 patent.

So we're on Slide 9. You've obviously had a chance to review these claims?

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A. Yes.

Q. Okay. And you're aware that Dr. Albini has offered opinions in this case that those claims would have been obvious over various references, correct?

A. Yes.

Q. How does your opinion at a high level differ from Dr. Albini's?

A. Yeah. I mean, I differ in that there was really nothing in the literature that would have led the POSA to this type of approach.

Q. Okay. And do some of your opinions in that regard also relate to some of the safety concerns we were just addressing?

A. Yes. Yes. Absolutely. So there was, again, this issue, especially as we see here in these diabetic patients in particular -- again, we'll talk about what happens when you inhibit systemic VEGF, the risk of stroke and heart attacks that was known; and of course in diabetics in particular, that was something that we were very concerned about.

Q. I'd like to talk a little bit -- we can take those down.

I'd like to talk a little bit about what was going on with diabetic macular edema in particular during the pre-2011 time period. And let's start with Dr. Albini's timeline slide, if we can pull that up. And so this is PDX 8.010 which

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references Dr. Albini's Slide 6.40.

Dr. Csaky, there's a lot going on here. Did you commission a version of this slide that focuses just on the references that relate to DME?

A. Yes. I thought for clarity it would be helpful to separate out the DME world in this period from the AMD world.

Q. Okay. And let's advance to that next slide, which is Slide 11.

Why did you want to look at DME separately?

A. Well, again, you know, for several reasons. You know, first of all, it's a separate disease completely, right, so we have to understand what was the POSA thinking, what was available to the POSA for diabetic macular edema as opposed to a completely different disease, which is macular degeneration. So I think it's important, just for accuracy, to separate out hose two.

And then, of course, what I was trying to highlight then was specifically his references in that regard.

Q. What are the four things that are left here on this slide? If you can just walk through them briefly.

A. Right. So what we see here is essentially a reference to the '747 patent. We see a reference to Diana Do's Phase I trial. We see a reference to Dr. Lalwani's review article. And then we see a reference to the press release in September 14th of 2009.

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Q. Okay. And that's the Regeneron press release that is at issue?

A. Correct, that's the Regeneron press release.

Q. And to be clear, is this collection representative of the prior art prior to 2011?

A. No. And, again, so when I looked at this, I wanted to make sure that we could represent more fully kind of all of the available references and all of the available work that was being done during this period of time.

Q. Did any of the references, either on this slide or from Dr. Albini's testimony, report on five loading doses as a strategy?

A. No. On this -- on Dr. Albini's timeline there was nothing that called out five loading doses.

Q. All right. And we can take that slide down.

I'd like to turn to some of what Dr. Albini cited on efficacy issues related to diabetic macular edema. And let's pull up for starters what was Dr. Albini's slide in that regard, which we have called in our slide deck PDX 8.012 which references his Slide 152.

Were you here for Dr. Albini's testimony about this slide?

A. Yes, I was.

Q. And why don't we first take a look at what Dr. Albini said about this chart, if we can scroll forward to our

Slide 13.

What did you understand Dr. Albini to be saying about this chart?

A. So, again, I think he's indicating that -- he says this details the clinical trial results that would have been available to the POSA prior to the filing of the patents.

Q. Okay. And just so the record is clear on this point, in your opinion is Dr. Albini's summary slide of these efficacy results a comprehensive list of information from the prior art for either AMD or DME?

A. No. No. And that's, again, what I tried to do was ensure that we saw the entire landscape of what was happening both for AMD and for DME.

Q. So let's take a look -- let's pull out two things, the two things on this list that relate to DME, if we can advance forward.

What kind of trials are these two trials that were on Dr. Albini's chart, the one that says there READ 1 and Phase I DME which referenced DTX 2733 and DTX 3102?

A. Yes. Again, these are relatively small, early-phase studies, right, that are just at the very beginning of our understanding of either the effects of ranibizumab and, again, in the case of aflibercept, a very early Phase I study of aflibercept in DME.

Q. If we go forward one slide to Slide 8.015, how many

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patients were in those two trials that we just looked at?

A. So you see, again, these are very small trials, right? So the READ 1 had ten subjects; the Phase I aflibercept study had five subjects. So, again, this fits into kind of these early category studies where we're trying to get some degree of, you know, is there some safety or something about these drugs that would raise some concern.

Q. Prior to 2011 would the POSA have viewed either of these Phase I trials as a valid basis for projecting the magnitude of visual acuity gains you could get using aflibercept?

A. Yeah. So, again, especially with aflibercept, I mean it's very difficult to take five subjects, inject once your drug, and then make some projection into the future about all the aspects that are around drug development, not only the efficacy when you start changing regimens, but also the safety.

So I think it would have been very difficult for us to, you know, make any conclusions other than interesting, hopeful, but nothing conclusive, nothing even that would point anything to how -- what's eventually going to happen to aflibercept.

Q. Okay. We can take that slide down.

One of the two references we were just looking at on that slide was DTX 3102. If we can pull that one up.

And Dr. Csaky, what is this reference that is up on

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the screen?

A. Right. So this is a Dr. Do reference, this kind of Phase I study where, essentially, five patients were injected once with aflibercept.

Q. Okay. And would the POSA have understood Do 2009 to provide a reasonable expectation of success with respect to the use of aflibercept in DME patients?

A. No. Again, as I said, you know, if I present any kind of series of five patients where I inject once the drug, and if I ever stood up and said this is fantastic news, I think I would lose all my credibility to the audience. So that's not something that the POSA would look at.

Again, we were intrigued about the molecule, but this isn't teaching us anything about where it will end up in our armamentaria.

Q. Would the POSA have understood Do 2009 to provide any reason for using a five loading dose 2q8 regimen for treating DME or DR?

A. No. There's nothing in here. There are no details about other regimens.

Q. Does Do 2009 teach anything about five loading doses?

A. No.

Q. Did it use any loading doses at all?

A. No. It does -- it used one -- simply one injection and the idea was to assess safety.

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Q. I want to turn -- and we can take that reference down.

I want to turn to talking about loading doses as a strategy in DME. And first of all, I just want to be really clear. Was five loading doses a strategy that had been employed in any clinical trials that you have been able to find prior to 2011?

A. Right. There was really nothing in the literature that had any trial that was based off of a design of five loading doses.

Q. And what about six loading doses?

A. There was nothing in the literature that referenced six loading doses.

Q. And is that true just for DME, or is that a broader proposition?

A. That's a broader proposition. There was nothing in the literature on any of the ongoing trials for either AMD, DME, and even some of the other trials for looking at five or six loading doses.

Q. Okay. I want to take a look at Dr. Albini's slide about loading doses. If we can pull up PDX 8.016, which refers and turn to Dr. Albini's Slide 91.

Do you see that slide?

A. Yes.

Q. And do you recall Dr. Albini offered some testimony

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about this slide?

A. Yes.

Q. And let's pull up Slide 17.

What did you understand Dr. Albini to be saying about the loading dose slide that he presented?

A. Again, I think what he was doing is taking these various examples and indicating this range. As he says, I think this slide nicely encompasses that range. And he was trying to indicate that these all represented loading doses.

Q. And just for the sake of a clear record, Slide 17 refers to Dr. Albini's testimony at page 804 of the trial transcript.

So, Dr. Csaky, do you agree with Dr. Albini's characterization of this issue on his slide?

A. No.

Q. Have you assisted in preparing a demonstrative to illustrate some of your issues with Dr. Albini's slide?

A. Yes.

Q. So let's scroll forward. And why don't we just walk through -- and we'll deploy some light animation. But why don't we just walk through some of your issues with Dr. Albini's slide.

A. Again, I think -- so we were focused on a discussion about loading doses in DME, right? And so I think the first thing you have to do is remove references to AMD, or macular

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degeneration. As I said, it's completely different disease. The POSA's not going to sit there and equate those two diseases. So that's the first thing I did.

Q. Okay. And then I want to focus your attention on the Number 6 in the bottom left hand of the exhibit. What is -- do you have an issue with the Number 6?

A. Yes. So this is, again, in relationship to the COPERNICUS trial, which was a trial to central retinal vein occlusion.

Central retinal vein occlusion, again, completely different disease from diabetic macular edema, for one, has a completely different etiology. And what's interesting about the trial designs for vein occlusion is that the end points are six months.

So the FDA requires only six months of treatment to get approval. And so when you look at the Number 6 in this regard, it really represents a six fixed monthly loading -- not loading -- six fixed approach to treatment, and that's really what the intent of treatment is for a vein occlusion. You give six treatments every month. It's almost always if you were doing an ANCHOR or MARINA. So it's six fixed monthly regimen through six months because that's the approvable end point for the FDA.

Q. On Dr. Albini's presentation, the Number 6, the citation is the September 2009 press release, correct?

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A. That's correct.

Q. Why don't we pull up the press release, which is DTX 3198. And if we go to the second page of the press release and take a look at the very top paragraph on that page.

Dr. Csaky, is this the portion of the press release that talks about the COPERNICUS trial?

A. Yes.

Q. Would the POSA -- if we take a look in particular at the section that says "patients in both studies" and just highlight those few lines there.

Would the POSA have understood this reference in the September 2009 press release to be a reference to six loading doses?

A. No. I think, again, it clearly states -- and it was known to some degree that vein occlusions only needed six month of treatment, and this press release highlights essentially the regimens of six monthly injections. There's no reference to loading doses in this press release. And the POSA would know that that's the way this regimen was to be administered. It's a fixed six-month regimen.

Q. Okay. Is there any chance that the POSA would have understood this paragraph to be -- and the reference to six doses to be the same as the concept of loading doses?

A. No. No. This is, again, the idea -- and even our approach was based off of FDA approval -- was simply to get to

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six months and to do a fixed -- every-month six-month schedule. And that's, again, conceptually different than when we think of loading doses.

Q. Have you created a slide to set forth a more representative look at the loading dose regimens that were in use for DME?

A. Yes.

Q. And why don't we pull up Slide 19.

And what does this slide show?

A. So, again, what I tried to do was paint again a little more comprehensive picture of the landscape, right? I think it's important to recognize what was happening during this period of time. And these are -- include other studies that were being done for DME during this period of time.

Q. And in light of -- and the ones that you have listed there toward the bottom are READ 1, DRCR Protocol 1, and RESOLVE, correct?

A. Correct.

Q. And would this landscape have rendered it obvious to go to five loading doses followed by a fixed dosing interval?

A. No.

Q. Why not?

A. Well, again, I think you can see. I mean, there's -- the monthly loading dose range is three to four, and again, the maintenance dosing for the majority of these trials was then

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based off of a prn strategy.

Q. I want to take down this slide, and let's talk a little bit more about the September 2009 press release as relates to DME.

So if we pull up DTX 3198. I want to look again at the second page of this document and this time at the second paragraph at the top of this document, if we can pull that out.

Dr. Csaky, you understand this paragraph to refer not by name but to the DA VINCI trial?

A. Yes.

Q. Okay. And does this portion of the September 2009 press release describe five loading doses?

A. No.

Q. Would the POSA have understood these five lines of this press release to be a teaching to go to five loading doses?

A. No.

Q. And why not?

A. So, again, I think, first of all, there was five regimens. One regimen was laser, and the other four, if you look, was fixed monthly either at .5 or 2 milligrams. And then the other two regimens, as you can see, were included either three -- well, both of them included three monthly loading doses or three monthly loading doses followed by prn.

So in both cases this was teaching us that, if you

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were going to use a loading regimen, that you'd really want to stick with a three-monthly-loading-dose regimen.

Q. Okay. And you're familiar with Dr. Albini's opinions that the POSA just would have added an additional loading dose between loading dose three and the first eight-week extended interval date.

Do you recall that generally?

A. Yes, I understood that.

Q. Do you agree with that position?

A. No.

Q. And why not?

A. So, again, I think it's important conceptually to understand the concept of a loading dose, right? For the POSA, a loading dose was meant to indicate that these are the treatments that you give one after another, every month, again, fixed, meaning I don't look at OCTs, I don't do -- these are not conditional injections. And so the loading dose has a very specific context.

And so to simply start putting in an extra injection here or there and then somehow transfer that into a concept of loading dose would be -- would not represent the mindset of the POSA. The POSA was really -- again, a loading dose regimen had a very specific goal in mind. And so if you were going to change any of these regimens, you would want to then have two additional, specifically called-out monthly loading doses.

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Q. Thank you, Dr. Csaky.

We can take that slide down.

I want to turn back to the topic of safety for a moment in DME patients. I'd like to take a look at one of the references from your report, which is PDX-- I'm sorry -- DTX-- we have a slide containing DTX 3186.

If we can pull up Slide 20, please.

Dr. Csaky, this is a reference that you cited in your report?

A. Yes, I cited this report.

Q. Okay. And can you please just tell us briefly what this article is and what the authors of this article were relaying on the right-hand side of Slide 20.

A. So, again -- you know, this again, 2008, we're right in the heyday of all of these anti-VEGF therapies. And there's a concern, right? I won't go into the details because it's not in my report, but there was lots of issues about the safety that was on the minds of everyone.

And this report simply further accentuates those concerns, especially as it relates to diabetics, right? Diabetics, they are -- VEGF at low levels does good things. We talked about it in the eye. Systemically, you need some VEGF.

You start dropping VEGF systemically, bad things happen, especially for the POSA. All we care about are eyeballs. Somebody has a stroke, I freak because that's not

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something that I'm used to dealing with.

And so here he's outlining this concern that in diabetics, in particular, until we start getting some long-term safety data, long-term trial data, we need to be cognizant of the possibility that there could, in some patients, be a concern with injecting these anti-VEGF agents into the eye.

Q. Thank you.

We can take that slide down.

Can you provide -- in addition to the safety concerns about diabetics in particular, can you provide other reasons that the POSA would not have wanted to go up to five loading doses without a really good reason?

A. Yeah. So, again, I mean, beyond -- so we have the safety concern. We talked about injections. I don't think any of us were just saying we should do more injections at that time. So that was clearly something that we were concerned about.

Again, we didn't see anything in the literature that suggested that other trials were pushing towards five loading doses. And even in diabetes, as you saw, this prn dosing, this use of OCT, was really something that was driving our decision-making. And so these -- the ideas that we would just go to fixed five loading doses was really not something that we were heading towards in terms of our approaches.

Q. And a couple up other questions on a similar topic.

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Is DME typically a slow progressing disease or a rapidly progressing disease?

A. It's a slow progressing disease.

Q. And how would that fact affect what the POSA would or would not want to do?

A. Yeah. Again, there too we have a little bit of some flexibility, right? I can give -- and I think it's representative in these trials -- the thinking, I give three, maybe, and then I do some prn'ing. I know that I have a little bit of time to figure out what then is the right strategy after that with my OCT imaging and stuff.

So, again, this idea that I would then mandate five loading doses right up front was again not -- the disease was not driving us towards that.

Q. Okay. I want to talk about another reference that Dr. Albini included in his testimony, which is what has been colloquially called Lalwani 2009B but also has the evidentiary title of DTX 2733.

If we pull that up.

And, Dr. Csaky, is this a reference that you reviewed in forming your opinions in this case?

A. Yes, I did.

Q. What kind of article is this by Dr. Lalwani?

A. This is a review article, you know, that she's attempting to kind of summarize some of the various aspects at

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that time.

Q. Did Dr. Lalwani mention anything in her conclusions in this article about increasing the number of loading doses as a strategy for treating DME?

A. No. There's no place in her review article that she mentioned that has a potential strategy.

Q. And, instead, what was the approach tested in some of the studies that she mentioned in her review article?

A. Right. So I think, you know, the only thing we understood was that the VEGF levels in diabetics was a little bit higher at baseline. And so if you think about it, okay, I'm going to take my anti-VEGF agent, a reasonable alternative is just to give more drug at the beginning. And so that was -- she summarized two studies in this article that explored that option of just more drug at the beginning.

Q. After she summarized those two trials, if we can go to page 2 of this document, she has a section in the right-hand column that says "both these higher-dose trials."

Do you see that?

A. Yes.

Q. What was her conclusion after describing some of the things that were being tried?

A. Yes. So, again, I think it kind of showed us a little bit of the uncertainty in diabetes and diabetic macular edema. Again, lots of heterogeneity. We were still kind of

struggling to figure out what was the best way to do this. And I think she summarizes it nicely, right, that additional trials will be necessary to determine the most effective dosing and treatment interval strategies.

Q. Right below this section --

If we can take that down.

-- there's a section called "VEGF Trap." Do you see that?

A. Yes.

Q. Did Dr. Lalwani -- so -- and she refers to the ongoing Phase II trial here?

A. Yes.

Q. Did she say anything to suggest that the ongoing DA VINCI trial pointed to a solution for a DME dosing regimen?

A. No.

Q. Okay.

We can take that document down.

I'd like to talk about another reference that Dr. Albini focused on, which is the Do 2012 reference.

And first of all, why don't we start with PDX 22.

And we're going to talk more about priority date issues in a little while, but you understand there's an issue in the case about whether the priority date for Claim 11 of the '601 and Claim 21 of the '572 should be January 2011 or July 2013, correct?

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A. Yes. Yes, I've been told about this discussion.

Q. Okay. And you understand that the reference cited between those two dates by Dr. Albini is this August 2012 Do 2012 reference, correct?

A. Correct.

Q. So let's take a look at Do 2012, which is DTX 3105.

What is this article that we are looking at? What is Do 2012?

A. So these are the one-year results of this DA VINCI trial, some of which we just discussed. And so she's reporting the one-year outcomes.

Q. And what type of information is presented in this document?

A. So, you know, this is the type of information that, you know, is available to the POSA kind of as a nice summary of various aspects of the trial design, you know, what was actually happening. It could give us information, for example, about the various dosing regimens that were under investigation in the trial. It will give us information about patient selection, for example, also, inclusion/exclusion criteria.

One of the interesting things about here is already now we're starting to see, as part of the exclusion criteria, excluding patients -- these diabetic patients who had more systemic problems, again suggesting that we were concerned about enrolling patients that might be at higher risk for a

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stroke. So, again, it's starting to tell us that we need to be aware of some of these safety issues. And then of course it then gives us the outcomes.

So there's a -- you know, it gives us kind of now a little bit of a beginning overview of where we might be going with this technology.

Q. In your review of this reference, is there any language that suggests that an increase in loading doses should occur in future trials?

A. No.

Q. In your opinion, would Do 2012 have made obvious the use of a five-loading-dose 2q8 regimen for using Eylea with DME?

A. No.

Q. Or for DR?

A. No.

Q. And why not?

A. So, again, as I summarized in the press report, it's a very similar, you know, position, right? If I read this carefully, I'm looking for, you know, are there, you know, regimens of five loading doses? There aren't in any of these -- any of the groups, right? So that's the first thing I'm looking for.

And then I'm looking for potentially, you know, something that the authors would offer to say, you know, this

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would be a reasonable approach going forward. And so those are some of the kinds of information we would be looking for in trying to figure out what is our future strategies.

Q. And if we take a look at page 7 of this document, one of the conclusion paragraphs toward the bottom left of this page, it starts "because there is considerable individual variation."

Do you see that?

A. Yes.

Q. What was Dr. Do conveying in this paragraph?

A. So, again, I think, as we've talked about, this personalized approach using OCT -- you know, we use OCT in DME as well -- vision, and that perhaps because, again, these diseases have so much variability, that she's suggesting that some form of as-needed treatment may be the way to go and, again, just speculating about other approaches. But, again, all of us were waiting for the -- these critical Phase III clinical studies to really understand the full safety and efficacy of this agent in diabetic macular edema.

Q. Okay.

We can take that down.

I want to talk about the diabetic retinopathy claim, if we transition to that for a moment, and pull up Slide 23, which has Claim 19 of the '601 patent on it.

Do you see that?

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A. Yes.

Q. And you've obviously had an opportunity to review this claim?

A. Yes.

Q. Are diabetic retinopathy and DME the same thing?

A. It's a form, but not the same.

Q. And can you have diabetic retinopathy without having diabetic macular edema?

A. Yes.

Q. Over time, have there been different treatments applied to DME as opposed to the category of diabetic retinopathy patients?

MR. McLAUGHLIN: Objection, Your Honor. This is way beyond the scope of his expert report. In his expert report he talks about DME being a subset or complication of DR. He never goes into the different variations of diabetic retinopathy.

MS. OBERWETTER: I would say, first of all, I believe this is very similar to what Dr. Albini testified.

THE COURT: I got it. That's not the objection, though.

MS. OBERWETTER: Let's see. If we take a look at response report 220, which is at page 119, "This fundamental distinction has important implications for how ophthalmologists, including the POSA, would have thought about these conditions and their approaches" --

MR. McLAUGHLIN: I'm talking about the distinction between DME --

THE COURT: Okay. One at a time.

MR. McLAUGHLIN: Sorry.

MS. OBERWETTER: -- "would have thought about these conditions and their approaches to treatment of the same," which I believe is exactly what I just asked him.

MR. McLAUGHLIN: Again, this is talking about the distinction between AMD and DME/DR. Right here, these groups, DME and DR, as similar angiogenic eye disorders. And the distinction is between those two and AMD.

MS. OBERWETTER: Yes, Your Honor. I believe --

MR. McLAUGHLIN: Look --

THE COURT: I'm going to say this one more time.

One at a time.

Ms. Oberwetter?

MS. OBERWETTER: I believe this is a disclosure that he's talking about the difference in how the various disorders are treated.

THE COURT: Counsel?

MR. McLAUGHLIN: This is an opinion we're hearing for the very first time today. Look at the very next sentence. He has DME/DR.

THE COURT: Sustained. Sustained.

BY MS. OBERWETTER:

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Q. Dr. Csaky, you obviously listened to Dr. Albini's testimony in this case, correct?

A. Yes.

Q. Did you hear Dr. Albini identify any prior art that would have rendered obvious a five-loading-dose 2q8 regimen as to the overall disease state of diabetic retinopathy?

A. No, I did not.

Q. What was Regeneron's Phase III diabetic retinopathy study called?

A. The PANORAMA study.

Q. And if we pull up PTX 1794.

What is PTX 1794?

A. So this was a study to look at specifically the effects of aflibercept on patients who had essentially in this case nonproliferative diabetic retinopathy and -- without necessarily having diabetic macular edema, and trying to understand what the efficacy of aflibercept would be in this class of patients.

Q. Okay. And this article was published well after the priority date?

A. That's correct.

Q. Okay. And in light of the Brown reference or otherwise, would the POSA have found it obvious to use a five-loading-dose 2q8 regimen to trial diabetic retinopathy?

A. No. There would have been nothing to lead the POSA

to think that way.

Q. Okay.

We can take that document down.

I want to turn to talking briefly about some of Mylan and Biocon's anticipation arguments and Dr. Albini's testimony about those.

If we can pull up -- first of all, you're aware that Dr. Albini testified that the '747 patent would have anticipated the DME and DR claims, correct?

A. Yes. I heard him claim that.

Q. And you're aware that Dr. Albini provided some testimony on Example 17 of the '747 patent in particular, correct?

A. Yes, I did hear him say that.

Q. Okay.

And let's pull that up. Let's pull up PDX 8.025.

And you've had an opportunity to review the '747 patent in its entirety, correct?

A. Yes, I have.

Q. And if we focus on Example 17 for the moment, what do you understand that example to be describing?

A. So I think it's important to recognize that this is an example for the treatment of age-related macular degeneration. That's point number one.

The other thing that is really interesting about this

example is when you look at some of the descriptions that were provided that are talking about periodic exams, they're talking about continuously monitoring, performing periodic retinal examinations. They're talking about additional VEGF Trap protein may be required and may be given. So I focused and I found that very interesting that there were these words and sentences and descriptions in this example for macular degeneration.

Q. Okay. And in your view, did this paragraph describe loading doses and fixed extended intervals?

A. No. No, not at all.

Q. And why is that?

A. So, again, when I look at these kind of periodic examinations may be required, you know, I think -- you know, I look at this, and it sounds very much like prn or a personalized treatment regimen.

Q. Does the '747 patent provide any criteria to instruct the POSA to determine whether or not an injection should be administered on any particular schedule?

A. No. No, there's nothing here that gives me any guidance in that regard.

Q. So in your opinion, does the '747 patent disclose a method of treating patients with DME or DR using five monthly injections followed by an injection eight weeks thereafter?

A. No, it doesn't.

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Q. Does it disclose an approach of loading doses followed by fixed intervals?

A. No, it doesn't.

Q. In your opinion, does the '747 patent anticipate the asserted DME-DR claims?

A. No, it doesn't.

Q. In your opinion, does the '747 patent do anything to make obvious the asserted DME and DR claims we've been talking about?

A. No. I see nothing in here that would have led me to that.

Q. I want to turn now to the September 2009 press release again.

If we can pull up -- actually, we don't need to pull up the press release itself.

But you understand that Dr. Albini offered some testimony in this case that the September 2009 press release would anticipate the DME claims, correct?

A. Correct.

Q. Okay.

Let's put up his slide on this issue for a moment, which we have numbered as PDX Slide 26 and cites to Dr. Albini's Slide 75.

Can you -- as you understand it, what was Dr. Albini's argument in this regard?

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A. So, again, I think he -- as we've talked about, he was taking one of the regimens of three loading doses and then subsequent prn and trying to indicate that, in fact, this somehow could be equated with five loading doses.

Q. Okay. And what is your reaction to that position?

A. So, again, I think it's critical to understand -- and I think as we've talked this morning in the discussion of the critical difference between a loading dose and a prn applied dose, right? A prn is a conditional treatment, right? I wait, I see, I examine, take OCT, so -- whereas a loading dose is a fixed regimen. It's five loading doses that I do regardless.

So it's really -- and somewhat not correct to equate a prn strategy to a fixed-loading-dose strategy.

Q. Okay.

And let's take this slide down for a moment and go to the actual press release, which is, again, DTX 3198. And if we look again at the second page of this document and pull out that second paragraph at the top that refers to the Phase II development in DME, can we highlight the language there for a moment that describes the prn regimen.

And, Dr. Csaky, in your opinion, would a patient receiving that regimen necessarily receive the claimed regimen of five loading doses in an extended fixed-dosing arm?

A. No. No. Again, as we talked about, again, it's important to really understand from a POSA's perspective the

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fundamental difference between a loading dose and a prn injection.

Q. And does this section of the press release describe five loading doses followed by an every-eight-week regimen?

A. No.

Q. Does it tell you how often the prn examinations will happen?

A. No. I think that's the other thing that's quite -- that's missing from here, right? One of the issues -- again, we wouldn't even know from this press release when those prn exams were being scheduled in this trial. So beyond just some of the conceptional inconsistencies, this doesn't educate us as to how often I would be needing to see a patient in the prn dosing arm. Could it be once a month? once every two months? It doesn't give us those details.

Q. Okay.

We can take that slide down.

I'm going to change topics a little bit, Dr. Csaky, and we're going to turn now to talking about Claim 6 in the angiogenic eye disorder claim.

So, first of all, let's just look at Claim 6 of the '572 patent regarding angiogenic eye disorders.

If we can put that up. And that's Slide 29 from PTX 0003.

I want to start with the words of an independent

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Claim 1, if we just start there. You understand those are part of Claim 6, correct?

A. Yes. Correct.

Q. Okay. And you understand that Claim 6 depends, at least in part, from Claim 1, correct?

A. Correct.

Q. And you understand that there's been an issue in the case as to whether we should be looking at Claims 2 and 3. And so we will be focusing today on the Claim 1 portion limitations in Claim 6. Is that all right?

A. Correct.

Q. Okay. I'd like to discuss briefly a summary of some of your opinions as relates to Claim 6.

If we can pull up PDX Slide 30.

Can you explain to us what you are summarizing here as it relates to your opinions on anticipation and obviousness.

A. Right. So I think, you know, as -- from my perspective -- and I was using the perspective of an ophthalmologist reading Dixon -- I think the -- this idea of -- while it does not discuss isotonic solution, right -- and, again, as an ophthalmologist, we would always defer to some type of formulator to tell us what's going on from a formulation perspective.

So for the POSA, the Dixon article doesn't call out isotonic, and it really doesn't give the POSA much information

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as it relates to anticipation.

Q. And can you compare that, then, to the testimony you're offering about obviousness as it relates to Claim 6.

A. Right. So the other -- so, again, the issue with obviousness as it relates to Claim 6 is there is discussion of an approach. The approach is very similar to VIEW 1 and VIEW 2. But I think, you know, for obviousness, the POSA would have had to have some idea that this regimen would be -- have some reasonable expectation of success.

And, again, as we've talked about, as we'll talk about in AMD in particular, there was very little guidance to suggest that some of the regimens in VIEW 1 and VIEW 2 would be expected to reproduce some of these incredible results. And so, again, I think, from the POSA's perspective, they would have had a limited reason to expect that to be successful.

Q. Okay. We'll talk about all of that in more detail.

We can take this slide down.

I want to start just with the isotonic solution limitation of Claim 6. And I'm going to frame these around some responses to Dr. Albini's testimony which you heard on this topic, right?

A. Yes.

Q. Okay.

Why don't we first pull up PDX Slide 31. Sorry. I'm actually looking for the Dixon excerpt. Let's just start with

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that, DTX 204.

And this is a reference -- this is Dixon 2009, correct?

A. Yes.

Q. And this is a reference you've had a chance to review in connection with this case, correct?

A. Yes.

Q. I'd like to take a look at -- if we scroll forward to page 3 and take a look at that 2.3 section called "Chemistry."

Do you see that part?

A. Yes.

Q. First I just want to talk about your understanding of what practicing ophthalmologists know about. Would this paragraph of Dixon have informed an ophthalmologist that VEGF Trap-Eye was formulated as a "isotonic solution"?

A. No.

Q. And why do you say that?

A. Well, you know, ophthalmologists, we treat patients, right? We're not chemists. And so if you ask an ophthalmologist what a buffer is, he wouldn't be -- or she wouldn't be able to tell you, right?

And so the idea of what even an isotonic solution is, the ophthalmologist wouldn't be able to really talk to you about what an isotonic solution is. That's way beyond -- we look at eyeballs all day. We don't think about isotonic

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solutions or even what an isotonic solution is.

Q. In your experience, do ophthalmologists consult drug formulation books?

A. I mean, we can. It's not something that we do on a frequent basis, but I guess, if push comes to shove, I would try to find a formulator if I had to.

Q. If you wanted to know whether it would be obvious to use a particular formulation, would you talk to a drug formulator about that?

A. Oh, absolutely.

Q. As of January 2011, to the best of your knowledge, would the POSA have known the formulation of Eylea?

A. No.

Q. Okay. I want to --

We can take that slide down.

I want to talk briefly about some of the obviousness opinions that Dr. Albini offered as relates to the other limitations of Claim 6 and those limitations that are contained in independent Claim 1.

So why don't we go back first to Dr. Albini's timeline which we have marked in our deck as Slide 32.

Do you see that, Dr. Csaky?

A. Yes, I do.

Q. And this is again referencing Dr. Albini's Slide 40.

Did you commission, again, a project to make this a

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little more readable?

A. Yes. Yes.

Q. Okay. And if we now look at the next version of this slide, which I believe is -- we're going back to Slide 33. Recognizing -- so, first of all, is this a complete recitation of the art relating to either aflibercept or anti-VEGF agents generally prior to January 2011?

A. No. But still, I mean, this is -- there's incomplete -- there's still references that we could have included.

Q. Okay. And recognizing that this page is still pretty crowded, what are some of the things that are missing from this slide?

A. Well, I think, you know, there are -- you know, the references that call out the attempts that we were making to alter this fixed-dosing regimen in particular to extend it -- you know, this three-month fixed-dosing schedule, those are missing from this.

Q. We're going to talk about those in a little more detail. First of all, are you familiar with a trial called PIER?

A. Yes.

Q. What is the PIER trial?

And we can call up Slide 35, please.

A. Right. So, again, the PIER -- and I think, to put it

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in context, we have to remember, ANCHOR and MARINA come out. And I think it's really critical to fully appreciate how revolutionary it was. It was essentially penicillin in terms of its ability to take patients and not just stabilize their macular degeneration but actually allow them to see improvements -- dramatic improvements in their vision. So that was the bar, right?

However, it came at a high cost, right? Every month, every visit. And so the first thing that we talked about was, okay, well, let's just give injections -- rather than every month, let's give three loading doses. In the loading doses, try to quell the disease that we talked about, try to normalize the tissue, and then extend that to every three months. And that's what Carl Regillo did here in this trial.

Q. And this is -- up on the screen there are excerpts from DTX 4099, the Regillo 2008 reference, correct?

A. Correct.

Q. Can you just explain briefly what Dr. Regillo and his coauthors were saying on the left-hand side of the screen.

A. Yeah, I mean, he points out specifically the outcomes were not as strong as those observed with monthly dosing. And in a way what he's highlighting -- and I think it's important to know how to interpret these kind of graphs. Here's the vision over time, right? So these are the loading-dose phase, and the visions go up.

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And then what you see is these are the number of letters that change over time. And as these patients started to receive every-three-month injections, rather than stable or improving, their vision starts to go down. And so while it stabilized, they didn't lose vision as opposed to natural history, it did not get, again, these results that we knew we could give patients, these dramatic results with monthly injections. And so that's why he's indicating that they were not as strong.

Q. And just for the sake of the record, you are laser-pointing at the visual acuity chart?

A. Correct.

Q. Okay. And I want to take a look now back at one of Dr. Albini's slides. If we go back to -- if we take a look at PDX Slide 34. And this is a slide we started to look at a little bit earlier. And it has several AMD trials listed on this slide, correct?

A. Yes.

Q. Let's just take one moment. What was the ANCHOR trial? if we can just do these very briefly.

A. Right. So, again, the ANCHOR trial is our first trial. Monthly injections, tremendous vision improvements. That's our -- coming out of the box, we are incredibly elated.

The PrONTO study, that's our attempts at now converting to prn, as is the CLEAR-IT trial.

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Q. And CLEAR-IT was -- CLEAR-IT 2, that was the aflibercept Phase II trial, correct?

A. Correct.

Q. And, again, are these three trials representative of the efficacy information contained in the prior art before 2011 for AMD?

A. Right. So these are starting to give us a little bit of information, but there's still a lot -- this was an exciting time. We had lots of interest in trying to decipher what was happening. And so there's a significant amount of information that's being done and presented during this period of time.

Q. And some of what was being done were those efforts at extended 12-week intervals, correct?

A. Correct. So beyond this -- as we said, the PIER trial was one of those efforts. There were other efforts as well in parallel to do that.

Q. Okay. And if we advance forward one slide, have you added some material on Slide 36 to Dr. Albini's slide?

A. Yes.

Q. If we go forward one more?

A. Yes. Yes.

Q. What have you added here?

A. Yes. And so these are these trials, these first attempts at trying to do a fixed extended dosing, right? These all have similar regimen. You can see at some point they're

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every 12 weeks.

And you can see, again, that these results, when you compare them to ANCHOR and MARINA -- ANCHOR and MARINA, 12 letters is an enormous gain in vision that you can offer patients. And none of these fixed every-three-month trials were able to come close at all to that outcome.

And so for the most part, this type of approach kind of fell into disfavor.

Q. Okay. And am I correct, Dr. Csaky, you have not attempted to compile every single trial that was being done prior to 2011, correct?

A. No, no, no. There were a lot of them.

Q. And why don't we advance forward to -- so if we just advance forward back to Dr. Albini's timeline, have you proposed some fixes to his timeline in light of what we just talked about.

A. Yes. Yes.

Q. And if we go forward, what have you attempted to change?

A. Well, a few things. I just wanted to correct the AMD reference to a slightly different time frame. And then as I said, I started to add, again, to just give a much more complete view of the landscape, the addition of these every-three-month fixed-dosing trials.

Q. And if we -- even this is not comprehensive of what's

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going on in AMD, correct?

A. No, no. There was a lot of work.

Q. If we go forward to PTX -- to Slide 39, have you reviewed a review article that we've referred to as PTX 1146 from the 2010 time period?

A. Yes.

Q. Why don't we advance forward through this, and you can tell us what we're looking at.

A. Yes. So this was a review article that Dr. Schmidt-Erfurth had put together in this time period, again highlighting some of these portion of all the trials -- not all the trials, but a portion of the trials for this review article.

Q. Okay. And, again, just so we're being clear, the CLEAR-IT 2 reference is on here because it was from Dr. Albini's list, not because she talks about it, correct?

A. Correct.

Q. What was the pattern that emerges from the trials that are summarized in Dr. Schmidt-Erfurth's review article?

A. Right. So I think if you look up here, what you see is, of course, our friend, the monthly injection regimen, which gave us the best results. They were an additional attempt to do monthly as well.

You can see there is this -- the PIER, these every-12-week. But I think what's really interesting is, when

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you look, you see the acronym "prn" quite frequently, right, again, just indicating that, really, the field was moving towards this, you know, prn personalized strategy, again, part of because of the advent of OCT and other technologies that allowed us to try to individualize treatment.

Q. I think we heard during Dr. Albini's testimony that Dr. Schmidt-Erfurth is from Austria.

Do you remember that?

A. That is true.

Q. Is she just talking about European studies here?

A. No. No. So Ursula, she's a world-renowned retina specialist. She lectures all over the world. And what she's really -- she's highlighting here is a compilation of trials. The majority of these, the vast majority, actually occurred in the United States.

Q. Okay. We can take that slide down.

I want to turn to talking about another reference that Dr. Albini mentioned in his testimony involving a quotation from Dr. David Brown.

Do you recall him talking about that generally?

A. Yes.

Q. Okay. Do you know Dr. Brown?

A. Yes, I know Dr. Brown.

Q. Why don't we pull up what we have marked as -- or what is marked as PDX 41, which is the slide cross-referencing

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Dr. Albini's Slide 37.

You remember Dr. Albini testifying about this excerpt from Dr. Brown, correct?

A. Correct.

Q. What additional context, if we can move forward to Slide 42, did Dr. Brown provide about his quote?

A. Yeah. So I think it's important to recognize, again, we're in this 2007 period, right? We're really pushing these personalized prn treat-and-extend strategies. And Dr. Rosenfeld, who was kind of a big proponent of these, was putting together experts to talk about this.

And you can see, again, we have this question, what is your strategy for keeping the macula dry? We know what dry macula means. And so the question is how do we achieve that in the best way possible for our patients?

And what the response to his -- the question from Dr. Rosenfeld to Dr. Brown is this, again, talking about various strategies. And Dr. Brown, his response is very indicative of what's happening. So he's talking about in this case selective patients with good initial visual acuities or dealing with primary eyes. And I think this is the key issue. "I treat and extend from the start. I give three monthly injections and see them in eight weeks if fluid is absent at that visit."

So, again, it's this conditional decision-making at

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that time which then would dictate, he says, "and then I give another injection," and you can see this is now the extension phase, right? The patient's come in in eight weeks. He does an active process, evaluating the patients. It's a conditional state. And at that point he makes a decision as to about, you know, if there's no fluid, then I start to extend to ten weeks.

So this is now the first iterations of treat and extend.

THE COURT: Counsel.

MR. McLAUGHLIN: I just want to object based on this being new testimony. This explanation was not provided in his expert reports.

MS. OBERWETTER: Your Honor, they didn't identify Dr. Brown's statement in Dr. Albini's opening report and certainly didn't use it to argue that there was a fixed extended dosing interval approach being used in prior art. So this is a perfectly fair response to what they did in Dr. Albini's testimony.

THE COURT: Overruled.

BY MS. OBERWETTER:

Q. Dr. Csaky, does this article describe a strategy of three loading doses followed by an eight-week fixed extended dosing interval?

A. Not a fixed eight-week dosing interval.

Q. We can take that slide down.

I want to turn to talking a little bit now about the aflibercept clinical trials. Why don't we start first by talking about Regeneron's VIEW 1 and VIEW 2 trials.

If we can please pull that up.

So we've put up on the screen PDX Slide 43, and what do you understand this to be, Dr. Csaky?

A. So these are the treatment regimens that were interrogated in the VIEW 1 and VIEW 2 trials.

Q. And one of those -- if you look at the third one, one of those is the three loading dose 2q8 regimen that ultimately went into the label, correct?

A. That's correct.

Q. All right. Given the state of the prior art at the time, would the POSA have had a reasonable expectation of success as of January 2011 as to whether the VIEW 2q8 regimen would allow the POSA to maximize vision gains?

A. So, again, the answer is no, right? Again, I think very important to put this in context, right? So we had to achieve these outstanding vision gains, right? That's -- we have this term "don't leave vision on the table," right? Would be a disservice to a patient to give them a regimen where they would not have the best possible vision. And so the bar was high. For any trial going forward, right?

And so that was the first issue that we were thinking about in terms of this q8-week dosing interval, right?

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The second issue, of course, was the fact that that had not been tried before. We did not have any evidence or data that extending out to between eight weeks was going to be as good. If anything, the fact that, when we went out to every 12 weeks, we got much worse, way below what we were wanting, was really a concern.

And as we just talked about, the field was definitely going full-on prn, treat and extend, right? That's where we were heading in terms of treatment strategies. And in my report I actually cite an interesting conversation. Dave Brown and Jeff Heier, who are both in this trial, both kind of opined that they were not very optimistic that this approach would work, again, because of all the reasons we just talked about. The bar was so high that to get to that bar was really hard.

Q. Is there anything about the design of the VIEW trial that would have had significance to the POSA at the time about the reasonable expectation of success as to this strategy?

A. Nothing.

Q. Okay. Let me ask a slightly different way. What would the POSA have gleaned from the very design of the trial about the expectation of success?

A. Yeah. So I think just looking at the trial design itself, right, I think the POSA would have said -- remember, MARINA and ANCHOR, major -- had a trial design, fixed monthly, two doses. And so we would have looked at that and said that

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makes sense, right?

And then we would have kind of scratched our heads and said, well, what's going on with this third regimen? I think many of us -- we understood kind of what it might be able to accomplish if it was successful, but we kind of thought it was the -- hate to say the Hail Mary of trial designs, hoping that it might work and be successful, but clearly the top two were the ones that -- were the ones that were the traditional trial designs that we knew had been shown in ANCHOR and MARINA.

Q. You've also had an opportunity to review the publications about the CLEAR-IT 2 trial, correct?

A. Yes.

Q. And why don't we pull up Slide 45.

And the CLEAR-IT 2 regimens are on the left side of this page, and the VIEW 1 and VIEW 2 trial designs are on the right side; is that correct?

A. Correct.

Q. And what would the POSA have understood in terms of a reasonable expectation of success, if any, that could be gleaned from CLEAR-IT 2 in terms of predicting what would happen in VIEW 1 and VIEW 2?

A. Yeah. So, again, I think it's really interesting in retrospect. So for the most part, most of the times when we look at Phase II, the CLEAR-IT 2, what's typically done is then that's just replicated in Phase III, right? And, in fact,

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there's articles written about this.

So the first thing that we would have noticed is the trial design of this 2q8 regimen wasn't in the CLEAR-IT 2. So where's the support for that that it's going to work, right?

I think the other thing is that we saw, you know, four loading doses if we're comparing it to the 2q8 rather than the -- and then suddenly now in VIEW 1 and 2 there's three loading doses, not four.

And then I think, again, the other critical feature is this is idea that, after this first 12-week period, all of the patients went to prn dosing, right? And so the relationship, as we just talked about, between prn and fixed-dosing, our experience with fixed-dosing every three months was much worse; some of the early data with prn were suggesting that that individualized approach was giving us some benefit; and the fact that, you know, Regeneron had chosen to essentially do a maintenance phase, if we would call it, of this trial with prn suggested to us that that's what was going to be the next step, right, that prn dosing would have been the next obvious way to go.

Q. Okay. We can take that slide down.

I want to touch briefly on another document that we've seen during this case. If we can pull up Slide 46.

And before I ask any questions about this document, just to clarify one thing. To be clear, as of January 2011,

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would you think that Eylea would at least have activity in terms of some effect on visual acuity?

A. I mean, I think, clearly, we were seeing from the various trials, even CLEAR-IT 2, that there was clearly activity. But, again, I really want to reiterate that it was this bar, it was this enormous bar that we had to hit. And to do that in a large trial, boy, that was tough. That was tough.

Q. And now we've got up on the screen our Slide 46, which refers to DTX 212. You were here for Dr. Yancopoulos's testimony back -- it feels like a while ago at this point?

A. I have -- I was here.

THE WITNESS: Thank you.

THE COURT: You're welcome.

BY MS. OBERWETTER:

Q. Dr. Csaky, you heard the testimony about DTX 212 and Dr. Stahl's comments back in 2006 that we see up on the screen?

A. Yes, I do.

Q. The line in Dr. Stahl's email says, "Their thoughts on their Phase II trial and end point, do they concur with our perspective that it is impossible to get meaningful VA" -- visual acuity -- "data without doing a Phase III study?"

Do you see that?

A. Yes.

Q. Would the POSA have agreed with the perspective reflected here in this email?

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A. Yes. I think I've overly expressed that opinion that that is the opinion of the POSA.

THE COURT: Yes, Counsel.

MR. McLAUGHLIN: Objection. This is outside the scope of his expert report, Your Honor. This document was cited once, and that's in the context of a conception, reduction to practice footnote with no analysis, no discussion of this document. Doesn't appear anywhere else in his expert report, at least that we've seen.

MS. OBERWETTER: I believe it is quoted, Your Honor, in paragraph 106 of the report and on page 49, spilling onto page 50.

MR. McLAUGHLIN: Which part?

MS. OBERWETTER: The responsive part.

THE COURT: Overruled.

BY MS. OBERWETTER:

Q. I believe I got an answer to the question; so I will proceed, and we can move on past DTX 212.

I want to talk for a moment, Dr. Csaky, about the reference called Dixon 2009 that we've heard quite a bit about over the course of the trial.

And for the sake of the record, that's DTX 204. If we could pull up our slide, PDX 47.

You've had an opportunity to review Dixon, correct?

A. Correct.

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Q. And I want to talk about a few excerpts of Dixon that have not yet had discussion in the trial.

First of all, what kind of reference -- let's just talk about Dixon for a moment. What kind of reference, what kind of article is the Dixon article?

A. So, again, similarly, it's a review article trying to summarize kind of the state of the art and where we are with treatments and understanding of disease at this period of time.

Q. Okay. And a big-picture question: In your opinion, did the Dixon reference tell the POSA that the Phase III VIEW trials would secure either efficacy or interval improvements for patients?

A. No. No.

Q. I want to -- let's just walk through some of the language in Dixon that relates to your opinion on that point.

Can you just walk us through -- let's go quote by quote. If you can start with the one at the top that's under "2. Background."

A. Right. So, again, if we look in the background section, there's a quotation that says, "These later studies seem to indicate that quarterly dosing is associated with poorer outcomes, but it may be possible to extend the time between injections if the patient is frequently monitored."

So, again, a reference that we've been talking about, prn, treat and extend.

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Q. And what would that portion of Dixon have told the POSA?

A. It would have told the POSA that the future of treatment is personalized treatment.

Q. Let's take a look at the line that's excerpted here from the Dixon references' conclusion, if you can walk us through that one.

A. Yes. So, again, it's still -- we were still unclear of what the full kind of ability of any alternative dosing to be effective, and they're just pointing out that there's still a degree of uncertainty about where we are and what new treatments may or may not be able to do as it relates to ranibizumab.

Q. Okay. And if we take a look at the last one -- and if you need to remind yourself of the further context around that, you should feel free to look at DTX 204 in your binder. But what does that last excerpt under "4. Excerpt Opinion," refer to where it says, "Its adoption into clinical practice will depend on efficacy at 4- and 8-week intervals"?

A. Correct. So I think this, again, highlights this idea that this enormous efficacy -- I keep saying that because, truly, unless -- when we lived through it, it was something that I'll never live through ever again in my life, that the efficacy was so high. And so what he's pointing out is that you've got to be able to reach that efficacy; and if you don't,

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any new approach, new treatment, new paradigm is not going to be adopted into clinical practice.

Q. In your opinion, would the POSA have found Claim 6 of the '572 patent to have been obvious in light of Dixon's disclosures about the VIEW trial?

A. No. That's exactly -- this question about efficacy was definitely on our minds.

Q. Okay. We can take that slide down.

I'm going to turn now to talking about some other issues that have been raised in the case, and we're going to pivot now to talking about some of Dr. Stewart's testimony and the Section 112 issue.

You were here for that testimony as well, correct, Dr. Csaky?

A. I was also here for that.

Q. I'm not sure I'll be able to be quite as speedy as Dr. Stewart was on some of those issues, but why don't we start with Claim 6 of the '572 patent, if we can pull up that slide again. And if we don't have that handy, I will come back to that just so we can refresh ourselves on the language.

Why don't I ask you this: First of all, were you asked to review Dr. Stewart's enablement and written description and indefiniteness opinions in this case?

A. Yes.

Q. Okay. And the first thing we're going to talk about

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is the language in Claim 6 relating to angiogenic eye disorders.

You recall Dr. Stewart's testimony about that language?

A. Yes, I did.

Q. Let's pull up the slide -- we're going to start with enablement. Let's pull up the slide, Slide 49.

Have you been asked to assume a standard for enablement in connection with rendering your opinions in this case?

A. Yes. This was provided to me in terms of the requirements to render an opinion on enablement and -- as well as to include evaluating this question of experimentation.

Q. Okay. And in answering questions about both enablement and written description, let's start first with the discussion of angiogenic eye disorders that appears in the specification. And for convenience, we're going to use the specification of the '572 patent which is PTX 0003. Okay?

A. Yes.

Q. And feel free to use your binder, although I think we're also going to have some snippets to put up on the screen.

With respect to the -- let's just start with what the specification says about angiogenic eye disorders. Let's start with Column 1, and let's look at lines 30 through 36.

And what does this language of the '572 patent

discuss?

A. So this is the field of the invention and discusses how the present invention relates to the field of therapeutic treatments of disorders and then specifies that to the invention as it's related to the administration of VEGF antagonists to treat eye disorders caused by or associated with angiogenesis.

Q. And let's take a look at the next portion of the specification at Column 2, lines 43 through 46. What does this section of the specification say about the methods of the present invention?

A. So it further defines and it gives us some of these angiogenic eye disorders, including age-related macular degeneration, diabetic retinopathy, and diabetic macular edema.

Q. Okay. If we go forward several more pages to Column 5, lines 30 through 48, there's a header on this page called "Angiogenic Eye Disorders," if we go about halfway down the page.

And what does this -- what do the inventors say about angiogenic eye disorders as a group as listed in this section?

A. Right. So what the inventor is describing is the -- he's defining the angiogenic eye disorder as a disease of the eye, which is caused by or associated with growth or proliferation of blood vessels or by blood vessel leakage. So he makes it very clear what -- how he's defining angiogenic eye

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disorders.

Q. Okay. And did he include any language here to address commonalities between angiogenic eye disorders?

A. Yes. So, again, what he's talking about here is that these common pathologic mechanisms by which these angiogenic eye disorders would be associated with.

Q. Okay. Let's move forward to another excerpt, which is at Columns 17 to 18. There we have it.

What else did Dr. Yancopoulos say about the use of the administration regimens described in the patent?

A. Yeah. I mean, he points out that these regimens that are being described may be used to treat these diseases, and --

Q. All right. So I want to talk -- we can take that snippet down.

Having gone through those, I want to turn for a moment to talking about some of Dr. Stewart's testimony about angiogenic eye disorder opinions.

First of all, you heard him testify about several conditions that he said he believed are not enabled by the patent.

Do you recall that generally?

A. I do recall that.

Q. Okay. Do you recall him specifically talking about pannus -- I hope I say this right -- pterygium, and one called PVR?

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A. Correct.

Q. Do you recall him also mentioning corneal neovascularization?

A. Correct.

Q. You recall -- this is just for orientation. He mentioned a series of exhibits which are DTX 5429, DTX 5430, and DTX 5431. I'm not going to put all of those up on the screen, but do you have a copy of those there in your binder?

A. Yes, I do.

Q. Are you familiar with the disease -- are you familiar with those diseases?

A. Yes, I am.

Q. And have you read all of those exhibits that Dr. Stewart referred to in his testimony?

A. I did.

Q. Have you had a chance to respond to those references yet?

A. Not officially.

THE COURT: One second, Doctor.

Yes, Counsel.

MR. McLAUGHLIN: Objection, Your Honor. This is, again, beyond the scope of his expert reports. He didn't address any of these references in his responsive expert report.

MS. OBERWETTER: That's because they were raised in

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Dr. Stewart's reply.

THE COURT: Rebuttal evidence. Overruled.

BY MS. OBERWETTER:

Q. Why don't we take one example. So you've not had a chance yet to provide a response to those, correct?

A. I have not had a chance to reply to a response, that's correct.

Q. Let's take one of these exhibits that Dr. Stewart referred to as an example, and that is the Shahraki reference, which is DTX-- for the record, DTX 5431, and I believe we have a copy of it up on the screen at this point.

First of all, just briefly, what is this article about that Dr. Stewart mentioned?

A. So this is, again, a review article about an update of the treatment of pterygium and some of its clinical features and management.

Q. Okay. And did you hear Dr. Stewart testify about his doubts that an anti-VEGF agent could treat pterygium?

A. Yes.

Q. Why don't we take a look at a portion of his paper that I think wasn't discussed earlier this week. If we go forward to page 11 of the document, and in particular there is a section starting down toward the bottom left, Shenasi and colleagues, if we could highlight that. That's the excerpt I was looking for.

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I know there is some technical material that is included in this discussion of the Shahraki reference, but what do you understand this reference to be describing here?

A. So, again, what this reference is to a study of an anti-VEGF agent, bevacizumab. And typically what happens is is that these pterygium are removed and then the vessels can then regrow on the sclera. And so the idea here was, if we add an anti-VEGF agent, can there have some efficacy?

And I think what we see here is the recurrence -- that is the recurrence of blood vessels -- after this surgery in the anti-VEGF group, the bevacizumab group, was 33 percent; if you didn't add the bevacizumab, it was 90 percent.

Again, that would suggest and demonstrate that anti-VEGF agent could be beneficial in the treatment of pterygium.

Q. Did any of the references that Dr. Stewart cited do anything in your mind to disprove that aflibercept in particular may allow for the treatment of the conditions that he mentioned?

A. No.

Q. And why not?

A. Because, again, I mean, there are, of course, additional references. And when we look at the pathology of pterygia, there's more and more evidence that anti-VEGF agents could be used. And, obviously, bevacizumab is one of them.

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Aflibercept is an anti-VEGF agent; so it's reasonable to presume that it would be equally as effective as bevacizumab in the treatment of pterygium.

Q. Okay. Did you understand Dr. Stewart, in fact, to agree, at least in part during his testimony, that these disorders are mediated by VEGF?

A. Yes. Yes. I think he did say that.

Q. And do you recall him saying that there may be more complex mechanisms associated with those diseases but that they include VEGF?

A. Correct.

Q. And is that your opinion as well?

A. Yes. Yes.

Q. I'm cognizant we're about to be at our break, but one more additional question.

In your opinion, would the POSA think that aflibercept could be used to treat pannus, pterygium, corneal neovascularization, and the PVR indication that we -- disorder that we've been talking about?

A. Yes.

Q. And why?

A. Well, again, without going into too much technical detail, there's more extensive literature, especially on these conditions as it relates to anti-VEGF therapies, right? So with the advent especially of bevacizumab, a lot of my

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colleagues -- corneal colleagues are using bevacizumab for corneal neovascularization. They've shown some very nice results.

There's a whole field of research on anti-VEGF therapy in PVR. Andrius Kazlauskas at the University of Chicago, Illinois, has been studying this extensively. And there have been successful trials in PVR with anti-VEGF agents. And so there's really a very complete -- if you look at the entire landscape, there's support for all of these conditions to some degree with an anti-VEGF agent.

THE COURT: Yes, Counsel?

MR. McLAUGHLIN: Objection. Again, this is not cited anywhere in his expert report. These are brand-new opinions that we're hearing for the first time today.

THE COURT: Counsel?

MS. OBERWETTER: I respectfully submit that the references should have been provided before the reply report if they did not want to hear a response for the first time here.

MR. McLAUGHLIN: He still could have provided these opinions in his response report. Dr. Stewart's opinions were set forth in his opening report. He had -- Dr. Csaky had every opportunity to respond to those at that point in his response report. These are new opinions. They shouldn't be coming in for the first time today.

MS. OBERWETTER: Your Honor, they bear the burden of

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proof on these issues. And so I don't think Dr. Csaky had to guess about which references and which disorders were going to be the source of a responsive point.

THE COURT: But were those references disclosed in the opening report?

MS. OBERWETTER: I do not believe so, Your Honor. I'm happy to be corrected on that if they were in the opening report.

MR. McLAUGHLIN: I don't recall if those specific references were identified, but Dr. Stewart's opinions about the inability to treat these disorders with aflibercept, that was certainly in his opening expert report. It could have been responded to at that point.

THE COURT: We're in a game of telephone. Coming down the table to you, Counsel.

MS. MAZZOCHI: Your Honor, if I may.

Dr. Stewart specifically identified these diseases in his opening report. Dr. Csaky, in his responsive report, then complained, well, I don't see a literature reference. So then Dr. Stewart in response said, well, here's literature references. So he was initially basing it on his opinion, experiences, et cetera.

THE COURT: So Dr. Csaky identified this as a criticism of Dr. Stewart in his report?

MS. MAZZOCHI: Right.

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THE COURT: Objection overruled. Thank you.

We're going to take our break at this point.

Doctor, you've been here throughout; so these will be familiar words to you. No one can communicate with you. They are required to feed you, assuming the change in schedule's been accommodated by our local eateries. But you're a man without a country for the lunch break, sir. Thank you. You may step down. Thank you very much.

Counsel, as I mentioned, we do have a criminal proceeding that we need to take up that's scheduled for 12:15. So if I could ask you to sort of just move everything back a row, it would be much appreciated. Then we should be in good shape to resume at 12:30 with Dr. Csaky's direct.

Thank you all very much.

(A recess was taken from 11:04 a.m. to 12:48 p.m.)

THE COURT: Good afternoon, Doctor.

Ms. Oberwetter, if you're ready to proceed, you may.

MS. OBERWETTER: Thank you, Your Honor.

Before we proceed with Dr. Csaky, I've been informed I should clarify one exhibit reference in the record. There was a reference to a Dr. Schmidt-Erfurth reference, and that should be PTX 1145, not PTX 1146, as the source of the underlying document.

BY MS. OBERWETTER:

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Q. Dr. Csaky, I'm now going to turn back to asking you just a few more questions about the angiogenic eye disorder topics that we were discussing prior to the break.

Dr. Stewart noted during his examination that aflibercept has not become the standard of care for angiogenic eye disorders since the patent issued. In your view, why is that?

A. Well, I mean, the approval --

Q. Let me clarify my question. I'm talking about pterygium, PVR. Apologies for the unclear question.

A. Sure.

So the main reason, of course, is the availability of bevacizumab, right, which is obviously a very cheap anti-VEGF agent that we can use off-label. And so in the majority of these cases, we're going to be using something that's off label and cheap. That's one of the advantages to bevacizumab. And so the efforts that my colleagues have made in these angiogenic disorders in which aflibercept has not been approved for is with bevacizumab primarily.

Q. In your opinion, would the POSA have found that the method of treating described in Claim 6 is enabled to treat a full scope of angiogenic eye disorders?

A. Yes.

Q. Okay. And I want to focus for a moment on Dr. Stewart's opinions suggesting that it would take undue

experimentation to practice the invention. And if we pull up for a moment again the enablement standard that you used. And that's Slide 49.

What would the POSA need to do to practice Claim 6 as to any of the angiogenic eye disorders that were listed in the specification we looked at from the '572 patent?

A. Right. And so, you know, as I was instructed to do when I made my opinion in regards to enablement, right, so I read the standards, applied that to the specifications, went through the various, you know, exercises and thinking about what was in the specifications, what was available that a POSA would already know going in. There's a lot of ground evidence -- I mean, ground knowledge that a POSA would have.

And then I also, of course, went through some of these factors for experimentation. And, again, when I kind of checked the box and going through the list of my understanding of the ophthalmologist POSA person, it really didn't require a lot of experimentation. There's clear guidelines in the specifications. You know, we're familiar with doing intravitreal injections. It's something that we do all the time.

We knew -- I mean, the wordings and the descriptions are very clear to the POSA, right? We understood the state of the prior art. We understood that, you know, this is what we do for a living. We inject people's eyes. And we understood

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that we already had some evidence that using antiangiogenic agents seemed to have some effect on these diseases. And, again, the breadth of the claims were relatively modest and fit into our wheelhouse of the POSA.

Q. Okay.

And we can take that slide down.

I'm going to change topics a little bit, Dr. Csaky, to talk now about the diabetic macular edema and diabetic retinopathy claims, so Claim 25 of the '601 patent and Claims 11 and 19 -- I'm sorry; I have this backwards -- Claim 25 of the '572 and Claims 11 and 19 of the '601 patent.

You understand that Mylan and Biocon are arguing that the DME and DR claims in the patents lack written description and enablement. You understand that position?

A. Yes.

Q. And why don't we take those arguments one at a time.

Have you considered whether those claims have adequate written description support in the specification?

A. Yes.

Q. And let's pull up again the slide with the standard for written description. If we take a look at slide -- if we take a look at Slide 50.

First of all, as we've been discussing throughout this examination, you understand these claims to disclose a regimen that includes 2 milligrams of aflibercept, five loading

doses, and every-eight-week extended-dosing intervals, correct?

A. Correct.

Q. With respect to the portions of those claims reciting a method of treating DME or DR, what indicated to you that the inventor had possession of the invention if we again start taking a tour through the specification?

And let's just start with Column 1 at lines 40 to 50. And, again, we're looking at the '572 patent, which is PTX 003.

A. Right. So, again, I walked through the various words in the claims and then went back into specifications and said, okay, is there angiogenic eye disorders that are outlined and the specific -- as it relates to diabetic macular edema? And here in part of the specification, it clearly calls out a diabetic macular edema as an angiogenic component as one of these diseases as outlined in the claims.

Q. And does he single out DME in particular in this paragraph?

A. Yes.

Q. Okay. Let's take a look -- if we move on to Column 2 of the patent, what else is in the patent specification identifying diabetic retinopathy and DME?

A. Yeah, I mean, here's another section of the specification where it clearly states that the present invention can be used to treat. And these include diabetic retinopathy and diabetic macular edema. So, again, from a

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POSA's perspective, it's pretty clear this patent, what it is detailing for us.

Q. Let's go forward to Column 3 and see what else is in the specification on these issues.

What -- are some of the diseases that we're talking about in the particular claims called out in the angiogenic eye disorders paragraph?

A. Yeah. Again, there are certain diseases that are called out: the age-related macular degeneration; as you see here, diabetic macular edema; and diabetic retinopathies.

Q. Those were all disclosed within the face of the specification?

A. Absolutely. These are all in the specifications.

Q. I want to turn a little bit forward. I think we have an excerpt that's numbered 22.6. And were there other places in the specification that talk about diabetic macular edema and diabetic retinopathy?

A. Right. So here too is now a further reference in the specification towards these -- what the regimen can be used for. And so it's clearly giving me the guidelines to say, you know, Dr. POSA, if you want to use these regimens to treat diabetic macular edema or vascular retinopathy -- which, in our world, can include diabetic retinopathy -- yes, here are the specifications for those.

Q. Okay. I want to focus --

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We can take that down.

I want to focus on portions of the specification that identify loading doses and numbers of loading doses, if we can take a look at some of that material for a moment.

Did you identify portions of the specification directed to loading doses?

A. Yes.

Q. Okay. And let's take a look at Column 4. And what does this portion of the specification describe?

A. Right. So this is, you know, some -- an outline of the specifications where the inventor is communicating to the POSA, saying, look, my invention comprises administering to a patient any number of secondary and/or tertiary doses. And then goes on and says, look, in certain embodiments, two or more secondary doses will be administered. And, of course, in that sequence there's the number 4, which would again -- you know, it's something that we'd be quite familiar with in terms of saying, oh, yes, I understand I have to give four secondary doses.

Q. And four is part of a list of numbers that's contained in this section, correct?

A. Correct.

Q. And what does the four secondary doses correspond to as relates to the DME and DR claims that we've been talking about?

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A. Right. So these would follow the initial dose. And so it would be a total of five loading doses.

Q. And that is within the list conveyed by the patent?

A. That's within the list conveyed in the patent.

Q. I want to proceed further to a portion of the patent under the header "Example 7." So if we go ahead to that section of the patent.

You reviewed Example 7 that's in the specification?

A. Correct.

Q. What does Example 7 contain?

A. Yeah. So, I mean, if I'm looking here and questioning whether the inventor is in possession of the specification, in this case in line 35, this wording is almost identical to what the claims are. It's an intravitreal injection once every four weeks for the first 16 weeks -- that would be the five loading doses -- followed by intravitreal injections once every eight weeks.

Q. I'd like to turn to another component of the claim limitations. And let's focus for a moment on the monthly interval that occurs in connection with the loading doses.

Let's take a look at Column 3, the portion that spills onto Column 4. What does this portion -- so we're looking at Column 3 around line 66 spilling onto Column 4 toward the very top of Column 4. And, again, this is PTX 003.

What does this disclosure tell the POSA?

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A. Well, again, you know, we're looking at now injections. And we're looking to see, okay, what are the intervals that this invention may be communicating to us? And I'm reading the specifications. And I see that there is this delineation that each secondary dose be administered two to four weeks after the immediately preceding dose in the initial line.

So I now can see that, okay, there is this option to do it four weeks after each dose. And, in effect, it goes on to then, in a redundant fashion, say it again, that each secondary dose may be administered to the patient four weeks after the immediate preceding dose.

Q. Okay.

We can take that slide down.

With respect to -- sorry.

Now we're going to turn to another portion of the claim limitations. If we -- with respect to the portion of the claims that recite the use of an eight-week interval between those fixed dosing periods after the secondary doses, what indicated to you that the inventor had possession of that aspect of the invention if we pull up, to start with, Column 3?

Again, I think we're looking at that same section, just with some different language highlighted.

A. Correct. So this is now -- you know, I'm looking for language that says, you know, is there something that tells me

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that he's in possession of thinking about tertiary dosing every eight weeks? And in this section it clearly states -- in fact, it's interesting that that's the first number that it tells me -- each tertiary dose is administered at least eight weeks after the immediate preceding dose. And then of course down at the bottom, again in a repetitive fashion, it says the same thing again.

Q. Okay. Let's advance forward again to Example 7.

And does Example 7 from the '572 patent -- in this excerpt we're looking at around line 35 referring to four weeks for the first 16 weeks, what does that example have to say about the extended-dosing interval?

A. Yeah. So, again, it delineates quite clearly that these tertiary doses -- in this case, once you finish the four weeks -- every-four-week injections. So once you finish those five loading doses, you now advance to injecting once every eight weeks.

Q. In your opinion at the time of the January 2011 priority date, would the POSA have recognized that Dr. Yancopoulos was in mental possession of the dosing regimens set forth in Claim 25 of the '572 patent and Claims 11 and 19 of the '601 patent?

A. Yes. I mean, I think there's clear language that would have directed a POSA to say yes. I mean, the aspects of the claim are within the specifications.

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Q. I'm also going to ask you some questions related to enablement about that same language that we were just looking at.

And, again, if we can call up Slide 49, the standard for enablement.

Have you considered the specification disclosures we just went through relating to the increments associated with the dosing regimen from the standpoint of enablement?

A. Yes. Yes.

Q. And have you reached a conclusion as to whether Claims 25 -- Claim 25 of the '572 patent and Claims 11 and 19 of the '601 patent are sufficiently enabled?

A. Yes. You know -- and, again, injections in our world are very common. This is what we do for a living. We dose certain numbers. We have intervals. And in these specifications we're being guided and told, look, here are some number of doses, and we -- but we have specific intervals that we have to follow. So I think these are not for us outside the scope of what we're used to doing in our day-to-day practice.

Q. Would the POSA, with the benefit of the disclosures we just looked at and the language of these claims, be able to perform the method of administering aflibercept in the five monthly loading doses every eight weeks -- every-eight-week dosing to treat DME or DR?

A. Yeah, absolutely.

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Q. And would the POSA, with the benefit of the disclosures we just looked at and the language of these claims, understand that that method could be used to treat DME or DR without undue experimentation?

A. Yes.

Q. Okay. I want to go back for a moment because I believe there is a small unit that I forgot to cover when we were addressing angiogenic eye disorders.

So if we take that slide down for a moment.

Dr. Csaky, we talked about angiogenic eye disorder argument that Dr. Stewart advanced with respect to enablement, but I have just a few questions about that with respect to the written description standard as well.

You understand that Dr. Stewart advanced an argument in connection with angiogenic eye disorders that the disclosure of those disorders did not provide a sufficient written description.

A. Yes.

Q. Okay. And what is your opinion in that regard with reference to the section of the specification -- the sections of the specification that we looked at in our angiogenic eye disorder unit?

A. Yeah. I mean, as I said this morning, I mean, these are descriptors and identification of diseases that are well known and, in part of our world, involve vascular leakage,

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vascular growth, and so it falls well within our scope of angiogenic eye disorder.

Q. Okay.

And if we pull up Slide 50 for a moment, please, just so we have the written description standards available.

In your opinion, did Dr. Yancopoulos have possession of Claim 6 of the '572 patent as of the January 2011 priority date?

A. So this is the -- so as it relates to the treatment of an angiogenic eye disorder, yes.

Q. Okay.

We can take that slide down.

I'd like to change topics just a little bit. First of all, you understand that portions of the -- what issued as the '572 patent and the '601 patent were added after January 2011, correct?

A. Correct.

Q. Okay. And you watched Dr. Stewart's testimony earlier this week, correct?

A. I did.

Q. And did you see the two demonstratives that he used for the '572 and '601 patents that were highlighted to indicate in which years certain disclosures were made?

A. Yes.

Q. Do you have any disagreement with the way he

highlighted that demonstrative?

A. Yes. I did not agree with his position.

Q. So let me just back up for a moment.

As to the actual highlighting, I'm not asking your substantive opinion at the moment. Just as to the actual highlighting in the document, did you agree with what he --

A. Yes. Yes. So he highlighted the difference -- I apologize -- the highlighted differences where I agreed that there were differences between the provisionals between those two documents.

Q. Okay. And if we pull up for a moment -- we have a snapshot of what is PTX 304, which is the cover of the '245 provisional application.

Do you see that?

A. Yes.

Q. Okay. And this is a document that you reviewed, correct?

A. Yes.

Q. And you don't have any -- this document contains certain language that ultimately appeared in the '572 and '601 patents, correct?

A. That's correct.

Q. And you are in agreement with Dr. Stewart on the point that some language was added after that?

A. Yes. Yes. Yes. There's definitely language added

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that I agree with him on that.

Q. Okay. With the actual words that were added later and the way he highlighted those on his patent demonstrative?

A. Yes.

Q. Does the absence of any of the language that was added later from the '245 provisional alter your view as to whether the DME and DR claims should be entitled to a January 2011 priority date?

A. No. So that's, I guess, what I was trying to answer initially, is that when I reviewed that addition and if the question is did that change my view of the specifications, the answer is no.

Q. Okay. And we looked, for example, at Example 7 in the patent, correct?

A. Right.

Q. And if you assume the patent specification without Example 7, would your written description opinions in this case remain the same?

A. Yes.

Q. Okay. And you heard Dr. Stewart testify that he thought Example 7 also is not a disclosure that would support the claimed regimens, correct?

A. Correct.

Q. Do you agree -- what is your response to that?

A. So, you know, the way I viewed Example 7 was it was

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a -- again, a detailed aspect of the specification. But in my view, when I looked in previous sections of the specifications, I saw that it's simply another kind of redundancy in terms of detailing the approach. But the substance of these approaches were also present in the previous sections of the specifications.

Q. Okay. I'd like to turn to talking about a different argument that Dr. Stewart made which relates to the concept of indefiniteness.

Do you recall --

A. Yes.

Q. Okay.

And let's put up on the screen Slide 51 which has the indefiniteness standard.

And, Dr. Csaky, is this a standard that you took into account in connection with your opinions?

A. Yes.

Q. Okay. And, in particular, you recall that Dr. Stewart offered testimony about the meaning of the word "approximately."

Do you remember that?

A. Correct.

Q. And that is a word that exists in the claims in this case?

A. That's correct.

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Q. Why might a patient not be able to receive an aflibercept injection at, for example, exactly four weeks?

A. Well, there's lots of reasons. His physician may be testifying in West Virginia for a while, and that would be an approximate change in his or her schedule. So there's lots of reasons why we use the word "approximate." It's a term we use day to day in our lexicon in taking care of patients.

Q. As a POSA, do you have any confusion around the word "approximately"?

A. No.

Q. Okay. And why not?

A. Again, you know, in medicine -- in real-world medicine, we don't live in absolutes. And so we live in a world where there's issues on scheduling, there's issues around doctors' schedules. There's a bunch of issues. And so we're very comfortable living in a world of approximate, about, those kinds of term.

Q. Have you considered whether the POSA would have reasonable certainty as to the scope of the claims at issue in this case in light of the use of the word "approximately"?

A. I would have no concerns.

Q. Okay. We can take that slide down.

So I'd like to change topics again, and I'd like to talk about something that relates to some of the obviousness opinions discussed earlier in your testimony, and that's

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specifically with respect to objective indicia of nonobviousness and some of those indicia that are outlined in your report.

Dr. Csaky, have you offered an opinion in this case as to whether objective indicia of nonobviousness support the nonobviousness of the claims of the '601 and '572 patents that are at issue in this case?

A. I have.

Q. Okay. And we're going to take some of these one at a time, but why don't we start with the concept of long-felt need.

In January of 2011 did there exist a reliable fixed extended dosing regimen for the treatment of any angiogenic eye disorders?

A. No. And, again, we talked about this, the fact that what we had tried did not come close to equating to the very strenuous monthly dosing regimen that we had.

Q. Why was it important to find a reliable fixed extended dosing regimen for the treatment of angiogenic eye disorders?

A. Well, you know, again, as we talked about, the field was moving towards prn, and there was some advantages. Obviously, prn was something that we were using OCTs. But the challenge with prn or fixed dosing was that it did require, lots of times, multiple visits. And so having this idea that

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you could have an extended fixed-dosing schedule is something that would be in certain cases very attractive.

You know, as somebody who's practiced in small clinics, you can well imagine that our OCTs sometimes don't work, and getting a technician to come in and fix that machine doesn't happen overnight, right? And so if I have a patient --

THE COURT: Doctor, could you tell me which machine that is? As I made reference to a couple times during the last couple weeks, I wear contacts; so I go for my annual and all that. And my treater, they just have a room with all these fancy machines in it, and they make me take my contacts out so I'm blind, and they just steer me around.

Which of these machines are we talking about?

THE WITNESS: This is called the optical coherence tomographer. It's not invasive. You put your chin up there, and you'll see sometimes a little blue light or a light. And what it does is it gives them a cross-section real-time view of your retina. And it scans the retina, and so you can really see if there's any pathologies, changes in the anatomy, that you might have.

And so as we talked about, in prn dosing, treat and extend, we use that extensively. It's almost a requirement. And so if I'm using prn, I've got to have my OCT working. I can tell you in these smaller clinics, sometimes it ain't working. And if it ain't working, then I got to -- I have a

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new patient, want to be able to have a regimen that I can kind of go to, and fixed extending dosing would be one that I would have gone to because I wouldn't have needed always to have my OCT to make those treatment decisions that we talked about.

BY MS. OBERWETTER:

Q. Thank you, Dr. Csaky.

I'd like to talk briefly also about the concept of failure of others. And we've just talked about how prior to January 2011 there was not a reliable extended dosing regimen for the treatment of angiogenic eye disorders.

Had others besides Regeneron attempted to develop such regimens?

A. Yeah. I mean, the only attempt for these 12-week or three-month extended dosing, and as we've talked about extensively, those just did not meet these criteria of really very, very high bar. And so those had failed.

Q. Okay. I want to focus your attention for a moment on a drug you talked about a few times, Macugen, if you can turn your attention to that one.

Had there been efforts to develop extended dosing regimens for Macugen?

A. Yes. So Macugen originally was a loading and a six weeks' interval for Macugen. The Macugen data was really quite poor. I mean, very few patients actually saw any degree of vision gains whatsoever. And so that was quickly abandoned,

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even though when it was partnered with Pfizer, Pfizer then tried to extend it and use it for diabetic retinopathy in a 12-week dosing schedule as well with Macugen. And all we know is there was no data reported; so we have to assume that that didn't work.

Q. Okay. I'd like to turn to a different topic, the concept of industry praise. And if we can pull up Slide 53.

Dr. Csaky, does Slide 53, which cites to DTX 3112, PTX 0841, and PTX 1155, does this contain some of the discussion of industry praise that you included in your report?

A. Yes.

Q. And can you please just walk us through some of the reaction after Eylea with its extended regimen was launched.

A. Yeah. I mean, I think we've got folks at the Food and Drug Administration talking about how Eylea is an important new treatment option for adults. I think they recognized that their two-month dosing schedule was the same as monthly dosing schedule, and so that was a big win.

And that was similar to some of the reports by my colleagues who also then talked about, again, this idea that, again, we could attain these visual gains. And, again, I think really want to reiterate that the bar was high, and so everybody was really impressed with the fact that, by reducing the number of fixed dosing, you could still maintain that high bar and then, of course, this idea that, because of that and to

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achieve that high bar, we might have an option for reducing the number of injections.

Q. Okay. And one of those references identified up on the screen is Ohr and Kaiser 2012. Do you see that one?

A. Yeah.

Q. And can you describe the concept that's discussed in that quote.

A. Yeah. So the idea was they're discussing the results. And these are both well-respected retina specialists. And they're talking about the fact that you could not just generate the visual gains, obviously, but maintain them with this significantly smaller number of injections compared with ranibizumab.

And, again, they're pointing out, which I think was really this bar and how that was really impressive that we could continue to maintain these high degree of visual gains in these large studies over this period of time.

Q. Okay. And we can take that slide down.

Dr. Csaky, there have been suggestions made in this trial that the fixed extended regimens of the claims are not actually beneficial to ophthalmologists or their patients.

Do you agree with that suggestion?

A. No.

Q. And can you explain why? And I know we've touched on some of this.

A. Again, we've talked about it in my prior deposition, right? I mean, talked about how in certain settings for patient scheduling and for their -- we use that and we -- I referenced certain of my colleagues as well in other -- and I do think that it's, like I said, important to recognize where it kind of fit into our -- the landscape.

And, again, this idea, while treat and extend and prn were clearly the dominating treatment regimens, the fact that you could have this alternative approach in certain settings with certain patients was an enormous advantage in our whole armamentaria of treating patients during this period of time.

MS. OBERWETTER: Thank you, Dr. Csaky.

I pass the witness.

THE COURT: Understood.

Cross.

MR. McLAUGHLIN: Your Honor, Neil McLaughlin on behalf of Mylan and Biocon. May not surprise you to hear that we have a few binders for the Court.

THE COURT: That, in fact, does not surprise me.

MR. McLAUGHLIN: May we approach, Your Honor?

THE COURT: You may.

Whenever you're ready, Counsel.

MR. McLAUGHLIN: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. McLAUGHLIN:

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Q. Dr. Csaky, you stated to your peers that, looking at overall practice patterns, there is not a significant difference in terms of the use of ranibizumab versus aflibercept based on the trial data from VIEW 1 and VIEW 2; isn't that right?

A. I'm sorry. Repeat that question. I'm sorry. I reported...

Q. Dr. Csaky, you have stated to your peers that, looking at overall practice patterns, there is not a significant difference in terms of use of ranibizumab versus aflibercept based on the trial data from VIEW 1 and VIEW 2; isn't that right?

A. If you can direct me to where I said that to my peers. I don't recall. I'm sure I did. I'm sure you'll show me where I did.

Q. Why don't we pull up DTX 9008.

This is from a publication called *Retina Today* from the January-February 2012 issue. Do you see a statement attributed to you at the top of page 14?

A. Yes. Exactly.

Q. And there you're quoted as saying, "Ultimately, however, if you look at our overall practice patterns and how frequently we are routinely injecting patients with ranibizumab, which might add up to seven or eight times per year, there is not a significant difference in terms of use of

ranibizumab versus aflibercept based on the trial data from VIEW 1 and VIEW 2."

Do you see that?

A. Yes.

Q. And you also stated that there's not any huge difference, huge price difference, between ranibizumab and aflibercept when it comes down to clinical use; isn't that right?

A. I did say that, correct.

Q. And you go on to say, "We can agree" -- this is further down -- "that because the two drugs are similar in a safety and efficacy, whether a clinician chooses ranibizumab or aflibercept may come down to personal preference."

Do you see that?

A. I do see that.

Q. We can take that down now.

Now, the Heier 2012 publication that we just heard you rely upon, you said that that's persuasive and you've relied upon it for your unexpected results opinions; is that right?

A. I'm sorry. Could you refer me to the Heier -- which Heier?

Q. Heier 2012.

A. Is that this?

Q. That's the publication that reported the VIEW 1 and

VIEW 2 results.

A. Yes.

Q. You relied on that publication, correct?

A. I've relied -- can you direct me just so I can open it up and refresh my memory of the details.

Q. Actually, let me ask you a couple follow-up questions first.

You are aware that that publication was rejected from the *New England Journal of Medicine* when it was originally submitted, are you not?

A. I have been told that, correct.

Q. And you've previously referred to the *New England Journal of Medicine* as the top medical journal in the country.

Do you remember that?

A. If I said it somewhere in my report or in my deposition, then I'll trust that I've said that.

Q. Their opinions are widely read and respected.

Would you agree with that?

A. So the *New England Journal*, I think -- you know, the critical aspect of the *New England Journal of Medicine* is it's across all specialties, right? So it's not ophthalmology-specific, right?

And so the reports that go in there, there has to be decisions by the editors as it relates to the articles that they accept, and that has to be across all specialties --

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pulmonary, cardiology, cancer, everything.

So it's a widely respected journal in general medicine. That would be a true statement.

Q. Did you have occasion to review any of the documents documenting the Regeneron email traffic that occurred after the rejection of that manuscript?

A. I may have. I just don't recall exactly, but if you can --

Q. Sure. Why don't we go to DTX 916. We'll go to page 1.

A. If you'll bear with me just for a second, there's --

THE COURT: Is that Volume I or II, Counsel?

MR. McLAUGHLIN: Actually, that may not have made it into the binders.

THE COURT: Doctor, that's just up on the screen.

MR. McLAUGHLIN: Okay. May I approach?

THE COURT: You may.

BY MR. McLAUGHLIN:

Q. And it's also displayed on the screen for you here, Doctor. We're going to page 1. There's an email from Peter Kaiser dated June 9th, 2012.

Do you see that?

A. Yes.

Q. In that email Peter says, "We cannot let the VIEW 2 team derail us from being published quickly. Get Andy to

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publish this in *Ophthalmology* and get this nightmare behind us."

Is that what he said?

A. That's what Peter was telling this group.

Q. Do you know who Andy is?

A. Yes.

Q. Who is Andy?

A. Andy Schachat.

Q. Was he the editor in chief at *Ophthalmology* in 2012?

A. At that time he was.

Q. Is that typical for authors that articles have just been rejected from the *New England Journal of Medicine* to call up the editor of another journal and get a paper published?

A. You know, actually, it's not uncommon for us. It's not so much to get it published, but for example, just recently I submitted an article to *American Journal of Ophthalmology*, and we wrote to the editor and asked the editor if he or she -- in this case it's a he, a Dr. Richard Parrish. We asked the editor if this was appropriate for the journal and if he felt that this was something that would be reasonable to be reviewed by that journal.

So that's not an uncommon procedure that we sometimes do in trying to figure out, you know where to publish certain things. And so, yes, we -- it's not uncommon for us to have conversations with the editor, again, just more about is this

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appropriate, what their initial thoughts are.

And then, of course, the way this works is the editor doesn't have the decision-making. He can then -- he or she can then take it in for consideration. It gets sent out to multiple reviewers. The reviewers will then make their recommendations. And based off those recommendations, something may or may not get published.

But this type of conversation is not -- I know Peter. He's a little -- should I say bombastic with his comments, but the overall gist of what he's trying to say is something that is not uncommon in any medical field in terms of trying to get a discussion with the editor and seeing what their thoughts are about is this worthy of review in their journal.

Q. We can take that down.

Let's move on to opinions you've provided about industry praise.

Do you recall providing those opinions just a few minutes ago, Dr. Csaky?

A. I did.

Q. You talked about industry praise for the VIEW 1 and VIEW 2 clinical trial results?

A. I did.

Q. Now you report -- and your slides today didn't report any praise, any industry praise for the DME or DR dosing ranges relating to five monthly loading doses; isn't that right?

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A. I did not.

Q. And the industry praise evidence you provided didn't say anything about the tonicity of the Eylea formulation; isn't that correct?

A. No, no. As I said, I'm not a tonicity person; so I wasn't looking for tonicity clips.

Q. Let's move on to the long-felt need. You also provided opinions on reported long-felt need; is that right?

A. Yes, I did.

Q. You would agree, though, that Dixon reported in that publication in 2009 the VIEW Phase III three loading dose, every-eight-week dosing regimen, correct?

A. Yes. Can we just -- if we're going to talk about Dixon, because I want to pull it up so I can just refresh my memory. Would that be okay?

Q. Sure. That's DTX 204. We're going to page 4 of that reference.

A. Found it. Okay. Yes, please. I'm sorry.

Q. It's also displayed on the screen here for you.

A. Yes. Thank you.

Q. You don't disagree that set forth here is the 2q8 dosing regimen that was being used in the VIEW 1 and VIEW 2 clinical trials, correct?

A. Oh, yes. So this is indicating the dosing regimens that were going to be tested in the VIEW 1-VIEW 2 trials.

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Q. This was in 2009?
A. This was in 2009.
Q. That's well before the filing dates of the '601 and '572 patents, correct?
A. That's my understanding.
Q. Now, at this point we pull up Claim 10 of the '601 patent, PTX 1, page 21.
Is it in front of you on your screen?
A. Could you just repeat that DTX number. I'm sorry.
Q. That is PTX 1.
A. PTX.
Q. It's also on the screen in front of you.
A. Okay. I'll look at the screen.
Q. Could we agree there's nothing in Claim 10 requiring a Phase III efficacy result?
A. Correct. I mean, this is a claim and doesn't relate anything to clinical trials.
Q. And, in fact, the word "efficacy" doesn't appear anywhere in this claim, correct?
A. Correct. Again, my understanding is there were subsequent claims that were dismissed that related to efficacy. But in this alone, there are no efficacy details.
Q. While we're here on this claim, it doesn't say "loading" anywhere in this claim, does it?
A. The word "loading" is not used. But, again, you

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know, when we talked about lexicon in our world, right -- so this is a claim wording, but if I were to show this to an ophthalmologist or a POSA and I asked him or her to say, "Okay. What do you think this is telling you to do?" and it says you will inject 2 milligrams approximately every four weeks for the first five injections, that in our world would be five loading doses.

Q. But the word "loading" doesn't appear anywhere in this claim, correct?

A. The word -- absolute word "loading" is not available.

Q. I want to move on to another document here, DTX 4135. I'd like to see what the Patent Trial and Appeal Board said about whether these eight-week dosing regimen claims that are silent on efficacy have any efficacy requirement.

Do you see that highlighted text up there?

MS. OBERWETTER: Objection, Your Honor. Foundation.

THE COURT: Fair. What's the --

MR. McLAUGHLIN: I'm sorry. I didn't hear the objection.

THE COURT: Foundation. What are we looking at? What are we talking about?

MR. McLAUGHLIN: You've heard a lot of discussion from Dr. Csaky today about efficacy and meeting efficacy --

THE COURT: What document do we have up that we're asking about?

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MR. McLAUGHLIN: This is an IPR. This is a decision from the Patent Trial and Appeal Board that I think would have been very informative to Dr. Csaky had he considered in formulating his opinions on whether efficacy was something that was read in these claims.

THE COURT: Let's start there and see whether he's ever been provided this, reviewed it, or researched it at all.

MR. McLAUGHLIN: Sure.

BY MR. McLAUGHLIN:

Q. First of all, let me ask you this: Do you recall relying on a declaration by Dr. Diana Do in the process of formulating your opinions?

A. There were portions -- as I recall, portions of her declarations that I relied on.

Q. And that declaration, you understand, came from these IPR proceedings?

A. I would have to review exactly those declarations that I reviewed in relationship to this document.

Q. Well, I'll represent to you that those did, in fact, come from these prior IPR proceedings.

Have you seen this document before, Dr. Csaky?

A. I said in -- if I reviewed it, I was reviewing it in the context of forming my opinion as it related to infringement, for example, and gathering information that would inform my opinion as it related to, in this case, infringement.

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So I -- if I did review it, it was specifically for that purpose.

Q. Okay. And if I could go back to page 23 of that document. I'm going it read this language to you briefly here.

"Based on the foregoing and our review of the record as a whole, we find no persuasive support for considering the preamble recitation of a method for treating a patient with an angiogenic eye disorder as requiring such treating to achieve any particular level of effectiveness, much less a high level of efficacy."

Do you see that?

MS. OBERWETTER: Objection, Your Honor. I think Mr. McLaughlin has established there's no foundation for him to ask Dr. Csaky about this document with respect to these opinions even if the preference would be to put PTAB decisions in front of the Court.

THE COURT: Overruled.

MR. McLAUGHLIN: I'll also note this is also in his Tab B of things that he's considered in the context of formulating --

THE COURT: It's been overruled. Ask your question again.

BY MR. McLAUGHLIN:

Q. Did you factor this language into your opinions as you were developing your opinions in this case?

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A. I may have -- you know, I can't recall exactly the specifics of this since I'm not that familiar with PTAB and those proceedings; so I couldn't put that into context of my world and what informed my opinion.

So these are the kinds of discussions and, again, that I may have seen, but I don't know how much role it played. I would have felt uncomfortable about allowing it to form my opinion if I wasn't sure what the context, who was it, what are the different requirements and things like that, as opposed to a -- something that someone that I'm familiar with, another POSA and what other folks commented on about their use of Eylea in their clinical settings.

So I can only comment at this point about I may have seen it, but again, because of my uncertainty about, again, all the details and the impact and where it was being -- so I may have seen it, but I don't think I would have used it to -- in a big way because of my uncertainty about the context.

Q. Let me ask you this, Dr. Csaky: Even with the Phase III data in hand from VIEW 1 and VIEW 2, we can agree that, when it comes to treatment of angiogenic eye disorders, there's still many patients with these disorders whose needs are still not met. Isn't that correct?

A. That's true.

Q. And in fact, you're the moderator of an HCP live peer exchange review titled "Unmet Needs for Patients with AMD."

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Isn't that right?

A. That's very true.

Q. If we put up DTX 9204.

Do you recall participating in this discussion?

A. Yes. And it's pretty recent, December 2021. So yes.

Q. The title is "Unmet Needs for Patients with AMD"; is that right?

A. That's correct.

Q. If we go to page 1 of that document, is that you in the upper left?

A. It's a resemblance of me. I hope that isn't the best picture you have of me, but yes, it is.

THE COURT: You're an adverse expert, Doctor. They picked that one on purpose. Just kidding. Just kidding.

MR. McLAUGHLIN: Promise that's not the case, Your Honor.

THE COURT: I know.

BY MR. McLAUGHLIN:

Q. So I'd like to turn to this selection on page 1. There's a quote attributed to you where you asked one of your colleagues a question, "Jennifer, is the race over? Are we going to be able to crack the durability nut? Is that the only nut that we have left to crack?"

Do you recall asking that?

A. Yes. I asked it. I don't recall, but I asked it.

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Q. Dr. Jennifer Lim, her response is that "I believe the durability question has been addressed to some point between the PDS" -- port delivery system -- "and faricimab."

Do you see that?

A. Yes.

Q. Lim does not mention -- Dr. Lim does not mention aflibercept, does she?

A. No.

Q. When this question was posed to another one of your colleagues, Dr. Holekamp, she mentioned visual acuity. And she says, "I must throw up my hands and say we don't control visual acuity. There's no agent we've tested so far reliably, at least in Phase III, that produces superior visual acuity outcomes."

Do you see that?

A. Yes.

Q. We can take that down.

I want to move on and try and get a little bit of clarity from you about where you stand on this question of the value of fixed regimens versus office visits.

Now, we can agree that there is nothing in the claims -- we just looked at Claim 10 of the '601 patent -- there's no language in the claims about excluding office visits, correct?

A. Correct.

Q. And now, even once clinicians had the VIEW 1-VIEW 2 data, you were still of the position that ultimately the issue for retina specialists will be which of those patients you were going to be able to inject and see back in three to four months versus patients who received an injection and may need to come back in every six to eight weeks. Until we can figure this out, we will have to continue to see our patients on a regularly frequent basis.

Was that a position you took in front of your peers?

A. Yes. I think it's always important to understand the context. And I'm assuming -- can you give me the date of that discussion?

Q. Sure.

Why don't we actually pull that up. That's DTX 9022.

And is that you that's third from the right there on the cover of this magazine?

A. Yes. Yes, that's me.

Q. If we go to page 10.

I'm sorry. Let's stay here for a second.

Top right, do you see the date, January-February 2012?

A. Correct.

Q. That refreshes your recollection about when this occurred?

A. Yeah. Exactly.

Q. If we go to page 10, the title of this selection in this magazine is "Ophthalmic Formulations: Safety and Efficacy of VEGF Neutralizing Drugs."

Do you see that?

A. Yes.

Q. So let's jump over to the page where you made that statement. This is on page 13, bottom left corner.

Can you see this?

A. Yes.

Q. And it's true that you made this -- you made these comments in the context of the VIEW trials; isn't that right? If you look at the top of this paragraph.

A. Yes.

Q. And yet, again, even with that data in hand, you still don't know which patients you're going to need to see in three to four months and which you're going to need to see in six to eight weeks; isn't that right?

A. That's correct.

So I think, again, it's important to understand the context in which we were -- so this is very soon after Eylea became available, right? And in many ways it's -- we're learning, obviously, as I think I've said multiple times, that prn and treat and extend were the directions that we were going. Right?

It doesn't mean that this is -- that I exclusively --

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or anyone at that point exclusively used prn and treat and extend. This was in the context of trying to figure out how best to use Eylea. You know, we've learned a lot over the years.

For example, it's a very interesting aspect that when I -- even in this context I look back in 2012, and we thought -- I'll give you a good example. We thought that fluid -- I've showed you the prns. And we had to dry things completely. Turns out that wasn't always necessary. So a lot of this, you know, was a work in progress.

And it was clear that, while that was the direction that we were heading as a group, it was nice and of course to have this availability of fixed dosing if we needed it under certain circumstances.

So I don't think this necessarily indicates that I never used fixed dosing. I think it kind of reflects our enthusiasm at the time of trying to see where we were with prn, treat and extend. So it's kind of -- it's context- and time-dependent. But at the same time, under certain circumstances, as I've testified on numerous occasions and as we've seen Dr. Do's testimony that I relied on and other forms, that there was a role for a fixed every-other-month dosing in certain patient populations in certain conditions.

So while this is -- and we've said this over. This was the direction of the field. It didn't preclude the fact

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that we had this in our back pocket, fixed dosing.

Q. And turning now to those -- the fixed-dosing regimens that you're talking about having in your back pocket back in that time frame, you, in fact, called these fixed-interval dosing regimens, including the eight-week regimen, burdensome; isn't that right?

A. Well, again, if you were going to think about this from a -- from every patient, it could have been construed at that time as burdensome. But at the same time, I would have hoped that I would have also said that prn dosing was burdensome. And so there were different approaches that we were trying to take.

And, again, I would have said that, for certain patients -- again, this was not a treatment regimen that I would have given to everybody, but it's something that I definitely would have said -- given to certain patients under certain circumstances. And, again, we're always trying to balance -- when we say burdensome -- all of the context for that patient and his or her family.

Q. Sure. And let's go ahead and take a look at what you've said about prn treatments and treat and extend in relation to fixed dosing.

A. Sure.

Q. Let's go to DTX 9013.

This is an article from just last year, is it not?

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A. Correct.
Q. From 2022?
A. Correct.
Q. This is titled "YOSEMITE and RHINE Phase III Randomized Clinical Trials of Faricimab for Diabetic Macular Edema: Study Design and Rationale."
So in this -- and you're a coauthor on this publication, correct?
A. Yes, I am.
Q. Here in the bottom left of page 1, going from the left-hand column to the right-hand column, you say, "Personalized treatment regimens such as treat and extend and pro re nata are often used to reduce treatment burden associated with fixed interval, every-four-to-eight-week intravitreal injections."
Is that what you said in 2022?
A. That was in the article, correct.
Q. And the reasons that a POSA like yourself would use personalized regimens is because, unlike in a clinical trial where you try to have a defined patient population, in the real world, as you state here, these personalized approaches may also address heterogeneity in individual anti-VEGF responses; isn't that correct?
A. Yes.
Q. Let's turn to another document, DTX 9009, and page 7.

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I want to direct you to page 7. I want to direct you to a quote from a Dr. Singh where he states near the bottom of this paragraph, that "In CATT, ranibizumab and bevacizumab had equivalent visual outcomes when injected on the same schedule. But that's not how we treat patients in the real world. We use treat and extend. We try to get them as dry as possible as fast as possible. We need to extend them as quickly as we can."

Do you see that?

A. Yes.

Q. Now, it doesn't sound like an endorsement for a rigid, extended fixed-dosing regimen, does it?

A. So again, I think with -- I think, as you've seen and as I think as I've presented to the Court, clearly this treat-and-extend prn dosing was a strategy that we were all pushing for, right? But the reality is that even in treat and extend, it can be burdensome because in some cases you can have patients that come in even more frequently than fixed every other month.

So while this is a nice general statement, the reality is that, as you pointed out, there's lots of heterogeneity. And in some cases this idea of having a fixed-schedule approach with a drug and a patient can obviate multiple visits and trying to find in certain patients that sweet spot.

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The other issue, of course, is, you know, treat and extend is such an unusual concept for patients, right? As we try to explain to certain patients how this is going to work, there are -- again, as I mentioned in my initial deposition, there are circumstances where, again, just explaining something simple is -- it's a very easy way to communicate to a patient to make sure that that patient understands what's happening.

So yes, this is the world -- this is relatively, you know, recent after CATT and HARBOR. And so we are still in this world of struggling what's the best way to treat. And as I said, even some of this data is what I would call outdated. So when Dr. Singh said dry as possible, there's now newer publications that says a little bit of fluid, actually, you do okay.

So this is the constant evolution. And I think in many ways it allows us to think about, in some cases, looking back at these fixed-dosing schedules and seeing that there was some degree of certainty that you would have these great outcomes that we saw in VIEW 1 and VIEW 2.

Q. Would it surprise you to learn that this was published in 2021?

A. No, not at all.

Q. Further down after Dr. Singh made his comment, you were quoted as saying, "Where I practice in Texas, it can take some time to process the insurance paperwork. We start with

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bevacizumab, but usually the patient is approved for a branded treatment in time for their second visit."

Do you see that?

A. Yes.

Q. Was that a true statement?

A. Yeah, there are some patients -- depending -- the majority of patients who are on anti-VEGF are on -- usually have CMS and copay. And then depending on the type of CMS and copay, you may or may not have to have prior authorization and other aspects that dictate what you can begin with and then what you can follow up with.

So yes, it's -- this is not an uncommon situation. It's also -- there's been many patients where I've started right off the bat with Eylea without having to have preauthorization.

Q. There are many patients that you've started off with bevacizumab; is that right?

A. For some patients, I start off with bevacizumab.

Q. And that's an off-label use of bevacizumab; is that right?

A. That's an off-label use of bevacizumab.

Q. So you're not discouraged from using bevacizumab in the absence of an FDA-approved intravitreal injection label; is that right?

A. Well, it's -- you know, it really depends on kind of

the time frame of bevacizumab. So I do think we have to be careful. It depends on the time period, right? So if we're talking when Phil Rosenfeld first presented his early data with using bevacizumab in 2005, that enthusiasm about bevacizumab is dramatically different than what happened in 2012, 2013, '14, and going forward.

So there was an evolution in bevacizumab. And having been involved in a lot of those discussions and at the CATT trial, there was a fair amount, as I think -- of concern about using an off-label drug. I mean, you use an off-label drug, guess who bears the liability burden? Thank you, attorneys.

And so there was a lot of concern, which is one of the reasons that Dan Martin -- and I actually helped Dan Martin with the CATT study because there were some people who either wouldn't use it because it wasn't absolute evidence that it worked. We actually in some cases had a separate consent form to make sure that patients fully understood that it was off-label back then.

So the evolution of bevacizumab is an interesting and -- evolution -- you really need to tell me if this is now in 2005 or '6 or is this in 2010, '11, or '12 when I made this comment.

Q. I think we just established this is 2021, Doctor.

A. Oh. So even more so that now in 2021 we've got CATT data, we have, obviously, millions of injections. And I think

we now have a much higher comfort level with bevacizumab.

Q. And you've been using bevacizumab for years; isn't that right?

A. Yes.

Q. Now, I'd like to direct your attention to page 10 of this article. Specifically, I'd like to direct your attention to this portion here that's highlighted on the screen where you say -- this is attributed to you, Dr. Csaky, right?

A. Yes.

Q. It says, "Aflibercept is an immunoadhesin, which is essentially a synthetic antibody but it's still the construct of an antibody."

Did you make that statement?

A. I did.

Q. Let's go on to page 12.

A. Can I just -- I really want to make sure I clarify that statement. Okay?

Q. No. That's okay. I'm moving on to the next question, Doctor.

THE COURT: Just respond to the questions posed, Doctor.

THE WITNESS: Okay. Thank you.

BY MR. McLAUGHLIN:

Q. Let's flip to page 12 of this document. There are a couple of quotes attributed to you on this page. And I'd like

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to direct your attention to one towards the bottom where it says "Dr. Csaky" -- this is attributed to you, Dr. Csaky, where you say, "My hope is that we'll have agents with better durability a year from now to help relieve that treatment burden for our patients."

Do you see that?

A. Yes.

Q. Was that a true statement you made in 2021?

A. Yes.

Q. Now let's turn to the second page of this article, page 2. Now, that's you pictured here in the center top?

A. Yes.

Q. Now, in connection with publishing this article, you had to disclose your financial relationships and commercial interests; isn't that right?

A. Correct.

Q. If we turn to page 3, it states here you're a paid consultant for Regeneron Pharmaceuticals; is that right?

A. That's correct.

Q. And also Genentech?

A. Correct.

Q. And then below your name is Diana Do, MD; is that right?

A. Correct.

Q. And is that the same Diana Do whose IPR declaration

you relied upon in this matter?

A. Correct.

Q. You'll see that here Dr. Diana Do discloses her financial and commercial interests, right?

A. Correct.

Q. And there she lists Regeneron Pharmaceuticals; is that right?

A. Correct.

Q. I'm going to shift gears a little bit. Let's turn to PTX 311. This should be the Heier 2012 article that you've relied upon in formulating your opinions in this case.

So, first of all, let me take you to the back. I just want to establish some information. This is on page 12, where it indicates the -- who the authors are associated with, which entities the authors are associated with.

Do you see that?

A. Yes.

Q. And the superscript 10 indicates a Regeneron Pharmaceutical association; is that right?

A. Correct.

Q. And superscript 11 indicates a Bayer HealthCare association; is that correct?

A. Correct.

Q. So if we turn back to page 1 of this article, there are at least one, two, three, four, five authors that are

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Regeneron employees or associated somehow with Regeneron that are authors on this article, correct?

A. Yes.

Q. And one of those is George Yancopoulos, the listed inventor of the '572 and '601 patents.

Do you see that?

A. Yes.

Q. Then there are four authors here with associations with Bayer; is that correct?

A. I'm assuming. I don't know those individuals, but their references seem like they work for Bayer.

Q. Because they're indicated with the superscript 11?

A. Yes.

Q. Now, you understand that in this VIEW trial both monthly ranibizumab and monthly aflibercept were evaluated head to head?

A. Correct.

Q. And aflibercept was never shown to be superior when dosed at the same frequency as ranibizumab; isn't that right?

A. Can you show me the -- I think -- can we look at the article VIEW 1. I think -- do we have that -- am I allowed to look at the entire article? Would that be okay?

THE COURT: Yes, Doctor.

BY MR. McLAUGHLIN:

Q. You don't recall, sitting here today?

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A. Well, I haven't -- no, I have not memorized the VIEW 1-VIEW 2 results. So if I could look at the results, I could refresh my memory, if that's possible.

Q. Sure. Let's take a look at those.

So I believe what you're looking for is found in Table 2?

A. No. It would be the --

Q. Page 67.

A. -- the visual acuity results --

Q. Yep.

A. -- of the two trials, VIEW 1 and VIEW 2.

Q. Let's go to change in ETDRS. Do you see that?

A. Right. But the way we look at these is similar to what I show with the PIER where we show the change in visual acuity over time. I think that is part of these -- of this publication. If you look at the -- there are these line graphs. I'm sorry to make this complicated, but that's the way we analyze this data. If you can go to --

Q. Sure. Why don't we look at that. That's Figure 3.

A. Okay. Yeah, there we go. Okay.

Q. Why don't we take a look at Graph C, the integrated data for the VIEW 1 and VIEW 2 trials.

A. Well, I also want to look at VIEW 1 as well.

Q. So let's start by looking at Graph C. 2q4 is the aflibercept monthly dosing arm, correct?

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A. Correct.

Q. And R q4 is the ranibizumab monthly dosing arm, correct?

A. That's correct.

Q. And the integrated data across both those studies shows that aflibercept was only -- the patients on average gained 9.3 letters of visual acuity.

Do you see that?

A. Yes. 2.2 milligrams q4, 9.3, correct, yes.

Q. And the ranibizumab arm patients showed on average gains in visual acuity of 8.7 letters.

Do you see that?

A. That's correct.

Q. Now, this data presented here was never considered adequate enough to come to the conclusion that monthly aflibercept was superior to monthly ranibizumab; isn't that correct?

A. The integrated data was, but there was some, you know, suspicion, if you look at the VIEW 1 data in particular, that -- if you look in that -- remember, there were two trials, VIEW 1 and VIEW 2. And if you can highlight the VIEW 1 results --

Q. I'm not asking about the VIEW 1 results. We looked at the integrated data. My question was about the integrated data.

A. Okay.

Q. And based on that integrated data, aflibercept has never been determined to be superior or show statistical superiority when dosed monthly compared to ranibizumab monthly; isn't that correct?

A. If you limit your analysis to the integrated data, that's correct.

Q. I'm going to switch focus a little bit here and let's -- I want to ask you some questions about some of the related patents in this family that you've reviewed in the process of formulating your opinions in this case.

So you've considered the prosecution histories of the '601 and the '572 patents; is that right?

I can show you the covers of those. We didn't bring them today because they're huge.

We can provide digital copies to the Court.

If we show you DTX 28, the cover page.

A. So these are -- I'm sorry. Refresh -- these are the -- what documents? These are the --

Q. These are the prosecution histories --

A. Okay.

Q. -- that, according to your Tab B, you've reviewed in connection with formulating your opinions in this case.

Do you recall reviewing that?

A. Yeah. To some degree as needed for my -- in forming

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my opinion, correct.

Q. What's shown here is the file history from the '601 patent. Do you see that?

A. Yes.

Q. Did you also review DTX 29? Do you recall doing that?

A. Yes. Again, as much as I was not aware of all of the details, I did a cursory review of these to begin to understand how this might help form my opinions.

Q. And did you -- and you also reviewed DTX 33, didn't you, the prosecution history for the '338 patent from this family?

A. Inasmuch as I could understand and how it might help in forming my opinion as a POSA as it related to these claims, I did that review, correct.

Q. Okay.

I'd like to call up PTX 3 at this point, the '572 patent. Now, what's shown here is a list of related U.S. applications. Do you see that?

A. Yes.

Q. And do you see there are a number of patents listed there --

A. Correct.

Q. -- that are related to the '572 patent?

A. Correct.

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Q. Those include the '338? That's at the bottom.
A. Correct.
Q. This is going kind of in reverse chronological order. Then next is '069. Do you see that?
A. Yes.
Q. Then '681?
A. Yes.
Q. '345?
A. Yes.
Q. And then the patent we're talking about here today, the '601.
A. Yes.
Q. The '205 patent?
A. Yes.
Q. Then, of course, the '572 patent, which all of this appears on the face of, correct?
A. Correct.
Q. Now, if we look at the earliest patents in this chain, U.S. Patent Number 9,254,338, are you aware that Mylan challenged and then the Patent Trial Appeal Board invalidated claims from that patent?
A. No, I was not aware.
Q. Are you aware that the '338 patent is directed to the same eight-week dosing regimen that's claimed in the '601 patent?

MS. OBERWETTER: Objection to the foundation with this witness.

THE COURT: Let's rewind a little bit, Counsel.

BY MR. McLAUGHLIN:

Q. I'll represent to you, Doctor, that the eight-week dosing regimen was claimed in the '338 patent.

And then are you also aware that Mylan challenged and then the Patent Trial and Appeal Board invalidated claims of the '069 patent?

A. So, again, you know, just so we're clear, if I stated or -- in my report these documents, I just want to make sure I'm clear to the Court that I'm not a patent attorney. So when I'm looking through these, I'm looking for help in forming my opinion as an ophthalmologist, as a POSA, right, not as a patent attorney litigating various aspects of patents and various procedural steps.

So I feel I'm entering into an uncomfortable area where that's not my role as an expert. I don't have expertise in assigning what the import is of various decisions and how this relates to the various claim constructions and things that are kind of patentese, we want to call it, rather than ophthalmology stuff.

THE COURT: Understood.

Repeat your question, Counsel.

BY MR. McLAUGHLIN:

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Q. Actually, why don't we do this.

Can we pull up DTX 4135 and put it next to DTX 9007.

You see on the left-hand document it says, "Determining all challenged claims unpatentable"?

Do you see that?

A. Correct.

Q. Under "Judgment"?

A. Correct.

Q. And this is with respect to the 338 patent?

A. Yes.

Q. And then on the right-hand side, same final judgment, determining all challenged claims unpatentable? And that's with respect to the '069 patent?

A. Correct. That's what's stated here.

Q. So is it safe to assume, then, that you've not factored these decisions into your analysis in this case?

A. I was asked kind of to -- specifically to look at the '572 and '601 patents in particular as an expert witness. And so I did not go back into the patent history of the various issues that are within the Court's purview. And so no, I did not do an extensive legal analysis of these types of documents, the implications, what the rulings mean. That's not what I did.

I was looking through these and seeing if there was anything that might help. And, again, recognizing the

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limitations of my knowledge base, my review was very cursory. So this is really not -- my area of expertise is not, surprisingly, patent law.

Q. Let's go to DTX 9015.

This relates to the '205 patent, which is directed to monthly dosing of aflibercept. Do you see at the top here it says, "I hereby disclaim the following complete claims in the above-identified patent, 1, 2, and 3"?

A. I see that written.

Q. Were you aware that Regeneron, rather than contest Mylan's IPR petition, chose to disclaim all claims of the '205 patent?

A. Again, I was -- I'm not aware -- and these are, again, documents that I may have used very cursorily in my report. But I'm not aware or I'm not really perhaps experienced enough to make any comment about what the implications, what's happening here, who are the parties, what this means in terms of disclosures. This is really not something that I would feel is in the area of my expertise.

Q. Let's move on to DTX 6444. This is Docket Number 433 from this case, titled "Regeneron's Stipulation Regarding Summary Judgment and Claim Narrowing."

So looking at the second bullet, the stipulation states, "Regeneron accepts summary judgment of invalidity of Claims 5 and 6 and 9 of U.S. Patent Number 10,888,601."

Do you see that?

A. I see that.

Q. And those were claims that you've previously opined are all valid; isn't that right?

A. I opined at the time -- when I reviewed these documents at the time, my working constructs were -- I was instructed on which claims were being contested, and I made my opening report based off that. And so I was told, I think, at some point that there was some changes in the visual acuity outcomes, as I was told. And that's the extent to which I then went back and said -- looked at my opinions and looked at, again, the -- kind of the sections and my perspectives kind of -- you know, in the absence of these claims.

Q. Turning to DTX 405, this is another patent disclaimer filed by Regeneron in connection with the '601 patent.

Did you know that, prior to this litigation, Regeneron had disclaimed Claims 3, 4, 13, 14, 22, 29, and 30 of the '601 patent?

A. Again, I'm not -- I can't comment on any of these. I wasn't involved in the litigation. I wasn't involved in the discussions. This is not something that I'm privy to or can offer or render an opinion or any statement in this regard.

Q. So you did not incorporate these developments into your opinions in this case, correct?

A. No. I was simply told to -- here were the specific

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claims that were now under considerations, and went back into my reports and looked at how I had constructed my arguments as it related specifically to the claims that we've been discussing during this trial.

Why and how it came to be that those were, I was not privy to any of those discussions and to the reasons for those decisions.

Q. So now that we've gone through some of the things where invalidity is decided or not contested, let's focus on a few elements that you think are contested.

So let's start with your Slide 30, PDX 8, and talk about the '572 patent, Claim 6.

A. Sure.

Q. The only thing you've pointed to as a disputed element is the isotonic solution element; is that correct?

A. For the anticipation analysis, that's correct.

Q. And you did not offer any opinions here on isotonic; is that correct?

A. I deferred all of my opinions to Dr. Trout.

Q. All right. Let's turn to the September 14th, 2009, DME press release. This is DTX 3198. You can go to page 2.

Your only complaint with respect to this reference is that it expressly says three loading doses rather than five loading doses; is that right?

A. That's correct. The major -- when I reviewed this

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press release as it related to the five loading doses, I did not see a five-loading-dose regimen outlined here.

Q. But you admit that there is a 2-milligram as-needed regimen after three monthly loading doses, correct?

A. Correct.

Q. There's also a 2-milligram monthly arm, correct?

A. There is a 2-milligram monthly arm, correct.

Q. So Regeneron went with a 2-milligram every-single-month arm despite these systemic side effects that you were talking about earlier today, correct?

A. So I think, again, it's critical to put this in context, right? Well, for one thing, this is a --

Q. That was a yes-or-no question, Doctor.

You opined earlier today that there were systemic side effects that would have discouraged somebody from going from three loading doses to five; isn't that right?

A. That's correct.

Q. What Regeneron did was design an arm of their Phase II trial that was straight monthly dosing; isn't that correct?

A. That is correct.

Q. It's also true, when you were discussing the Lalwani reference, what she did or what she described was the doubling of doses, correct, in the treatment of DME?

A. Yes. If I recall, it was a doubling from .5 to 1.

It may have been .3 to .5. I can't recall the details of the result. It was an increase in the dose, for sure.

Q. That's despite these supposed concerns about systemic side effects; is that correct? That she made that proposal?

A. Well, I don't know -- I mean, these considerations at the time -- first of all, we were focusing on ranibizumab. And so we had some data from ranibizumab, but the -- as I recall, she would -- she did not recommend continued dosing with multiple high doses of ranibizumab. I don't think that was part of the strategies.

And the issues of safety still existed. I mean, we're still in the -- in this period of time when we're trying to navigate what exactly is happening as it relates to patients and their potential for stroke and heart attacks when getting intravitreal anti-VEGF injections.

Q. And in view of those concerns, in Lalwani they still recommended the doubling of ranibizumab doses, correct?

A. Yes.

Q. Now, I want to talk to you about the -- this hypothetical -- a hypothetical prn protocol. So I'm going to take you to PDX 1.124. This may be a slide that you've seen before. And I want to talk about the prn dosing for DME as it relates to the press release, DTX 3198, okay, as if you were one of the clinical inventor investigators in that study.

Do you understand?

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A. Correct.

Q. So I want you to assume for purposes of my next set of questions that we're going to be using the row here that says 2q prn. Do you see that?

A. 2q prn, correct.

Q. So you don't dispute that in the press release were described three monthly loading doses, correct?

A. Correct.

Q. So that's a dose at Week 0, one at Week 4, one at Week 8; is that correct?

A. That's correct.

Q. Then at Week 12, according to the DA VINCI protocol, the clinical trial subject would come into the office for evaluation at Week 12; isn't that right?

A. That's correct.

Q. And you performed an assessment on that subject, right?

A. Correct. Along with OCT and vision and a full examination, correct, to assess activity or no activity of the macula in terms of dryness or not.

Q. And then upon performing that assessment, if the patient meets the re-treatment criteria, you would provide an injection at that visit, correct?

A. Correct. If it met the -- typically on these prn trials, there are strict criteria that dictate when you could

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not re-treat, right? So there are -- whether it was a little bit of fluid, maybe not; if there was more fluid, maybe yes. So there's these criteria that investigators would use during these prn visits that will then inform us as to whether or not we should or should not inject.

Q. Right. So this patient came in, they met the re-treatment criteria, they got an injection at Week 12. Okay?

A. Correct.

Q. The subject comes back to your office at Week 16. You perform the assessment. And once again, the subject meets the re-treatment criteria. You inject at that visit, correct?

A. If they met the injection criteria, then you would inject.

Q. Okay. It's now Week 20. And as before, the subject returns to your office for an evaluation, but here now the retina looks dry. The patient doesn't meet any of the re-treatment criteria. You withhold an injection; is that correct?

A. You would not inject at that visit, correct.

Q. And that brings us to Week 24, where once again the subject comes in for their monthly visit. If they meet the re-treatment criteria, you administer an injection; is that correct?

A. That's correct.

Q. And that's one scenario that any competent

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ophthalmologist could work out under the 2q prn regimen; isn't that correct?

A. If you mean the regimen that a competent ophthalmologist would have said is three loading doses plus prn, you can't look into the future and say if a patient will or will not need an injection. That's why it's a conditional injection, right?

So an ophthalmologist would have said, question mark, does that person need an injection? Question mark, does that person need an injection? So that would have been the protocol that an ophthalmologist would have designed under a prn dosing regimen.

Q. And what we see here is one scenario in which that would have happened. And what we're looking at are five monthly injections, correct?

A. We see -- again, we see injections being given on a conditional basis, right? So I think --

Q. That wasn't the question, Doctor. I'd like for you to answer my question.

What we're seeing here are five monthly injections, correct?

A. These are injections, if the patient meets prn criteria, that they would receive injections on a monthly basis.

Q. Now, Dr. Csaky, before the patent's issued here, you

had used Avastin to treat AMD; isn't that right?

A. That's correct.

Q. And you recognized back then even that some patients may need more injections for DME; isn't that right?

A. That's correct.

Q. So let's turn to DTX 9014.

This is a January 2010 article from *EyeNet* titled "Avastin: New Hopes and Hesitations." Now, if we go to page 4, there's a quote that's attributable to you, Dr. Csaky, where you say, "Avastin is becoming standard of care for AMD."

Do you see that?

A. Correct.

Q. And you go on to say, "Sometimes you have to give more injections for DME."

Do you see that?

A. So I just want to make sure we qualify, "standard of care for AMD if you use the definition of what the community is doing."

Q. Was this a true statement that you made in front of your peers at this meeting in January of 2010?

A. Yes.

Q. So you managed to figure out how to give more injections even without any FDA-approved label for Avastin for ophthalmic use; isn't that right?

A. Again, in this scenario it's -- in this construct

during this period of time, as I was talking about, where we were actively interrogating patients, right, using OCT, determining how many injections, what the degree of fluid was, with the caveat again that with DME we had a little bit more wiggle room. So yes, we could, depending on that individual patient, change and manage their strategy on this kind of personalized approach.

Q. And then you go on to comment about the use of Avastin further. This is from page 1, where you say, "We don't know how to use Avastin. We don't know when to stop it. We don't know if the dose is correct."

Do you see that?

A. Correct. And --

Q. The article goes on to say, "Who will respond? Do you give seven injections and then stop? It's all seat of the pants, and it's made more implicated because we don't have guidelines."

You said that, correct?

A. Remind me of the date of this.

Q. January of 2010.

A. Right. So again --

Q. You said those words, correct, Doctor?

A. I did say those words.

Q. All right. I'm going to shift gears a little bit here.

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Do you recall providing opinions pertaining to the written description of the claims of the '601 and '572 patents?

A. I did.

Q. And in connection with providing your opinions on written description support regarding the five monthly injection DME-DR claims, you relied on Example 5; is that right?

A. Can I pull up the patent to remind myself what Example 5 is?

Q. Sure. Actually, why don't we bring up your -- call up a snippet from your report, DTX 2027, page 224, paragraph 406.

Here you state, "Example 5 clearly identifies the treatment of DME using a similar dosing regimen," correct?

A. Can I just have one second to find the patent? Would that be all right?

Q. Sure.

THE COURT: What exhibit tab is the patent available at, Counsel?

MR. McLAUGHLIN: Should be PTX 1.

BY MR. McLAUGHLIN:

Q. Do you have that, Doctor?

A. Yes, I have it. Thank you so much.

Q. Example 5 shows up on page 17 of PTX 1.

A. I'm sorry. Example 5, we're on page 17, correct?

Q. We're on page 17 of the PTX number, Column 14.
A. Correct. Yes. I see that now.
Q. Towards the top, Example 5.
A. Yes.
Q. You understand this to be a recitation of the DA VINCI Phase II clinical trial?
A. That's correct.
Q. Is it still your opinion that Example 5 clearly identifies the treatment of DME using a similar dosing regimen to those that are claimed?
A. This is an example that -- in the specifications as one of several areas in the specification that outlines the treatment of DME.
Q. Do you recall using Example 7 of the '572 patent to illustrate that the specification provides various examples of a finite number of secondary doses?
A. I'm sure I did if you're going to bring it up for me.
Q. Okay.
Why don't we pull up DTX 2027, page 211, paragraph 378. You state here, "The patent specification provides various examples of regimens with a finite number of secondary doses."
Do you see that?
A. Correct.
Q. You state that "Example 7 discloses dosing regimens

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having two, three, four, five, six, and seven secondary doses."

Do you see that?

A. Correct.

Q. I want you to keep that statement in mind, and I want to turn to PTX 722, which I believe you've seen before. This is the October 1st, 2007, *Retinal Physician* article. Do you recognize this document?

A. Yes.

Q. And if we go to page 1 and we look at this comment from Dr. Hariprasad where he describes one of the ways that he treats AMD, he states that "I treat with ranibizumab monthly until optical coherence tomography (OCT) shows the macula to be completely free of fluid. Some patients reach that point after two injections. Others require as many as eight injections."

Do you see that?

A. Correct.

Q. So he talks about starting off loading doses with as few as two, as many as eight; isn't that right?

A. Well, he's defining these injections in order to achieve using OCT a macula which is free of fluid.

Q. Right. And, actually, I'm going to come back to that.

Let's use the parlance of the '601 and '572 patents and its use of the term "secondary doses." Okay?

A. Sure.

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Q. So using that definition, what he's talking about is anywhere from one to seven secondary doses; isn't that correct?

A. In the context of evaluating patients, he's defining -- again, the minute you start using conditions like -- he even says, "I use OCT to demonstrate the macula to be completely free of fluid." Then in -- my perception of this is he is not necessarily in this sense using a fixed-dosing approach; he's using a prn approach or a regimen that requires that he create a dry macula.

Q. And in that context he identified one to seven secondary doses, correct? Yes or no.

A. Yes.

Q. And that same article articulated the concept of eight-week dosing intervals, correct, as explained by Dr. Brown?

A. No.

Q. That's not an eight-week dosing interval that we're looking at right there?

A. No.

Q. "I give three monthly injections and see them in eight weeks."

Do you see that?

A. Correct.

Q. So that's an eight-week interval that he's seeing the patients; isn't that correct?

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A. He's seeing them; he's not necessarily treating them.

Q. In the act of seeing them, he's going to evaluate them. And if they need an injection at that eight-week mark, the patients are going to get that injection, correct?

A. Well, it depends.

Q. It depends on what?

A. So, for example, if I see --

Q. It depends on the OCT readings, correct?

A. OCT and vision. And so in doing my -- like I said, this conditional evaluation, what happens is -- for example, let's say there was fluid. Could very well be that at that step I start to rethink my diagnosis. I start to think about doing additional testing.

So this approach of seeing them first -- and it's critical that he says I see them -- or that I treat them and see them, but I see them, is exactly what's meant by this personalized approach. You're seeing these patients. And then based off what you see, you can make a treatment decision. There is situations -- I'm just asking -- I mean --

Q. Are you making a statement, or are you answering my question, Doctor?

THE COURT: We need to get back to a question-and-answer setup here.

THE WITNESS: Sure.

BY MR. McLAUGHLIN:

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Q. We're going to be here for a very long time.
A. I'm sorry. So say that again.
Q. Let me take you to the very next sentence in his statement. He says, "If fluid is absent at that visit, I give another injection."
Do you see that?
A. Yes.
Q. Thank you.
THE COURT: Counsel, why don't we take a break at this point.
MR. McLAUGHLIN: Sure.
THE COURT: We'll take ten minutes.
Doctor, you are still off limits for conversation.
But we'll take ten minutes and resume at that point. Thank you all very much.
(A recess was taken from 2:35 p.m. to 2:51 p.m.)
THE COURT: Counsel, you may continue.
MR. McLAUGHLIN: Thank you, Your Honor.
BY MR. McLAUGHLIN:
Q. Let's go to DTX 3089.
Doctor, this is a Chun reference from 2006 reporting on ranibizumab in DME. I'd like to take you to page 3.
Can you confirm that -- and I want to go to the visual acuity and central retinal thickness measurements

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section of this on page 3.

Can you confirm that this reference reports the low-dose group gained a mean of 12 letters?

A. Yes.

Q. Let's move on to DTX 4069.

This is the Nguyen 2009 reference looking at ranibizumab again in the treatment of DME. If we look at the abstract, this involved 126 participants, correct?

A. Yes.

Q. And under the results it's reported that the patients in Group 1 achieved 7.24 letters in visual acuity gain, correct?

A. Yes.

Q. Let's go to DTX 3096.

This is a DRCRN 2010 article. This is a report of the design and outcome of a clinical trial using ranibizumab in the treatment of DME.

If we go down to the results, you see that patients gained on average nine letters in visual acuity?

A. Yes. The ranibizumab and deferred laser group gained nine letters.

Q. And it further reports that no systemic events attributable to study treatment were apparent.

Do you see that?

A. Yes.

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Q. Let's get on to DTX 4215.

It's the Arevalo reference from 2007.

In this reference under "Participants," it reports there are 110 eyes that were assessed.

Do you see that?

A. Yes.

Q. Then this study reports in the "Results" section that 55.1 percent improved by greater than or equal to two ETDRS lines of BCVA.

Do you see that?

A. Yes.

Q. That's the same as a ten-letter gain?

A. Yes.

Q. Now, I want to ask you a little bit about PrONTO. I know that's been a topic of discussion today.

Let's pull up DTX 3215.

This is the Engelbert 2010 reference. And let's go to page 2, where the Engelbert authors were commenting on the PrONTO study on the left-hand column.

And they note -- towards the bottom of that paragraph that begins "the PrONTO study," they note about midway there, "As a result of the PrONTO study, PrONTO-style dosing has become popular in the retina community."

Do you see that?

A. Yes.

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Q. So now I'd like to turn to paragraph 352 of your responsive expert report. This is DTX 2027 at pages 201 and 202.

Do you recall providing a chart along with your opinions that described the ranibizumab clinical trial dosing regimens?

A. Yes.

Q. So it's the case, though, that the prn PrONTO-style protocol that had become popular and has shown visual acuity gains was omitted from your chart on this page; isn't that correct?

MS. OBERWETTER: Objection. Outside the scope of direct.

THE COURT: How is this related to the direct, Counsel?

MR. McLAUGHLIN: This goes -- all he did today was talk about prn and PrONTO, and this goes right to the heart of that matter.

THE COURT: Overruled.

THE WITNESS: So this graph is --

BY MR. McLAUGHLIN:

Q. I'm not asking you what it is; what I'm asking you is you left PrONTO off this graph, correct?

A. I did not make this graph.

Q. And you didn't endeavor to correct the graph to add

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PrONTO?

A. I did not add PrONTO to this graph.

Q. All right. Now I want to turn to talking about the q12 regimen that you've talked about today. And you've provided an opinion in your opinion that Genentech repeatedly tried and failed to demonstrate that Lucentis could be used effectively on extended dosing regimens, right?

A. I indicated there were several trials on quarterly following three monthly doses that did not get to the same visual acuity as monthly dosing.

Q. But you are aware that the FDA approved Lucentis for 12-week dosing, are you not?

A. Yes.

Q. And that's in the Lucentis label, correct?

A. That's correct.

Q. Since 2006?

A. That's correct.

Q. It's not your testimony that the FDA would approve a drug dosing regimen that it deemed a failure, right?

A. That's correct.

Q. Let's go to the Mitchell reference. That's DTX 4061.

And I'd like to draw your attention to page 6. What's shown here, as indicated in the Figure 3 legend, is a subpopulation study of the PIER trial patients. I'd like to direct your attention to the top line with the triangles.

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Now, according to this substudy, 40 percent of initial responders in the PIER study were able to maintain the gains from the loading-dose phase; isn't that correct?

A. That's correct.

Q. So for these 40 percent of patients that were able to maintain their vision while receiving far fewer injections in their eyes, this was certainly not a failure, correct?

A. Unless you were -- happened to be in the other groups that lost vision, then you're --

Q. I'm asking you about the 40 percent of the patients that were in this arm that showed the ability to maintain vision while receiving far fewer injections. They would not have considered that a failure, would they?

A. If you happened to be fortunate enough to be in that group in this one study, then this would not have been a failure.

Q. And you agree that the PIER 12-week regimen was a fixed-interval dosing regimen, correct?

A. Correct.

Q. Now let's go back to Dixon. That's DTX 0204.

I'm going to ask you a little bit more about Dixon. Let's see what the prior art was saying about the CLEAR 2 trial, the Phase II trial aflibercept.

So let's get to page 5 of Dixon.

While we're waiting for Dixon to come up, I'll ask

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you this: You understand that there were several treatment arms in the CLEAR-IT 2 trial, right?

A. Correct.

Q. And one of those arms involved the administration of four monthly injections followed by prn dosing?

A. That's correct.

Q. Do you recall that?

A. Yes.

Q. Now, if we go to page 5 of Dixon in the right-hand column, there's a paragraph that begins "data from the Phase II study."

A. Correct.

Q. This states, "Data from the Phase II study of VEGF Trap-Eye were positive," correct? It says that?

You see that, Doctor?

A. Yes, I see it says "were positive." Correct?

Q. And it also goes on to say, "Results from the noninferiority Phase III trials will establish its efficacy versus ranibizumab."

Do you see that?

A. Yes.

Q. Let's look and see what else Dixon disclosed about the CLEAR-IT 2 regimen and results.

Do you recall providing testimony today about the CLEAR-IT 2 study design?

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A. Yes.

Q. But in that discussion you didn't touch on the CLEAR-IT 2 results, did you?

A. No.

Q. All right. Let's go to page 4 of Dixon and Section 2.6.2. And the Phase II section there on the left.

So you would agree --

Actually, let's go to the next paragraph, the one just below this, where it says, "Patients initially treated with 2 milligrams of aflibercept, or VEGF Trap-Eye, monthly achieved mean improvements of 9.0 letters."

Do you see that?

A. Yes.

Q. And 29 percent of those same patients achieved greater than or equal to 15 ETDRS letters at 52 weeks.

Do you see that?

A. Yes.

Q. It also reports that the median time to first reinjection in all groups was 110 days.

Do you see that?

A. Yes.

Q. That means that after the loading dose phase, the median time to patients receiving their first -- the next first injection was 110 days, right?

A. In all the groups, correct.

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Q. That's almost four months, correct?
A. Almost four months, correct.
Q. And Dixon cites to Reference 45 of the Dixon reference, correct, for this clinical trial data?
A. Correct. That's the 45 reference.
Q. Okay.
Why don't we pull up DTX 3173.
And this is entitled "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results."
Do you see that?
A. Yes.
Q. And it's indicated this was presented on September 28th, 2008?
A. Yes.
Q. Let's turn to page 6. This section that's highlighted here, that's the arm that received four monthly injections of aflibercept, correct?
A. Yes.
Q. Followed by prn treatment?
A. Yes.
Q. Let's see what happened to those patients. Let's go to page 12. If we highlight the Row 2 2 mg q4, what this reports is that these patients needed on average only 1.6 injections over the course of that prn dosing period from Week 12 to Week 52, right?

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A. Yes.

Q. And the range is indicated as 0 to 4, meaning that one or more patients required no injections between Week 12 and Week 52, correct?

A. Yes.

Q. Let's go to slide -- or page 13 of this document.

And again, the 2 mg q4 arm, the second row, indicates that the median number of days to first reinjection was 150 in this arm.

Do you see that?

A. Yes.

Q. That's about five months, is it not?

A. Yes.

Q. Let's jump to page 19 of this document. You understand that the fewer than 15 letters lost is a common primary end point in these types of clinical trials?

A. Yes.

Q. And in this clinical trial, the 2q4 arm showed that 100 percent of the patients in that arm hit that end point, correct?

A. Yes.

Q. Let's go to page 26. "Safety: Serious Adverse Events" is the title of this slide. It says, "Systemic serious adverse events: None deemed to be drug-related."

Do you see that?

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A. Yes.

Q. Let's jump to the conclusions slide, page 28.

"VEGF Trap-Eye achieved clinically meaningful and durable vision improvement over one year."

Do you see that?

A. Yes.

Q. Up to nine mean letters gained in Week 52?

A. Yes.

Q. And up to 160 microns reduction in central retinal lesion thickness, correct?

A. Yes.

Q. I want to shift gears a bit here and pull up a DTX 917. This is a November 22nd, 2010, email from -- looks like somebody called newsdesk@broadcast.shareholder.com to George Yancopoulos.

Do you see that?

A. Yes.

Q. And it states, "Today announced" -- I'm sorry. Regeneron and Bayer "today announced that in two parallel Phase III studies in patients with neovascular form of age-related macular degeneration (wet AMD) all regimens of VEGF Trap-Eye (aflibercept ophthalmic solution), including VEGF Trap-Eye dosed every two months, successfully met the primary end point compared to the current standard of care, ranibizumab, every month."

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Do you see that?

A. Yes.

Q. And then going down further where it says "About VEGF Trap-Eye."

Do you see that section on page 2?

A. You have to highlight it for me, please.

Q. It states there on November 22nd, 2010, that "VEGF Trap-Eye is specially purified and contains iso-osmotic buffer concentrations allowing for injection into the eye."

Do you see that?

A. Yes.

Q. This is what is disclosed here?

A. Yes. It says that it's an iso-osmotic buffer concentration.

Q. Let's jump to DTX 918, page 1.

This is an email from the same date, November 22nd, 2010, that reports that more than 33 million -- there were more than 33 million views of that morning's announcement.

Do you see that?

A. Yes.

Q. So if the person of ordinary skill in the art needed to have these Phase III results to ensure the need was solved, those results were publicly known before the earliest filing date for the '572 and '601 patents, correct?

A. This would have been shared with those individuals

who were seeing this report, correct.

Q. All right. Dr. Csaky, you've reviewed Regeneron's '758 patent in offering your opinions in this matter, correct?

A. Correct.

Q. If we could pull up DTX 4213.

Would you agree that the cover page of this document states this patent term extension petition is with respect to 7,374,758 U.S. patent number at the top there?

A. Yes.

Q. And if we go to page 2 of this document, do you agree, looking at Bullet 1, that Regeneron identified Eylea as the relevant approved product covered by the '758 patent?

A. Yes.

Q. Then turning to page 4, Bullet 9.

Let's go down a little bit further where we see the claims.

Regeneron stated to the patent office that at least the following claims of the '758 patent claim a method of using the approved products, Claims 1 and 2.

Do you see that?

A. Yes.

Q. When you were looking at questions of nexus in this case, did you consider that fact?

A. Again, I'm not sure I included a comprehensive understanding and perspective of nexus as it relates to claims.

I looked at this simply from the viewpoint of a POSA as whether or not this was informing us about the claims.

Q. Okay. Let's go to another document, DTX 3501. We'll go to page 1, the cover here.

This indicates that this relates to U.S. Patent Number 7,070,959. Do you see that?

A. Yes.

Q. This is another patent term extension petition. Do you understand that the '959 patent expired last Friday?

A. No, I did not.

Q. And when you were looking at questions of nexus, did you consider this document?

A. Again, I don't think I went into a complete detail of nexus as I was making my opinions on the -- from the POSA's perspectives on patents that were under consideration.

Q. Let's go to another document, DTX 4956.

This is a Regeneron 10-K form filed with the SEC in March 2005.

Do you see that?

A. Yes.

Q. Are you aware that in March 2005 Regeneron filed a Form 10-K with the SEC publicly disclosing that Regeneron was starting clinical trials of aflibercept through intravitreal injection in mid-2005?

A. No.

Q. If we could turn to another document, PTX 1027.

So you mentioned your publication coauthored with Dr. Diana Do in your direct exam. Do you remember that?

A. Yes.

Q. You talked about these systemic safety risks associated with aflibercept?

A. Correct.

Q. So if we turn to page 9 of this document, can you confirm that when you wrote this paper you -- both you and Dr. Do reported that this study had been supported by research funding from Genentech?

A. Did we report that?

Q. You did report that, did you not?

A. Yes, I did report that.

Q. So you were receiving -- so at the time that you were talking about potential risks of using aflibercept, you were a paid consultant with Genentech, correct?

A. Yes, but --

Q. All right. Next --

THE COURT: Yes is good enough for now, Doctor. Thank you.

BY MR. McLAUGHLIN:

Q. Let's take a look at DTX 2027.

This morning at around 9:47 a.m. you talked about justification of striking references from Dr. Albini's slide

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for loading doses.

A. Yes.

Q. That a POSA won't apply any results from CRVO or AMD to DME. Do you remember that?

A. Yes.

Q. Why don't we take a look at DTX 2027, your responsive expert report in this case, page 213.

And in the middle of paragraph 382 here's what you say:

"The POSA would have understood that the specification defined angiogenic eye disorders as any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage according to the common characteristic of their etiology and thus their ability to be treated by anti-VEGF therapy."

Do you see that?

A. Yes.

Q. So your report you said that when you're looking at angiogenic eye disorders, which includes AMD and DME and DR, you said that a POSA would have understood that they had a common etiology; namely, they're able to be treated by anti-VEGF therapy. Correct?

A. Yes, but --

THE COURT: Yes is good enough for now, Doctor.

BY MR. McLAUGHLIN:

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Q. Let's turn to PTX 1145.

This is the Schmidt-Erfurth publication that you were talking about earlier today. At the time that she wrote this publication, are you aware that she was running the VIEW 2 clinical trial for Regeneron?

A. She was involved, as far as I recall, in the -- part of the -- I think, one of the VIEW trials.

Q. And you talked about there being no reasonable expectation of success that a POSA could use these regimens to maximize vision gains.

Do you recall saying that?

A. And "these regimens" would be?

Q. The claimed regimens that are at issue in this case.

A. Yes.

Q. Let's use the '601 patent Claim 11 as an example.

Does the '601 patent Claim 11 -- actually, I'll withdraw that.

Actually, I want to bring you to DTX 5431.

I believe this is another publication that you were presenting information about earlier today, the Shahraki publication?

A. Yes.

Q. Let's go to page 11 of that document.

A. Yes.

Q. Let's see what the authors say here.

So starting with the "Shenasi and colleagues" comment, they say, "Shenasi and colleagues evaluated the effect of subconjunctival bevacizumab immediately after the excision of primary pterygium. They concluded that the combination therapy is well tolerated, but it cannot significantly reduce the recurrence of pterygium."

Do you see that?

A. Yes.

Q. Now let's go to the first page of that Shenasi reference that they refer to there, DTX 9030.

MR. McLAUGHLIN: And we have copies.

MS. MAZZOCHI: May I approach?

THE COURT: You may.

BY MR. McLAUGHLIN:

Q. Let us know when you have that in front of you, Doctor.

A. I do have that in front of me.

Q. Let's go to the first page, the "Methods" section.

A. Uh-huh.

Q. Here it says that bevacizumab was being injected into the eye, correct?

A. Into the -- under the "Methods" section in the first page?

Q. Correct, about halfway through this paragraph.

"Subconjunctival bevacizumab, 1.25 milligrams,

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injected immediately after surgical excision."

Do you see that?

A. Correct. That was not into the eye.

Q. So that was a direct injection into the eye?

A. It's not into the eye.

Q. I'm sorry. I didn't hear that?

A. That's not into the eye.

Q. What is that?

A. That's into the conjunctiva.

Q. And the conjunctiva, that's the surrounding tissues --

A. Correct.

Q. -- around the eye?

A. Correct. You don't enter into the eye.

Q. It's not intravitreal?

A. At this point it's not intravitreal. That's correct.

Q. And the conclusion was still that this administration of bevacizumab cannot significantly prevent the recurrence of pterygium, correct?

A. Correct. This study did not show that.

Q. Now, let's turn to the other one that you relied upon, the Kasetsuwan paper.

I believe this is DTX 9031. And if we blow up the methods section and the purpose.

Let's go about halfway down where it begins

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"Topical" -- I'm sorry. Also under purpose.

"This study was designed to assess the efficacy and tolerability of topical bevacizumab."

Do you see that?

A. Yes.

Q. And if we go down into the methods section, it states, "Topical bevacizumab and placebo were applied in the respective groups four times daily for three months."

Do you see that?

A. Yes.

Q. That is not a method as claimed in the claims of the '601 or '572 patents, correct?

A. As far as -- it is not intravitreal.

Q. And it's not on the same schedule, correct?

A. It's not on the same schedule.

Q. Let's look at the next reference that the Shahraki publication referred to.

This is DTX 5431. This is at paragraph 11 -- I'm sorry -- page 11.

This is the Shahraki reference, and it mentions on page 11 a Hwang and Choi article.

Do you see that?

A. Sure. Yes.

Q. What they report here about that study is that they compared the recurrence rates of pterygium removal surgery

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associated with topical MMC, cyclosporine, and bevacizumab. And what they reported is that they observed no difference between the control group and the group that received topical bevacizumab.

Do you see that?

A. Yes.

Q. And then the last reference that the Shahraki publication mentions -- this goes over onto the next page. And it has a citation of 148.

Do you see that?

A. Yes.

Q. What they report there is that "In a recent study, two different concentrations of topical bevacizumab were used following pterygium removal of 90 patients, and the recurrence rates were compared between the groups. Pterygia recurred in 13.3 percent in the 5 mg/mL group, while no recurrence was observed in the 10 mg/mL group. Thus, the authors concluded that the 10 mg/mL concentration of topical bevacizumab is more effective than the 5 mg/mL dose in preventing pterygium recurrence."

Do you see that?

A. Yes.

Q. So, again, that is not an intravitreal injection of bevacizumab, is it?

A. At this stage it is not an intravitreal injection.

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Q. Let's go to page 20 of DTX 5431. And there's a reference to -- a reference number 148 which cites to an author Motarjemizadeh.

THE COURT: Would you mind spelling that for the record, counsel?

MR. McLAUGHLIN: Absolutely. That's M-O-T-A-R-J-E-M-I-Z-A-D-E-H.

THE COURT: Thank you.

MR. McLAUGHLIN: We're going to mark that paper as DTX 9032. Let's pull that up on the screen.

BY MR. McLAUGHLIN:

Q. If we take a look at this one, at the abstract, what we see again is that bevacizumab was given topically, correct?

A. Correct.

Q. And not only that, but it was given topically four times a day for one week, right?

A. Yes.

Q. And the low dose didn't work; only the high-dose group did?

A. Yes. The 10 mg/mL concentration was more efficacious.

Q. We can agree that Claim 6 does not permit dosing regimens of topical administration four times a day for a week, right?

A. That's correct.

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Q. Now, you also mentioned that you believed aflibercept would work for PVR. Do you recall that?

A. Yes.

Q. Let's take a look at what we will mark now as DTX 9033, "Efficacy of Intravitreal Injection of Bevacizumab in Vitrectomy for Patients with Proliferative Vitreal Retinopathy, Retinal Detachment: A Metaanalysis of Prospective Studies."

Do you see that on the screen?

A. Yes.

Q. And if we go to the conclusion on the first page, can you confirm that the conclusion there reads, "Based on the available evidence, intravitreal injection of bevacizumab in vitrectomy for patients with PVR-related retinal detachment did not decrease retinal redetachment rate or improve visual acuity," correct?

A. That's what it states.

Q. This was published in 2018; is that right?

A. That's correct.

Q. Let's take a look at a couple more. Let's start with DTX 9034. This is a Tousi reference, "Intravitreal Injection of Bevacizumab in Primary vitrectomy to Decrease the Rate of Retinal Redetachment: A Randomized Pilot Study."

And if we can go to the abstract.

So, again, this was an intravitreal injection of bevacizumab, correct?

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A. It is intravitreal bevacizumab.

Q. And if we look at the conclusion there, it says, "Our preliminary results show neither benefit nor any harm from intervention in both anatomic and visual outcomes."

Do you see that?

A. Yes.

Q. Let's take a look at DTX 9035. This is a Falavarjani reference.

And I can spell that again. That's F-A-L-A-V-A-R-J-A-N-I.

This relates to the "Intrasilicone Oil Injection of Bevacizumab at the End of Retinal Reattachment Surgery for Severe Proliferative Vitreal Retinopathy."

Here again, if we take a look at the abstract, bevacizumab was injected, correct?

A. Yes.

Q. It was injected into the silicone -- I'm sorry -- injected into the silicone oil at the end of retinal reattachment surgery for rhegmatogenous retinal detachment.

Do you see that?

A. Correct.

Q. All right. If we go to the conclusion, it states here that "intrasilicone injection of bevacizumab at the end of vitrectomy for RRD with severe PVR does not eliminate the risk of postoperative PVR."

Do you see that?

A. Yes.

MR. McLAUGHLIN: I have no further questions. Pass the witness.

THE COURT: Redirect?

REDIRECT EXAMINATION

BY MS. OBERWETTER:

Q. All right. Good afternoon, Dr. Csaky.

A. Good afternoon.

Q. I have a few additional questions based on some of the questions that Mr. McLaughlin had for you.

First of all, if I can direct you back towards the beginning of the cross-examination, you had some questions about what was marked as DTX 9024, which was a roundtable discussion that I believe you participated in.

Do you still have DTX 9024 in front of you?

A. Just please project it. If I have to look for it, it's going to be a problem.

Q. I'm not sure we actually have it loaded onto our system as it was not a produced document.

THE COURT: Do you know in which binder or stack that might be? I'll join the doctor's position on finding something.

MS. OBERWETTER: I do not know, unfortunately, which binder it was in.

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THE COURT: What's the exhibit number again?

MS. OBERWETTER: It's DTX 9024. And I'm sorry we're doing this old school.

THE WITNESS: DTX --

MS. OBERWETTER: I believe it was Volume 2.

THE COURT: Yeah, Volume 2, Madam Clerk indicates. Thank you.

The smaller of the two binders, Doctor.

Bear with us at the front of the room, please. Thank you.

BY MS. OBERWETTER:

Q. And if it's helpful, it has the picture that Dr. Csaky was not enamored of. And it's called "Unmet Needs for Patients with AMD."

THE COURT: It's in cross exhibits, Volume 2, 9024.

THE WITNESS: 9024. Yes, that's my mug. Okay.

BY MS. OBERWETTER:

Q. Do you have it, Dr. Csaky?

A. Yes, I do have it.

Q. Mr. McLaughlin directed your attention to the bottom of page 2 and the top of page 3 of that document and had some questions about one of your comments about durability.

Do you recall that?

A. Yes.

Q. And do you recall that one of the potential responses

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to that offered by the panelists was the port delivery system?

A. Yes.

Q. What's a port delivery system and what has happened to that?

A. Yeah. So the port delivery system is -- was a new technology that was developed by Genentech. It's essentially a -- basically a piece of plastic that goes into the eye, and it allows the injections to go through this little port rather than going through the skin of the eye.

We surgically place it. And the idea is that this little device can contain ranibizumab for longer periods of time and therefore increase the durability as it slowly releases ranibizumab.

Q. Is that device currently in regular and active use by a large number of doctors?

A. No. It's been recalled by the FDA because of problems with manufacturing. And the device actually has issues with consistency and was a probable safety concern.

Q. And the other reference in that paragraph I believe was to a drug called faricimab. How long after Eylea was approved did faricimab come out?

A. Faricimab was just approved as of February of last year.

Q. I'm going to change topics a little bit. And I'd like to direct your attention to some questions that

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Mr. McLaughlin had for you about whether aflibercept is an antibody.

Do you remember those questions?

A. Yes.

Q. Can you explain what is an immunoadhesin and whether aflibercept is a, quote, antibody?

A. Yes. So I happen to -- I actually worked on immunoadhesins. I actually made these. And so the idea is that they are a purely synthetic recombinant protein. Yes, they have a synthetic portion of the antibody, but they're not generated in any form or fashion like an antibody.

You make these in a purely genetic way. And so the construct has a portion that is -- has some sequences that are similar in the Fc portion; but unlike being made like an antibody is being made, you make these purely with recombinant DNA technology. And then of course the other portion is purely recombinant. So it's completely different than a naturally occurring or even any type of modified antibody.

So that's a very important distinction that I actually happen to have personal experience with.

Q. Thank you.

I'd like to change topics a little bit and take a look at the Heier 2012 reference, which was PTX 311, please.

And this one we should have -- we should be able to put up on the screen. And if we could take a look at that page

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marked 8 that had the tables that Mr. McLaughlin asked you about. You recognize this as the Heier reference, Dr. Csaky?

A. Yes.

Q. And we'll advance forward to page 8.

Mr. McLaughlin had some questions for you about the integrated table and what that showed. Could you please comment on what the VIEW 1 table that you wanted to comment on shows?

A. Yeah. I think one of the interesting aspects -- and it's one of the things that Regeneron was actually looking at. If you look at the VIEW 1 results, what you actually see at the top line is the 2-milligram aflibercept given every month. And what you see is that says 10.9 letters of gain, and in the exact same trial, that's the top line there. And, interestingly, if you look at the ranibizumab same regimen every four weeks, it actually is almost three letters worse.

So there was some interesting initial data from VIEW 1 that there could be the possibility that aflibercept was, in fact, better than ranibizumab.

Q. Okay. Was the primary benefit the extended interval?

A. Yes. So the ultimate -- because of the ultimate outcome and the fact that it was not inferior, the actual, as it went to the label, was this idea of extended fixed dosing.

Q. Okay.

We can take that document down.

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I want to go back to the September 2009 press release that Mr. McLaughlin asked you about.

If we can pull up DTX 3198 again. And, again, if we look at the second page of this document and pull out the DME paragraph there toward the top.

Mr. McLaughlin had some questions for you about the 2-milligram monthly arm. Do you remember that?

A. Yes.

Q. Can you please comment on whether the use of the 2-milligram monthly arm in the Phase II trial would have affected the reasonable expectation of success as to safety?

A. Again, in these kinds of trials, there's several limitations, right? One is the fact that there was a restriction. In this study in particular, some of the inclusion criteria included restricting patients who potentially were at risk for developing strokes and heart attacks. So, again, there was a reduction in the type of profile that we're having.

And the other thing that's really important to remember is in these trials there's data safety monitoring boards. And these review the data very, very carefully. And if there's any even hint of a safety concern, that arm gets stopped.

So in the context of a trial, as we're trying to decipher signals -- small signals, big signals -- the decision

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to include this in a trial carries with it lots of restrictions and boundaries that really relates to ensuring the safety of this type of 2-milligram monthly dosing.

Q. Thank you.

We can take that document down.

I'd like to talk about another document that Mr. McLaughlin showed you. And, again, I think this one you may need to fish out of your pile. It's DTX 9014. And it's that article printed in color that says "Avastin: New Hopes and Hesitations."

THE COURT: 9014?

MS. OBERWETTER: Yes, Your Honor.

THE COURT: I have 9015. There it is.

MS. OBERWETTER: It sounds close.

THE COURT: It does sound close.

Yeah, same binder, Doctor, second smaller binder.

THE WITNESS: Thank you.

DTX -- say that again.

BY MS. OBERWETTER:

Q. It's 9014, and it's that article printed in color.

A. Yes, yes, yes. I got it. Thank you.

Q. So I'm going to direct you to the bottom of the first page of the article. And it's one of the paragraphs that Mr. McLaughlin directed you to that contained one of your quotes. It's the one that includes the phrase "it's all seat

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of the pants."

Can you please explain what you were -- what that paragraph of this article is about.

You have me on the first page. You're looking down toward the bottom right of the first page.

A. I got it. Here we go.

So, again, this is now -- we've had some beginning experiences with Avastin. We don't have any clinical trial guidelines yet. This was in 2010. So we don't have any guidelines about the whole idea behind Avastin. And so I think the point of Avastin, even more so than with ranibizumab, we had very little guidelines as to, A, how effective it was, what type of approaches we should be using in patients.

So I think it's fair that, with Avastin in particular, we were really trying to kind of work out and figure out what were treatment regimens and approaches that we could use with Avastin since we really had only had it for five years, and we were beginning to get kind of some -- we didn't really have lots of guidelines.

So we were all a little bit -- not just me, but I think all of us were a little bit undirected. And we were trying to figure out exactly what was the full potential for Avastin.

Q. And how much experience was there with aflibercept at this point in time in clinical practice?

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A. None.

Q. I'd like to talk about a different document. And this one, I think we can put up on the screen. It's PTX 722. And this is the October 2007 reference that Mr. McLaughlin showed to you.

There's a quote that he showed to you on the first -- I believe it was on the first page that we looked at earlier.

If we can highlight or pull out those -- yes. Thank you. That is exactly the paragraph I was looking for.

And just to clarify for the record, is this a reference to a prn dosing strategy?

A. Yes.

Q. And how can you tell that?

A. So very simply. I mean, you look at these qualifiers, when the macula is completely free of fluid, when the macula is dry. So, again, these are all indicators that this OCT machine was being used and that in this case the physician was using those tools -- it even says that -- to make treatment determinations.

Q. Okay.

We can take that document down.

Mr. McLaughlin had a series of questions for you using the word "nexus."

Do you recall that generally?

A. Yes.

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Q. Were you able to tell from his questions exactly what nexus he was asking you about?

A. No.

Q. I'm going to change topics a little bit. And I'd like to talk about some of the references that arose toward the end of the examination. And, in particular, Mr. McLaughlin asked you a series of questions about pterygium.

Do you recall those?

A. Yes.

Q. You recall those additional references?

A. Yes.

Q. Did the additional references that were provided to you by Mr. McLaughlin affect the point that you were making about angiogenic eye disorders?

A. No.

Q. And why not?

A. No, because the point of these diseases is -- and of course they are much more complete and comprehensive review articles and ongoing trial results.

And the point of this was to indicate that these are angiogenic eye disorders and they could be treated with an anti-VEGF agent. Whether we're using topical or, down the road, some form of intravitreal is still to be determined, but the point is that these references -- there are, of course, many more. My colleagues -- in particular, my cornea

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colleagues -- are very excited about using anti-VEGF agents in the treatment of pterygia.

Q. And Mr. McLaughlin also asked you some questions about PVR.

A. Yes.

Q. And my question is the same. Do the additional references affect your point about angiogenic eye disorders in light of what you know about how aflibercept is being used?

A. No. I mean, I found an article -- an article, clinical trial, that showed that intravitreal bevacizumab was effective, right? And, again, if you look at the work of Andrius Kazlauskas and his work with the clinicians at the University of Chicago, Illinois, there was an ongoing trial -- actually, the beta trial -- that was in bevacizumab for PVR.

So there's been a lot of interest in interrogating with some success in the biology in particular of VEGF and anti-VEGFs in PVR. It's really good science. And so there's a lot more that we could add to this -- to the repository of articles that support my opinion.

Q. I'd like to take a look at -- I'm going to change topics a little bit. I'd like to take a look at PTX 1027, which is that article that you coauthored with Dr. Diana Do.

If we could pull that back up.

Mr. McLaughlin had some questions about a passage toward the end of the article where he pointed to who

participated in funding some of the work for the article.

Can you please provide the context and explanation for how this article came to be.

A. Yes. I mean, this is something that Diana and I talked about doing. It's not uncommon for us to reach out for kind of writing support. You know, we write the manuscript and then we need somebody to help kind of wordsmith it. And so the key thing that every journal wants to see -- and I think this is the key point. Both authors were involved in the design and conduct of the study, collection of data management analysis and interpretation of data and preparation, review, and approval of the manuscript. That was left up completely to Diana and I to write this in the way that we thought represented the state of the knowledge when we wrote this article.

Q. And what was going on in the art at the time that made you interested in writing this article?

A. Yes. It's exactly this point, that there was already some data, if we'd looked at ongoing trials, SAILOR, for example showed a slight difference in stroke rates between .5 and .3. There was this concern -- Bob Avery had started to look at systemic levels following an intravitreal injection.

And then we had this molecule, aflibercept, that again had these higher affinities and potentially higher duration in the systemic circulation. So we wanted to really

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call attention to our colleagues. And, again, it's not something that we typically think about in our day-to-day lives. And suddenly here we were faced with giving new medicines into old people, into diabetics who potentially were sick. And we really wanted to make sure that we raised the specter for everybody to be aware of this potential issue.

MS. OBERWETTER: Nothing further, Your Honor.

THE COURT: Recross?

MR. McLAUGHLIN: Just one question, Your Honor.

THE COURT: I'm going to hold you to that.

MR. McLAUGHLIN: Understood.

RECROSS-EXAMINATION

BY MR. McLAUGHLIN:

Q. Dr. Csaky, you just made reference to some various articles, references, clinical studies. However, today, despite having multiple opportunities to do so, you've not been able to identify anything from the published medical literature that showed intravitreal aflibercept dosed on the Claim 6 schedule that actually worked to treat formed corneal neovascularization, proliferative vitreal retinopathy, pannus, or pterygium in humans, correct?

A. That's correct.

MR. McLAUGHLIN: Thank you.

Thank you, Your Honor.

Thank you, Dr. Csaky.

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THE COURT: Redirect?

MS. OBERWETTER: No, Your Honor. Only exhibits if we should do that at this point.

THE COURT: Yeah. Let's go ahead and do that. If I could ask you, Ms. Oberwetter -- you can remain seated if you'd like. Just get closer to a mic so we can hear you clearly. And slowly, of course, the newest local rule we have.

Doctor, if you'll bear with us for one moment.

MS. OBERWETTER: Yes. We have DTX 212, which I believe we previously used on day two. And we probably misspoke and called it PTX 212, but it's DTX 212.

DTX 3105, DTX 3112, DTX 3186, PTX 821, PTX 841, PTX 1027, PTX 1143, PTX 1145, PTX 1146, PTX 1155, PTX 1447, PTX 1794, PTX 3225, and DTX 9014.

THE COURT: Seeing no objections from your own table, Counsel.

Any objections to any of those from the adverse party?

MR. McLAUGHLIN: No objection, Your Honor.

THE COURT: Without objection, each of those identified by Ms. Oberwetter will be hereby admitted.

(DTX 3105, DTX 3112, DTX 3186, PTX 821, PTX 841, PTX 1027, PTX 1143, PTX 1145, PTX 1146, PTX 1155, PTX 1447, PTX 1794, PTX 3225, and DTX 9014 were admitted.)

THE COURT: Exhibits from Mylan.

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MR. McLAUGHLIN: Yes, Your Honor. I tried to deduplicate as counsel was reading them off. I apologize if I repeat any.

DTX 9, DTX 10, DTX 12, DTX 28, DTX 29, DTX 33, DTX 405, DTX 917, DTX 918, DTX 2027, DTX 2733, DTX 3082, DTX 3089, DTX 3096, DTX 3051, DTX 4069, DTX 4135, DTX 4213, DTX 4215, DTX 4956, DTX 9007, DTX 9008, DTX 9009, DTX 9013.

DTX 9014, that might have already been read in.

DTX 9015, DTX 9022, DTX 9024, DTX 9030, DTX 9031, DTX 9032, DTX 9033, DTX 9034, DTX 9035, PTX 1027.

And then -- actually, I'm having to actually withdraw one of these, DTX 2027.

THE COURT: Off the list.

MR. McLAUGHLIN: Off the list. Thank you.

THE COURT: Thank you, Mr. McLaughlin. Does that comport with the rest of your table's list?

It seems so. Outstanding.

Any objections from the adverse party?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, the list -- with 2027 being withdrawn?

MR. McLAUGHLIN: 2027.

THE COURT: 2027 being withdrawn. Otherwise, Mr. McLaughlin's list, without objection, is hereby deemed admitted.

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(DTX 9, DTX 10, DTX 12, DTX 28, DTX 29, DTX 33, DTX 405, DTX 917, DTX 918, DTX 2027, DTX 2733, DTX 3082, DTX 3089, DTX 3096, DTX 3051, DTX 4069, DTX 4135, DTX 4213, DTX 4215, DTX 4956, DTX 9007, DTX 9008, DTX 9009, DTX 9013, DTX 9015, DTX 9022, DTX 9024, DTX 9030, DTX 9031, DTX 9032, DTX 9033, DTX 9034, DTX 9035, and PTX 1027 were admitted.)

THE COURT: Doctor, thank you, sir. You may step down. Thank you very much. Whatever's there, leave. We'll tidy up.

Why don't we take a ten-minute break. We'll let everyone reshuffle in here. I'd ask folks to use that time wisely and efficiently to distribute binders and the rest. I'm assuming we're going to do Dr. Trout next; is that correct?

MR. BERL: Correct, Your Honor.

THE COURT: All right. Let's take ten while we rearrange the courtroom. If I could ask counsel to grab whatever's left here from Dr. Csaky and pass out the rest, and then we'll get started with Dr. Trout. Thank you all.

(A recess was taken from 3:50 p.m. to 4:05 p.m.)

THE COURT: Yes?

MS. MAZZOCHI: A quick housekeeping matter, Your Honor. I know that you said that, as we got closer to the end of the trial days, people would either be happy with or angry with the keeper of the time. The way in which we've been

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calculating things, just based on Your Honor's average trial day, et cetera, by our estimates, defendants have about three hours left; plaintiffs have about 90 minutes left.

If we were to subtract out some of the time that plaintiffs have indicated they want to use for deposition designations, we can lower that a bit more.

Since there was an agreement for an even split between the parties in terms of time and we've been -- we've tried to be very judicious to make sure we have enough time for a full and effective cross-examination at the end, we just want to make sure that we're going to be able to get our full time to do the complete cross-examination of Dr. Csaky.

THE COURT: Trout?

MS. MAZZOCHI: I'm sorry. Trout. Apologies.

THE COURT: Yeah, I would assume we'll start and stop Dr. Trout, resume tomorrow with him. And then I know we've yet to talk about -- how long are the videos?

MR. BERL: Your Honor, I actually have some good news in that regard. We've decided, in view of how the evidence came in, we are not going to play any of those videos. So Dr. Trout is the last witness. I think we have some differences from the calculations. Honestly, I don't really think it matters. We're going to finish tomorrow.

THE COURT: Indeed we are.

MR. BERL: They'll have the time that they need.

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THE COURT: We don't have any choice.

Yeah. Okay. Noted. Understood.

MS. MAZZOCHI: Thank you.

THE COURT: Let me ask this before we get started. Any issues if we resume tomorrow at 8:30 a.m. to get a running start on the day?

MR. BERL: No issues at all.

THE COURT: All right. And for those lucky associates in charge of ordering lunch and the rest, I will know in the morning if we're taking another early lunch tomorrow based on the weather forecast and my 11-year-old daughter's softball schedule tomorrow. So I'll let everybody know as soon as I can tomorrow what our outlook looks like. But let's get started at 8:30 tomorrow and hit the ground running.

With all that, Regeneron may call its next witness.

MR. BERL: Your Honor, Regeneron calls Bernhardt Trout.

THE COURT: Doctor, if you wouldn't mind repeating from last week, I believe.

THE WITNESS: Yes, Your Honor.

BERNHARDT TROUT, PHD, PLAINTIFF'S WITNESS, SWORN

THE COURT: Thank you, sir. Once you're comfortable, if you wouldn't mind adjusting that mic.

With that, you may proceed.

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DIRECT EXAMINATION

BY MR. BERL:

Q. Good afternoon, Dr. Trout.

A. Good afternoon, Mr. Berl.

Q. We're here to talk about validity today. Did you evaluate validity from the perspective of the person of ordinary skill?

A. Yes, I did.

Q. Okay.

Can we put up Demonstrative 2 on the screen.

Can you read into the record your definition of the person of ordinary skill.

A. Yes.

"The POSA would have held an advanced degree such as a master's in a biopharmaceutical science or related discipline such as chemical engineering and several years of experience in the development of biologics product. Alternatively, the POSA could have a PhD in such discipline and less experience."

Q. Did you meet the definition of a person of ordinary skill in 2006?

A. Yes, I did.

Q. How so?

A. Well, I actually had a PhD then, and I had been doing relevant research since 1998, at least. So I met that definition.

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Q. Do you understand Mylan's definition of the POSA to differ substantially from yours?

A. No, not much.

Q. Would any of your opinions be different if Mylan's definition were used instead of yours?

A. No.

Q. And did you apply the Court's claim constructions in your validity analysis?

A. Yes, I did.

Q. I'd like to ask about some background issues before we get into the prior art itself.

What is aflibercept?

A. Well, aflibercept, as we've heard for the past couple weeks, is what's known as a fusion protein. So it's made up of three different pieces of three different proteins. And we could call it a Frankenstein molecule because it's a nonnatural molecule.

Q. Let's look at PTX 1826, the Aruffo article. Did you review this article in connection with your work in the case?

A. Yes, I did.

Q. And if we look at page 1 and blow up one excerpt, beginning with "fusion proteins" and "these proteins consist," can you explain what Aruffo is telling us.

A. Yes. And I guess just to be clear, it continues, "These proteins consist of the constant regions of

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immunoglobulin, typically mouse or human, fused to an unrelated protein or protein fragment."

So basically what I said, they're nonnatural proteins that are made by fusing various parts of other proteins.

Q. And what are the parts of the aflibercept fusion protein?

A. So one of the parts is what's called the constant domain of an antibody, so a piece of an antibody. And then there are two other parts from two different receptor proteins.

Q. You heard Dr. Rabinow testify last week about a fusion protein and an antibody being largely the same thing.

Do you agree?

A. No, I don't agree.

Q. How are fusion proteins different from antibodies?

A. Well, as I've been emphasizing, fusion protein is made of different pieces of other proteins. It's not natural. Antibodies have evolved over time or are part of nature.

Q. Were fusion proteins known as of 2006?

A. Yes.

Q. Were any commercially available?

A. Yes.

Q. Let's look at one of the slides shown by Dr. Rabinow. It was his Slide 47.

Let's put that on the screen.

Do you remember this chart you put up of stable

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protein formulations?

A. Yes, I do.

Q. Did Dr. Rabinow identify any fusion protein drug products on this slide?

A. No. And as a matter of fact, each of those is highlighted because they're all antibody, noting that ranibizumab is an antibody fragment, a piece of an antibody.

Q. And the next one in the chart, that's bevacizumab, is that also called Avastin?

A. Yes. That's correct.

Q. And is that a fusion protein or an antibody?

A. No. That's an antibody.

Q. Now, do fusion proteins and antibodies have the same properties?

A. No.

Q. Okay.

Let's bring up the Fast reference. That's PTX 1835.

Did you review this article in connection with your work on the case?

A. Yes, I did.

Q. And if we go to page 15. And we'll also show an excerpt from page 19 below it, beginning in the paragraph that starts "intact antibodies."

Can you explain the relevance of the Fast disclosure?

A. Yes. And I've highlighted, I think, the relevant

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pieces of that section.

"In comparison with native IgG proteins" -- like the ones on the previous slide -- "wherein interdomain interactions presumably here evolved to provide mutual stabilization, fusion proteins may lack such stabilizing interdomain stabilization."

And then a little skip there, but goes on to say, "This has been seen in other artificial fusion proteins as well."

And this referenced the Souillac, which is a bit more of a technical article.

Q. What is this conveying with respect to the relative expected stability of antibodies on the one hand compared to fusion proteins on the other?

A. Well, this is conveying that the skilled person or the person of ordinary skill in the art would expect that fusion proteins could be less stable than antibodies.

Q. And the Souillac reference that's cited for this proposition, in what year was that published?

A. That was published, as highlighted here, in 2005.

Q. And the proposition about the expected relative stability of fusion proteins compared to antibodies, would that have been consistent or inconsistent with the POSA's thinking as of 2006?

A. That would have been consistent. This is illustrative of what the POSA would expect.

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Q. Now, I'd like to turn to obviousness and invalidity over the prior art now, Doctor.

Do you understand that Dr. Rabinow testified that the asserted claims of the '865 patent are invalid on three bases: Fraser plus Lucentis; Fraser plus Liu; and, thirdly, Dix?

A. Yes.

Q. Do you agree with Dr. Rabinow's opinions?

A. No, I do not.

Q. Let's take them one at a time. And let's start with Lucentis plus Fraser.

Let's take a look at 2.13.47.

Now, you heard Dr. Rabinow -- or did you hear Dr. Rabinow testify first about Claim 1 and then about the asserted claims?

A. Yes, I did.

Q. Is that how you conducted your anticipation and obviousness analyses?

A. No, that is not. I started with the asserted claims -- for example, Claim 4 here -- noting that Claim 4 depends on Claim 2. Claim 2 depends on Claim 1. And I looked at all of that together.

Q. Now, in order to reference Dr. Rabinow's testimony and demonstratives, I'm going to go back to his demonstratives even though they address Claim 1 and the dependent claims separately.

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Is that okay?

A. Okay.

Q. Before we get into the various limitations of the claims and the details of these references, do you think a POSA looking to make a formulation to treat eye diseases would have selected Fraser and the Lucentis references from all of the available prior art?

A. No.

Q. Why not?

A. Well, there was quite a bit of prior art. And there's no particular reason why the POSA would be pointed to those two references.

Q. Do you think the POSA would have any reason to choose to combine Fraser and the Lucentis references of Gaudreault and Shams?

A. No. There's no reason.

Q. Is that how formulation research is done, to take a formulation form from one molecule and combine it with another and put them together?

A. No, it is not.

Q. Is there any reason that Dr. Rabinow provided that you heard to choose these references from amongst all of the prior art?

A. No.

Q. Now, Doctor, I understand your opinions, but unless I

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specifically say otherwise, I'd like you to assume for the rest of your testimony about this combination that the POSA would have combined Fraser with Lucentis as Dr. Rabinow urges.

Can you make that assumption?

A. Okay.

Q. Now, let's go back to Claim 1 for a moment.

What does Claim 1 recite with respect to the claimed VEGF antagonist?

A. Well, it's what's highlighted here. It's a VEGF antagonist. But it's not just any; it's a specific one. It's got to be glycosylated. And it comprises a specific sequence of amino acids that is specifically defined and described in the patent.

Q. Let's go to Dr. Rabinow's Demonstrative 51.

And what did Dr. Rabinow rely on to meet those limitations in his Fraser plus Lucentis combination?

A. Well, Dr. Rabinow relied on this disclosure in Fraser which says VEGF Trap R1R2.

Q. And does Fraser disclose the limitations that we're discussing relating to the VEGF antagonist in Claim 1?

A. No, it doesn't. It doesn't disclose this sequence.

Q. Do you recall that Dr. Rabinow relied on Holash as somehow being incorporated into Fraser?

A. Yes.

Q. And if we look at the next -- does Fraser incorporate

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Holash?

A. No. Holash is just one of the many references in Fraser.

Q. Now, I understand your opinion there, but I'd like to look at Holash nevertheless. That's DTX 3549. And we've shown part of page 2 of the Holash reference.

Does that disclose the amino acid sequence recited in Claim 1 of the '865 patent?

A. No, sir, it does not. It just discloses this schematic here which does not disclose or relate the sequence.

Q. Are these disclosures from -- are these the disclosures from Fraser and Holash that Dr. Rabinow relied on to meet these claim limitations about the amino acid sequence of aflibercept?

A. Yes.

Q. And to be clear, do either disclose the claimed amino acid sequence?

A. No, neither do.

Q. And did you highlight in red boxes for the disclosures that don't meet the claim limitations in Dr. Rabinow's demonstrative?

A. Yes, I did, right here on the screen.

Q. Now, do you recall Dr. Rabinow discussing the Papadopoulos reference, DTX 3619?

A. Yes, I do.

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Q. Do you understand Papadopoulos to be part of either of Dr. Rabinow's obviousness combinations?

A. It is not.

Q. Do any of the references in Dr. Rabinow's obviousness combinations cite or discuss Papadopoulos?

A. No.

Q. Now, Doctor, did you prepare a demonstrative exhibit summarizing the fusion proteins disclosed by Papadopoulos?

A. Yes, I did.

Q. And were those sequences voluminous in Papadopoulos?

A. Yes.

And the summary, Your Honor, is here in this table, all the different -- I just have the names here. You can imagine each of those sequences is about a page or longer. But the Papadopoulos discloses all of those.

MR. BERL: And for the record, this is marked as DTX 3619A.

BY MR. BERL:

Q. Doctor, can you explain what is shown here.

A. Yes.

So this is a list that I've prepared. On the right side are different names as disclosed in Papadopoulos. On the left side are the figures that are in Papadopoulos. Those figures actually contain the sequences listed out.

Q. Doctor, there are a lot of letters on this table.

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I'd like to discuss a couple of them with you. What is Flt1, or Flt1?

A. Yes.

So that, Your Honor, might be new in terms of the abbreviation, but all it means is the same as this VEGR1. Biologists may have a certain sense of humor in naming different proteins, but that's just the VEGF R1.

Q. So that's VEGF Receptor 1?

A. Yes. Correct.

Q. And there's also something in here that's referenced as Flk1. What's Flk1?

A. Well, again, Flk1 is just another name for the VEGF Receptor R2. So the Flt and the Flk together are the R1R2.

Q. And we saw earlier that there was a description in the references that Dr. Rabinow testified about to VEGF R1R2.

Do you remember that?

A. Yes.

Q. And how many fusion proteins does Papadopoulos describe that fall within that categorization?

A. Well, it describes these two. I've just highlighted in the table, the small reproduction of the table, the two that I just mentioned. And here on the upper right side is where they are in the text. And, again, it tells you that R1R2 are just the Flt1 and the Flk1.

Q. And are you showing on the right-hand side part of

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page 60 of DTX 3619, the Papadopoulos reference on about lines 4 to 5?

A. Yes. That's correct.

Q. Do these two fusion proteins that are denoted R1R2 have the same sequence or different sequences?

A. They have different sequences.

Q. How do you know?

A. Well, I did a comparison. I talked about a different comparison last week that I did. But I did a comparison here using the same National Institute of Health software. And I showed that the sequences, as we say, do not align. In other words, they're different.

Q. How would the POSA interpret the references to VEGF Trap R1R2 in the literature such as Fraser?

A. Well, the POSA would interpret them as meaning a multiplicity of different sequences.

Q. Now, the claims also require that the VEGF antagonist is glycosylated; is that right?

A. Yes. Correct.

Q. Very briefly, Dr. Trout, what is glycosylation again?

A. Very briefly, it's the addition of carbohydrate groups, or kind of extended sugar groups, to various sites in the protein.

Q. And why does glycosylation matter?

A. Well, I think it could be a number of reasons. But

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for the standpoint here, I think it matters because, if a molecule is glycosylated, it makes it bigger, more voluminous.

Q. You said that proteins can be glycosylated at certain sites; is that right?

A. Correct.

Q. Now, if those sites are present, if those amino acids are present, will the protein always be glycosylated?

A. Not necessarily, no. Not always, I should say.

Q. And let's look at the Sinclair reference. That's PTX 1773. Did you review this reference?

A. Yes, I did.

Q. And let's look at page 2 of that reference beginning with the sentence that says, "Most naturally occurring consensus sequences in secreted proteins are not glycosylated."

What is this conveying as relevant to your opinions?

A. Well, it's conveying, again, what a POSA would know and what I just stated, which is that not all proteins are glycosylated.

Q. And is that true even if they have the sites that would potentially permit glycosylation?

A. Yes. That's correct.

Q. Let's turn back now to Dr. Rabinow's slides and focus on the glycosylated requirement.

Now, does Fraser teach that VEGF R1R2 is glycosylated?

A. No, it does not.
Q. Does Fraser say anything about glycosylation?
A. No, it does not.
Q. Did you hear Dr. Rabinow refer to Papadopoulos with respect to glycosylation?
A. Yes.
Q. Did Papadopoulos describe glycosylation of the sequence recited in the '865 patent claims?
A. No.
Q. Is that disclosed anywhere in the prior art, as far as you know?
A. Not as far as I know. Not as far as I've seen.
Q. Now, if we go back to Papadopoulos at page 82 of the reference, what sequence did Papadopoulos disclose the glycosylation of?
A. Well, as I've showed here in this excerpt that there are five possible glycosylation sites. And it describes a different molecule or different fusion protein than the one in the '865 patent.
Q. So to be clear, what we have here at line 20 in Papadopoulos at page 82 of the exhibit, is -- that protein that's identified with the glycosylation sites, is that aflibercept or is that a different protein?
A. No. That's different protein. Again, I did a comparison between that and aflibercept. And this one is not

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the same.

Q. Would you know from the glycosylation of a different protein that the protein in the claims of the '865 patent, aflibercept, would be glycosylated?

A. No, you would not.

Q. Now, let's look at the claims of the '865 patent again and, in particular, if we could look to Claim 14 on page 13 of the reference.

Doctor, what does Claim 14 require?

A. Well, it requires glycosylation at these specific sites. There are five sites in sequence ID Number 4. These are asparagine sites, and they're numbered right here.

Q. Does Papadopoulos teach the glycosylation of aflibercept at those sites recited in Claim 14 of the '865 patent?

A. No, it does not.

Q. As far as you're aware, is that disclosed in any prior art that's been advanced by Dr. Rabinow?

A. No, it does not.

Q. Does Holash -- also I recognize not part of the obviousness combination -- teach glycosylation at these residues?

A. No, it does not.

Q. I'd like to shift to a different topic, Dr. Trout. I'd like to talk about retinal penetration and aflibercept.

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A. Okay.

Q. Based on the prior art as a whole, what kind of molecule would the POSA have wanted to use for intravitreal injection?

A. Well, the POSA would have wanted to use a relatively small molecule relative to aflibercept, for example, because of the limit of going through the various membranes to reach the retina.

Q. Now, Mylan's combination of Lucentis and Fraser relies on the Gaudreault reference as one of the Lucentis references, correct?

A. Yes.

Q. Okay. We've placed on the screen part of page 6 of the Gaudreault reference. That's Exhibit PTX 1839.

What does Gaudreault teach with respect to retinal penetration?

A. Well, it teaches what I've basically just said, highlighted here, "Notably, penetration of ranibizumab into the retina is critical for its clinical use. Retinal penetration suggests the availability of ranibizumab to inactivate VEGF at the site of AMD."

Q. Now, let's go back to page 1 of Gaudreault, Exhibit 1839 and beginning with this paragraph that starts "ranibizumab."

Can you explain what Gaudreault is teaching a person

of ordinary skill as it relates to retinal penetration?

A. Yes. So, again, with respect to ranibizumab, I'll just focus on that larger highlighted portion of this excerpt.

"Ranibizumab has also been shown to penetrate all layers of the rabbit retina, the first demonstration of retinal penetration of an anti-VEGF therapy intended for AMD."

Q. And was it the understanding -- what did the POSA understand about why ranibizumab was being developed by Genentech? For what kinds of diseases was it being developed?

A. Well, for anti-VEGF diseases; in other words, diseases of angiogenesis.

Q. Where in particular?

A. In the eye, of course, yes.

Q. Now, if we go further down on page 1 of the reference, Gaudreault, 1839, was the size of ranibizumab disclosed to be relevant for that purpose?

A. Yes. Extremely relevant.

Q. What is Gaudreault saying in that regard?

A. Well, again, just right below what I had read before, the "ability" -- that is, for retinal penetration -- "has been attributed to the small molecular size (48 kilodaltons) because a full-length antibody, trastuzumab (148 kilodaltons) was not able to penetrate all the retinal layers of rhesus monkeys."

It continues, "The small molecular weight of ranibizumab probably also contributes to its demonstrated

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ability to penetrate the retina."

Q. What is that conveying?

A. Okay. All that sort of technical terms basically says if you have a relatively small molecule, 48 kilodaltons -- I understand that's a weight, but it can also be reflected in the volume. So it's a small molecule. That can penetrate the retina -- or layers to get to the retina, I should say; whereas larger molecules, like antibodies or aflibercept, were thought not to be able to get through to the retina.

Q. What is molecular radius that's being described here by Gaudreault?

A. Okay. So that is the important term here. That's basically the size of the molecule. So it's related to the molecular weight in kilodaltons, but it's the size. And that's what's, at the end of the day, most important.

Q. Does glycosylation affect a protein size?

A. Yes, it does.

Q. And in what way?

A. Well, again, glycosylation means that carbohydrates are added, they're extended carbohydrates. So they're going to be added to these sites, extend out, and increase the effective volume.

Q. Was ranibizumab glycosylated?

A. No.

Q. Now, Gaudreault was a Genentech paper. Did

literature from other researchers inform your opinions as to the issue of size and retinal penetration?

A. Yes.

Q. And let's look at the Ghate reference. That's PTX 576. Did you review this article?

A. Yes, I did.

Q. And what did it disclose with respect to retinal penetration?

A. Well, here I've just highlighted an excerpt. It says, "The internal limiting membrane" -- that's the membrane to get from the vitreous to the retina, "that membrane is impermeable to" -- and then it talks about linear molecules, which aren't so important for this situation.

But what it also talks about are globular molecules greater than 70 kilodaltons. So the larger macromolecules would have a longer retention time, possibly weeks, but their effect on the retina after an intravitreal injection is limited.

Q. Did you look at other references as well?

By the way, was that pages 8 and 9 of Exhibit PTX 576?

A. Yes.

Q. Did you look at other references as well?

A. Yes.

Q. Okay.

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And let's put up the Jackson reference. That's PTX 1842.

Did you rely on Jackson in connection with your opinions?

A. Yes, I did.

Q. Okay.

And if we can put up page 1 of Jackson in the conclusion.

What is it disclosing?

A. Well, sort of the beginning of the conclusion here, "In humans, the inner and outer plexiform layers are sites of high resistance to the diffusion of large molecules, resulting in an REL of" -- about 76, 77 kilodaltons -- it says 76.5.

And REL is the retina exclusion limit.

Q. And did you prepare a demonstrative to help show the relative sizes of aflibercept compared to ranibizumab?

A. Yes, I did.

Q. Okay. And if we take a look at that, that's Demonstrative 4 on the screen.

Can you explain how these compare.

A. Yes.

And, Your Honor, I'll just focus on the middle and the right one.

So this is the aflibercept that we've been talking about. It's about 115 kilodaltons, remembering that the

retinal exclusion limit is in the 70s. It's close enough. Ranibizumab, on the other hand, is 48 kilodaltons, so below that limit.

Q. Now, Doctor, as of the priority date, was the efficacy of larger VEGF R1R2 proteins like aflibercept in treating retinal diseases compared by the intravitreal route and the subcutaneous systemic route?

A. Yes.

Q. Let's take a look at the Saishin article, Exhibit 1785, and at the time at the Ferrara review article, Exhibit 701.

Did you review both of these references?

A. Yes, I did.

Q. Now, Ferrara, is that a review article?

A. Yes.

Q. And what is a review article?

A. Oh, a review article is an article that summarizes what's already in the literature. It typically does not include new results, but it's an analysis of results that are already in the literature.

Q. And does it generally reflect the conventional wisdom in the field at the time?

A. Yes.

Q. Okay.

So if we look to -- if we can put up the

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demonstrative showing both of those together.

On the left-hand side, do we have Figures 1 and 2 of Saishin, PTX 1785?

A. Yeah, we do.

Q. And on the right-hand side, do we have Ferrara at page 5, also page 862?

A. Yes. Yes.

Q. And Ferrara is PTX 701.

Can you explain first what the left-hand side shows, Saishin, and then what the right-hand side, Ferrara, is saying about it?

A. Yes, I can.

And, Your Honor, you've seen this perhaps a couple times before.

So this is a comparison of the effect of the VEGF Trap. Well, the first one is without the VEGF Trap and the second one is with it. And this is subcutaneous injection; in other words, not intravitreal injection. And I think the analogy was used before this is like golf, not basketball. You want to have as low a score as possible.

And that's compared here with the intravitreal administration. And so this is, again, the baseline. You can see a much lower differential here versus subcutaneous.

Q. And what was said about this data in the literature?

A. Well, so Ferrara, in referencing this -- we can turn

to the screen here -- says, "The limited efficacy occurred in spite of the high binding affinity of the VEGF Trap for VEGF. And it may be due, at least in part, to the existence of a barrier to the transretinal penetration of large molecules such as the VEGF Trap."

Q. Does this reflect what the POSA would have thought at the priority date?

A. Yes. Exactly.

Q. And does Ferrara analyze the Saishin reference and account for the details of its experimental design?

A. Yes. Clearly, Ferrara looked at it closely and analyzed it and led to that conclusion, which would be the conclusion of a POSA.

Q. Doctor, on the basis of these data, if the POSA wanted to use a VEGF R1R2 Trap like aflibercept to treat retinal diseases, what kind of administration would the POSA have used?

A. Well, if it's going to be the VEGF Trap, the POSA would have used subcutaneous or some kind of systemic injection.

Q. Would the POSA who made that choice have practiced the claims of the '865 patent?

A. No.

Q. Does the '865 patent require intravitreal administration?

A. Yes, it does.

Q. Now, were there risks and drawbacks associated with intravitreal injection?

And we'll bring up on the screen PTX 576 again, the Ghate reference, at page 8.

A. Yes. And, again, just highlighted this one sentence from Ghate.

"It is also the most invasive and the route with the most serious complications," referring again to intravitreal injection right here in the header.

Q. And does it further in the next sentence explain one or more of those complications?

A. Yes. In the next sentence it talks about the various complications and the rates varying from 0.15 percent to as high as 0.87 percent.

Q. And it talks about endophthalmitis. Do you understand that to be infection inside the eye?

A. Yes. I wasn't going to go into the details of that term; but yes, my understanding is an infection. But it's a very serious infection.

Q. Now, does Saishin teach anything about the appropriate formulation for aflibercept?

A. No.

Q. Does Saishin indicate anything with respect to whether the VEGF Trap stays in native conformation in a

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formulation?

A. No, nothing.

Q. Now, if the POSA had decided to treat retinal diseases using an intravitreal injection, on the basis of all of the information you've reviewed, what molecules would the POSA have wanted to use, what kind of molecules?

A. Well, the POSA would have wanted to use smaller molecules such as ranibizumab.

Q. Was there also a VEGF Trap that fit into that category?

A. Yes, there was.

Q. If we bring up Demonstrative 6.

You've labeled now a third molecule in the demonstrative as Mini-Trap. Can you explain what that is.

A. Yes. The Mini-Trap is another molecule that Regeneron was working on.

And, Your Honor, you've already seen these two. So this is our favorite molecule here, aflibercept, and this is the ranibizumab.

The Mini-Trap is just this top part of aflibercept with a bottom part cut off to make it smaller. So it's about the same size as ranibizumab, maybe even slightly smaller.

Q. And did you look at literature relating to the Mini-Trap?

A. Yes, I did.

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Q. Okay.

Let's pull up Exhibit 1757.

Do you understand this to be the Daly application?

A. Yes. That's correct.

Q. And can you explain what Daly is disclosing here on page 11, paragraph 48.

A. Yes.

At the top it's referring to this Mini-Trap, nonglycosylated and glycosylated. And then it says this Mini-Trap has optimized characteristics for local intravitreal delivery, i.e., shorter serum half-life for faster clearance, and minimizing unwanted systemic exposure.

In addition, due to its smaller size, the Mini-Trap has the ability to penetrate through the inner limiting membrane, ILM, in the eye, and diffuse through the vitreous to the retina/retinal pigment epithelial RPE layer, which will help to treat retinal disease.

Q. Doctor, on the basis of the prior art as a whole, would the POSA who wanted to use intravitreal injections of a VEGF Trap have wanted to use aflibercept or the Mini-Trap?

A. No, the Mini-Trap, the smaller molecule.

Q. And was that designed specifically for intravitreal delivery into the eye?

A. Yes, it was.

Q. Now, we've heard a lot about Avastin during this

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trial. Wouldn't that have taught to use a large molecule for intravitreal injection?

A. No.

Q. Now, Dr. Rabinow addressed the Avery reference. That's DTX 2264. And for now I want you to assume that Avery is prior art.

Let's turn to page 368 of Avery. What is the article conveying to the person of ordinary skill?

A. Well, it's conveying, as you see in these two excerpts that I've highlighted -- this is in the discussion section -- "We acknowledge the shortcomings of this study: retrospective design, limited number of patients, nonstandard visions, and limited follow-up."

And then it further says in the same paragraph a little ways down there, "However, the visual results of this study are difficult to interpret."

Q. And did the Ferrara reference you've been discussing, PTX 701, did that address Avery's findings as well?

A. Yes, it did.

Q. Okay.

And if we can pull that up again at page 8.

What did Ferrara have to say?

A. Well, Ferrara says, "Although intriguing, these early findings are difficult to compare with data from rigorous double-masked controlled Phase III trials."

And then it continues. It's talking about ranibizumab, among others. And then it says, "It is noteworthy that initial uncontrolled Phase I or II studies with pegaptanib or verteporfin photodynamic therapy suggested a considerably greater benefit in AMD patients than that eventually demonstrated in randomized Phase III studies, further emphasizing the difficulty of interpreting early clinical results."

Q. So in view of all the references, including Saishin and Avery, what did Dr. Ferrara ultimately suggest and conclude in his 2006 review article?

A. Well, Dr. Ferrara concluded, again, what the person of ordinary skill in the art would understand, which is that that person of ordinary skill in the art would be turned to use the smaller molecules like ranibizumab and others.

Q. And so the record's clear, that excerpt that you were discussing on page 8 a moment ago from Ferrara, and it had the Footnote 114, was Ferrara discussing the Avery reference there?

A. Oh, yes. And you can see that on the right on the slide, the same Avery reference, correct.

Q. And that's the Avery reference that Dr. Rabinow discussed last week at trial?

A. Yes.

Q. Now, I'd like to shift again, Dr. Trout, and discuss the concentration required by the claims.

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What is the concentration that all of the asserted claims require?

A. Well, of the aflibercept, it's highlighted here, 40 mg/mL.

Q. And let's go back to the prior art on which Dr. Rabinow relied, Fraser at DTX 729 on the second page.

Does Fraser teach 40 mg/mL of VEGF Trap?

A. No, not at all. Fraser teaches, as underlined here, 24.3 mg/mL.

Q. Did you hear Dr. Rabinow's testimony that the POSA would have used the 40 mg/mL concentration from the Lucentis references if we look at Slide 93 of Dr. Rabinow's presentation?

A. Yes, I heard him say that.

Q. Now, let's look at the Lucentis references. Do you recall that Dr. Rabinow relied on two Lucentis references, Shams and Gaudreault?

A. I do recall.

Q. Let's take a look at Shams first. That's DTX 726. And we're showing on the screen page 32 of the exhibit.

What does Shams teach regarding the concentration of ranibizumab?

A. Well, just what's highlighted here regarding that concentration, 6 mg/mL or 10 mg/mL.

Q. And just to be clear, is that 40?

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A. No.

Q. And I think this was discussed last week, but what was the purpose for which Shams was using this ranibizumab?

A. Oh, so Shams is disclosing clinical approaches to using ranibizumab, so clinical trials.

Q. And let's look at Gaudreault, PTX 1839, and we'll look at page 2.

What concentrations does Gaudreault discuss?

A. Well, Gaudreault discusses 10 mg/mL and 40 mg/mL.

Q. Would Gaudreault have taught the POSA to use 40 mg/mL of aflibercept, Dr. Trout?

A. No, sir. On the contrary, Gaudreault teaches away from that. You can see some excerpts here. Actually, if we go back to the previous -- previous one.

Thank you.

It says that at the 2000 micrograms, that's the 40 mg/mL, it causes, at that concentration, moderate to severe inflammation; whereas it is not moderate to severe at the 10 mg/mL.

Q. And you're reading from pages 2 and 3 of Gaudreault, Exhibit 1839?

A. Yes.

Q. And how would the person of ordinary skill in the art have interpreted the findings of Gaudreault with respect to the 10 mg/mL compared to 40 mg/mL concentrations of ranibizumab?

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A. Well, that person again would understand that the 40 mg/mL is problematic from an immune response standpoint versus the 10 mg/mL. And this would teach the person away from the 40 mg/mL. And I emphasize the bottom two. It basically lasted two to eight days, so seven days.

Q. Why do you say that it lasted seven days?

A. Well, it says that the inflammation was present at day two. It was a monkey study. The eyes were monitored throughout. So it was present at day two but had completely resolved by day eight.

Q. And is that good news or bad news?

MR. RAKOCZY: Your Honor?

Objection, Your Honor. He obviously has testified about it from the protein formulation perspective. The witness is not an ophthalmologist; so I don't think he's qualified to talk about good or bad from a clinical standpoint here.

THE COURT: Understood. Sustained.

BY MR. BERL:

Q. Doctor, let's take a look -- well, what happened to the 40 mg/mL dose of ranibizumab?

A. Well, it wasn't used going forward.

Q. Now, I think we had another excerpt that we put on the screen from a moment ago from Gaudreault. Can you explain the relevance of the sentence beginning after administration of 500 micrograms per eye?

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A. Yes. This is another point from Gaudreault focusing on the 500 micrograms per eye. Again, in the table, you can see that corresponds to 10 mg/mL. And Gaudreault is saying that the retinal exposure was greater than 3,000-fold larger than the retinal exposure to VEGF.

So -- and it says suggesting that this ranibizumab dose provides maximum inhibition of VEGF. So the 10 mg/mL dose, according to Gaudreault, provides maximum inhibition. So you don't get more if you go higher anyway.

Q. Doctor, are you aware of any use of 40 mg/mL of ranibizumab after Gaudreault?

A. No, I'm not.

Q. Now, how does the potency of ranibizumab compare to the potency of aflibercept?

A. Well, aflibercept has a much higher potency than ranibizumab, 10 to 100 times more. I think I said in my report, 20 times more, so significantly more.

Q. Now, if the POSA had relied on ranibizumab as Dr. Rabinow suggests, how would the POSA have applied the teachings of Gaudreault and Shams regarding ranibizumab to the concentration of aflibercept?

A. Well, if anything, the POSA would choose a lower concentration. Again, as I said, aflibercept is much more potent than ranibizumab. Even accounting for the difference in the size or the weight, there would be much lower concentration

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based on Gaudreault of the aflibercept, much less than the 10 mg/mL.

Q. Now, let's take a look at Ferrara 2004.

Just for the record, this is a different Ferrara article. It's PTX 1838.

Did you review this article as well?

A. Yes, I did.

Q. Okay. And if we look to page 7 of the article, can you explain what Ferrara is disclosing here and how it's relevant to the consideration of an appropriate concentration to use.

A. Certainly.

So Ferrara -- and, again, different from the Ferrara that we just talked about a little while ago, it's referring to the VEGF Trap again and is basically just relating what I said earlier and what the POSA would know. Because of the fact that this not a natural molecule, it's completely constructed, the junctions between the various structural elements in such multicomponent molecules can generate an immune response, which, again, I think I talked about this last week too, is something that the formulator is very concerned about.

Q. What would the relevance of this discussion in Ferrara 2004, Exhibit 1838, have had on the concentration that the POSA would have wanted to use for an intravitreal injection?

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A. Well, it would teach the POSA to use a low concentration. Again, it's going to be much lower than the 10 mg/mL to try to minimize the risk of such an immune response.

Q. Let's take a look at the Wang reference. That's PTX 1556.

And we'll blow up part of page 1.

What is Wang teaching here, and how does it relate to the protein concentration that the person of ordinary skill would have wanted to use?

A. Well, Wang here -- again, this is a review article. It says, "Increasing protein concentration generally increases protein aggregation."

Q. And so how would that be relevant to the POSA who's trying to choose a concentration to use for intravitreal injection?

A. Well, it would teach the POSA to use as low a concentration as possible, again teach away from these higher concentrations like 40 mg/mL. Again, aggregation can cause serious problems, as the formulator would understand, not only in -- you don't want to inject aggregates as such into the eye, but also the possibility of these immune responses.

Q. Okay.

And for the record, this is page 9 of PTX 1556, the Wang reference.

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Doctor, in view of the -- all of the prior art that you reviewed, what would the POSA have thought in terms of an appropriate concentration of aflibercept for intravitreal injection if the POSA had wanted to use aflibercept for intravitreal injection?

A. Well, the POSA would choose a concentration probably lower than that of ranibizumab, so lower than 10 mg/mL.

Q. What would the POSA have thought about the idea of using 40 mg/mL?

A. Well, the POSA would be taught away from using 40 mg/mL. In other words, it wouldn't be a good idea.

Q. Now, I'd like to turn to a new topic, which is polysorbate 20.

Doctor, if we pull up the claims again, do all of the asserted claims require polysorbate 20?

A. Yes, they do.

Q. And do you understand Dr. Rabinow in his combination to have relied on Gaudreault and Shams for this limitation?

A. Yes.

Q. And what do the references -- well, let's first look at Gaudreault.

And, again, this is page 2 of Gaudreault. What does Gaudreault teach with respect to its formulation and polysorbate 20?

A. Well, Gaudreault teaches, as we have here -- this is

the formulation in the first -- or the top excerpt and the highlighted one -- highlighted sentence for polysorbate, which, again, I think Your Honor noted correctly that Tween 20 is a synonym for polysorbate. It teaches 0.05 percent.

THE COURT: I've been right about this for the last couple weeks, Doctor, if you ask all them out there.

Oh, come on. That was funnier.

MR. BERL: No comment. Too tired to laugh, Your Honor.

THE COURT: Limping to the finish line, but I thought that was better than that.

THE WITNESS: That was funny from up here.

THE COURT: Thank you.

BY MR. BERL:

Q. Doctor, did Genentech proceed with this formulation that has .05 percent polysorbate?

A. No, Genentech did not.

Q. Let's take a look at the Shams reference. And, actually, we'll look at Dr. Rabinow's discussion of the Shams reference in regards to this limitation. What does Shams teach with respect to its formulation and polysorbate 20?

A. Okay. So this is a cutout or excerpt on the bottom right, again, from Dr. Rabinow from Shams. And you can see highlighted here 0.01 percent polysorbate 20.

Q. And what is the concentration, Doctor, required by

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Claim 4 of the '865 patent?

A. Claim 4 is about 0.03 percent to about 0.1 percent polysorbate 20.

Q. And Dr. Rabinow put the .01 percent polysorbate 20 from Shams in green and colored also in green the about .03 percent to about .1 percent in Claim 4.

Do you agree with his analysis that Shams teaches that concentration required by Claim 4 of polysorbate 20?

A. No, because Shams teaches 0.01 percent, which doesn't fall in the range of polysorbate from Claim 4.

Q. What concentration did Genentech ultimately use for Lucentis?

A. 0.01 percent.

Q. Now, let's discuss Fraser, the last reference in this combination. Again, that's DTX 729.

Does Fraser say anything about intravitreal administration?

A. No.

Q. What concentration of Tween 20 or polysorbate 20 does Fraser disclose, looking at page 2 of the reference?

A. 0.01 percent.

Q. Now, reading --

A. I apologize. Sorry to interrupt.

0.1 percent -- added an extra zero.

0.1 percent, for the record.

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Q. My last case in West Virginia was all about something 0.001 percent, and everyone throughout the trial kept adding and subtracting zeros throughout the entire time. So the record was a mess. Thank you for correcting yourself.

Now, Doctor, reading Dr. Rabinow's combination as a whole, the Lucentis plus Fraser, and assuming the POSA combined those references contrary to your opinion, what concentration of polysorbate would the POSA have preferred to use?

A. Well, if one were going to do that, it would be 0.01 percent.

Q. Why?

A. Well, that's what the Shams teaches, and that's what it recommended for the clinical trials. And, in fact, that's what finally Genentech used.

Q. And the clinical trial that Shams is discussing, is that a systemically administered drug as in 729, Fraser, or is that an intravitreal trial?

A. No. Shams teaches intravitreal clinical trials.

Q. And would that have been more relevant to the POSA than formulations like Fraser?

A. Yes. Of course.

Q. Now, let's turn to the next limitation of the claim, the 98 percent native conformation as measured by size-exclusion chromatography limitation.

Do any of Fraser, Gaudreault, or Shams teach the

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98 percent native conformation limitation?

A. No, they do not.

Q. Did Dr. Rabinow present any evidence that any of the formulations in Fraser, Gaudreault, or Shams achieved the 98 percent native conformation limitation?

A. No, he did not.

Q. Now, did either of the Gaudreault formulations go into clinical trials?

A. No, they did not.

Q. You mentioned before that Shams went into clinical trials. Does that mean that it met the 98 percent native conformation requirement?

A. No, it does not.

Q. Why not?

A. Well, there's no indication -- it might be stable enough for clinical trials, but there's no indication that it met the 98 percent limitation here.

Q. Did either Gaudreault or Shams teach that the ranibizumab formulations had 98 percent native conformation?

A. No, they did not.

Q. Now, even if one somehow believed that the Shams formulation or the Gaudreault formulation had 98 percent native conformation of ranibizumab, would the POSA have expected that the same formulation with aflibercept would have 98 percent native conformation?

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A. Based on that of ranibizumab, no.

Q. Why not?

A. They're different molecules. They're going to behave differently. And as I mentioned, aflibercept is this fusion protein. It's not a natural molecule. So, if anything, if one were -- had that information and were to do the comparison, one would expect it to be less stable.

Q. Let's take a look at Wang again. That's Exhibit 1556. And we'll look at page 7 of the article.

What -- in this Section 2.3.1 in the sentence beginning "mutation of one amino acid," what is Wang teaching here?

A. Well, maybe just to read the whole sentence, "Mutation of one amino acid in a peptide or protein can dramatically increase the aggregation propensity."

That's just one. If we're talking about completely different molecules, that can make them substantially different in terms of --

Q. Was there one amino acid difference between ranibizumab and aflibercept or a lot more than one difference?

A. A lot more than one.

Q. Now, let's move on to discuss the pH limitation and in particular the pH limitation found in Claim 9 of the '865 patent.

And that says about 6.2 to 6.3; is that right?

A. Yes. Correct.

Q. Does the Fraser plus Lucentis prior art, even if combined, teach using the required pH range of Claim 9?

A. No, they do not.

Q. Now, if we look at Shams and Gaudreault again now side by side -- Gaudreault, 1839, and Shams, 726 -- what are the pHs used in those formulations that Dr. Rabinow relies on?

A. Well, the Gaudreault is in the upper left here. That pH is 5.0. The Shams is kind of the bottom right, and that pH is 5.5.

Q. Does that meet the limitation of about 6.2 to 6.3?

A. No. Neither do.

Q. Now, the third reference here, Fraser, if we -- we looked at that a moment ago. That had a pH of 6.0; is that right?

A. Correct.

Q. Would the POSA have just used that pH?

A. No.

Q. Why not?

A. Well, because, first of all, the POSA, in investigating a formulation for the '865 patent, would investigate that for aflibercept with intravitreal administration in mind, whereas Fraser doesn't teach intravitreal administration.

Q. Did Dr. Rabinow ever identify which precise

formulation in his combination the POSA would have used if combining Fraser, Gaudreault, and Shams?

A. No, he did not.

Q. If you assume Dr. Rabinow's hypothesis that the POSA would have substituted aflibercept into the ranibizumab formulation, what pH would the POSA have used?

A. Well, the ranibizumab is at 5.5. So if one were going to do that, it would be 5.5.

Q. What if you performed experimentation to find a different pH, as Dr. Rabinow suggests?

A. Well, then, that would be a whole formulation study, a whole investigation.

Q. Would you end up with the same formulation, or at that point do you have a different formulation than the one you'd have if you combined the references?

A. Well, then, you have likely a different formulation. You're doing a whole research project at that point.

Q. Now, let's turn to the turbidity limitation. And we can look at that in Claim 15.

Does that require a turbidity of 0.01 or lower at OD405 after two months' storage at 5 degrees?

A. Yes. That's correct.

Q. Did Dr. Rabinow present any evidence that a 40-milligram formulation of aflibercept would achieve the claimed level of turbidity in view of Fraser, Gaudreault, or

Shams?

A. No, he did not.

Q. Have you seen any such disclosure or teaching in those references?

A. No.

Q. Can you conclude that the Shams formulation meets the turbidity limitation of Claim 15 on the basis of a disclosure for use in a clinical trial?

A. No.

Q. Is the turbidity limitation synonymous with stable?

A. No.

Q. Is the 98 percent native conformation limitation synonymous with stable?

A. No.

Q. Why do you say no to those questions? Why not?

A. Well, because stable doesn't mean it has to be 98 percent or meet this particular turbidity requirement. It could be stable and not be at 90 percent and not meet this turbidity requirement.

Q. Based on the prior art on which Dr. Rabinow relied for obviousness, even if combined, would the POSA have had any expectation that the formulations Regeneron claimed of the '865 patent would meet the turbidity limitations of the claims?

A. No.

Q. Same question for the 98 percent native conformation,

would the POSA have had any expectation of success?

A. Same answer. No.

Q. Would the prior art formulations on which Dr. Rabinow relied, even if combined, necessarily and always have the turbidity required by the asserted claims?

A. No. There's no reason to think that.

Q. And how about for 98 percent native conformation?

A. Again, no reason to think that either.

Q. Is the claimed protein concentration relevant to turbidity?

A. Yes.

Q. How so?

A. Well, again, generally, the higher concentration leads to a higher aggregation propensity, hence higher insoluble aggregates and hence higher turbidity.

Q. Did Dr. Rabinow point to any prior art turbidity data on 40 mg/mL of aflibercept?

A. No.

Q. Did Dr. Rabinow point to any turbidity data on 40 mg/mL of ranibizumab?

A. No.

Q. In your view, Dr. Trout, are the asserted claims obvious over the combination of Fraser and Lucentis?

A. No.

Q. Now, we're done with Fraser and Lucentis.

MR. BERL: I can keep going, Your Honor. I'm at your pleasure.

THE COURT: Let's call it a day. Let's do that.

Is that all right with you, Doctor?

THE WITNESS: Yes, as long as you give the order that the attorneys can't talk with me.

THE COURT: Motion granted.

Yes, Doctor, because you remain midstream on your testimony, even though you've come and gone once but you're considered midstream again by our rules, you are prohibited from contact with other humanoids about your testimony here.

So you're welcome. You can go ahead and step down, sir. Have a lovely evening in quiet solitude.

THE WITNESS: Thank you.

Thank you, Your Honor.

THE COURT: You're welcome.

Everybody okay with starting at 8:30 tomorrow?

MR. BERL: Absolutely.

THE COURT: Let's do that. And we'll sprint through the tape at that point, as they say.

Anything we need to take up from Regeneron's standpoint at this juncture?

MR. BERL: Not from Regeneron, Your Honor.

THE COURT: Mr. Rakoczy, anything from Mylan?

MR. RAKOCZY: Nothing from Mylan.

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THE COURT: Okay. And we anticipate at this point that Dr. Trout will be the last witness; is that correct? Anybody being called by Mylan on the back end?

MR. RAKOCZY: Not as far as we know. He'll be the last one.

THE COURT: Okay. Al right. Well, let's do that. We'll see everyone at 8:30 tomorrow morning. And, again, my promise to be prompt with notifications about any change in the lunch run schedule tomorrow. Apologies for any heart palpitations I gave everybody.

With that, everybody have a pleasant evening, and we'll see you all tomorrow morning.

Thank you very much.

(Proceedings concluded at 5:07 p.m.)

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CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 22, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 22nd day of June 2023.

/s/Cindy L. Knecht

_____

Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 9

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 23, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

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Friday Morning Session,
June 23, 2023, 8:30 a.m.

- - -

THE COURT: I've gotten my coffee mishap out of the way back there; so it should be smooth sailing from here.

Good morning, Doctor. You remain under oath.

Mr. Berl, you may proceed.

MR. BERL: Thank you, Your Honor.

DIRECT EXAMINATION (CONTINUED)

BY MR. BERL:

Q. Good morning, Dr. Trout.

A. Good morning, Mr. Berl.

Q. I'd like to shift now to Dr. Rabinow's second combination, Fraser plus Liu.

Do you agree with Dr. Rabinow that Fraser and Liu combined render the asserted claims obvious?

A. No, I do not.

Q. Now, before we get into the various limitations of the claims and details of the references, do you think that there's any reason that the POSA would have chosen those two references, Fraser and Liu, from amongst all of the prior art?

A. No, no reason.

Q. And, Doctor, do you believe that there's any reason that the POSA would have sought to combine Fraser plus Liu?

A. No. And, again -- or I guess I'll say a little more

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about this, but Liu doesn't have anything to do with aflibercept or anything related.

Q. Now, I understand that opinion, Dr. Trout, but unless I specifically say otherwise, for this portion of the testimony I'd like you to assume that the POSA would have combined Fraser with Liu as Dr. Rabinow asserts.

Can you do that?

A. Okay.

Q. With that, let's look at the first limitations of Claim 1 --

If we can put that on the screen.

-- relating to ophthalmic formulations and intravitreal injection. Do either Fraser or Liu disclose ophthalmic formulations?

A. No.

Q. Let's look at Fraser. It's DTX 729 again, and this is page 1.

What is Fraser discussing?

A. Well, as highlighted here in this excerpt in the lower right side, the aim of the present study was to evaluate the effects of transient inhibition of VEGF on pituitary ovarian function in the macaque, so nothing to do with ophthalmics.

Q. Is there any disclosure in Fraser of intravitreal administration?

A. No.

Q. What kind of administration is Fraser using -- local intravitreal administration or systemic administration?

A. Systemic intravenous, so not intravitreal.

Q. Would the POSA interested in making an ophthalmic formulation for intravitreal administration have looked to Fraser either alone or in combination with Liu?

A. No.

Q. And why does this distinction matter between an IV formulation and an intravitreal formulation? What, if anything, is different about these ophthalmic intravitreal formulations?

A. Well, the current concerns are quite different. I think I testified last week to some of those differences. One major difference, of course, is having to go through this very narrow-bore needle -- which I think Your Honor saw earlier this week -- a very thin needle, which is going to encompass shear.

The other things, issue with particulates and other aspects of -- can be very different for intravitreal.

Q. Would Liu cause the POSA to want to use Fraser or a modified version thereof intravitreally?

A. No.

Q. Does Liu teach anything about intravitreal injections or formulations?

A. No.

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Q. Now, I'd like to move to the next limitations of the claim relating to aflibercept.

You already discussed that with respect to Fraser yesterday. Do those same opinions apply to the combination of Fraser with Liu?

A. Yes. That's correct.

Q. And do the opinions you expressed yesterday regarding glycosylation of aflibercept with Fraser, do those apply to the combination of Fraser and Liu?

A. Yes.

Q. Now, the new reference in this combination is Liu. That's DTX 730. Does Liu teach the aflibercept amino acid sequence?

A. No.

Q. Does Liu teach the glycosylation of aflibercept or the sites of glycosylation?

A. No. Of course, it doesn't teach aflibercept; so it doesn't teach the glycosylation of it.

Q. Okay. Let's go to the next limitation of the claim, 40 mg/mL. Dr. Rabinow again cites to Fraser for the 40 mg/mL limitation.

Do the opinions you discussed yesterday about that apply here?

A. Yes.

Q. Now, do you agree with Dr. Rabinow that the POSA

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would select an appropriate intravitreal dose based on the amount of a VEGF Trap used to inhibit ovarian function in monkeys in Fraser?

A. No.

Q. Why not?

A. Because they're different types of approaches, different indications, different organs, different parts of the body.

Q. What about Dr. Rabinow's suggestion that the POSA would use a 60-microliter injection rather than a 50-microliter injection for intravitreal administration, if one were applying the prior art, in order to be generous?

A. I didn't see any basis for that.

Q. If one used a higher dose volume than 50 microliters, would one change the concentration of the drug product?

A. Well, it depends; but, generally, one would increase the dosage.

Q. And so you'd use the same concentration if you had an overage?

A. Yes. Well, I think the overage, frankly, would have been in the vial, not in the syringe, but it was a little unclear. But the point is the concentration would be whatever the concentration is in the vial.

Q. Now, let's take a look at Liu with respect to the concentration. And we'll take a look -- again, this is

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DTX 730. And we've put on the screen part of page 35 of Liu.

Does Liu teach concentration ranges for formulations of other proteins other than aflibercept?

A. Yes. And I've highlighted a range here in paragraph 13 of Liu. It says -- a little hard to read maybe on the screen, but it does say antibody 40 to 150 mg/mL.

Q. What does Liu teach about the concentration of aflibercept?

A. Nothing.

Q. What about VEGF antagonists?

A. Nothing.

Q. What about an appropriate concentration for intravitreal administration?

A. Nothing.

Q. Would Liu alone or in combination with Fraser motivate the POSA to use a 40 mg/mL formulation of aflibercept intravitreally?

A. No.

Q. On the basis of the combination of Fraser and Liu, would the POSA have used a formulation of 40 mg/mL of aflibercept intravitreally?

A. No. There's no reason.

Q. Now, if we look to page 9 of Liu, Dr. Trout -- this is paragraph 6 of the reference DTX 730 -- did Liu have additional information relevant to the question of whether the

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POSA would have combined it with Fraser?

A. Yes. And I've highlighted a middle part of this paragraph. Again, this is just a reflection of what the POSA would know. Speaking, though, of antibodies, antibodies tend to form viscous solutions at high concentration because of their macromolecular nature and potential for intramolecular interactions. Moreover, pharmaceutically acceptable sugars are often used in large amounts as stabilizers.

Q. So what does that teach in laymen's terms?

A. Well, if you have a higher concentration of antibodies, for example -- because Liu is just about antibodies -- that's going to lead to a higher viscosity. Also, if you have a higher amount of sugar, that can lead to a higher viscosity. I think we're familiar with syrup; it's more viscous. And the combination together can lead to an even higher viscosity.

And, again, for intravitreal administration, which these references don't teach, we have a very thin-bore needle. High viscosity means potentially very long injection times, which I think we all don't want in the eye. And potentially, if it's too viscous, you won't even be able to use it.

Q. And what does Fraser have with respect to concentrations of sugar? Does it use low concentrations or high concentrations?

A. No, it uses high concentrations. This is not the

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Fraser, but it uses high concentration, 20 percent sucrose.

Q. So would the person of skill, in view of this teaching of Liu, have wanted to combine Fraser with a high concentration of sugar with Liu?

A. No, not at all. I mean -- again, they don't contemplate intravitreal, but certainly you wouldn't want to use these high concentrations for intravitreal.

Q. I'd like to move to the 98 percent native conformation limitation with respect to this combination.

THE COURT: Mr. Berl, before you ask that question, it just dawns on me I did the same thing today I neglected to do yesterday.

We're going to take our lunch break from 11:00 to 12:00 today for anyone who needs to -- I saw everybody turn and look at somebody in each corner of the courtroom. You all are the MVPs today. My apologies. I promised you I wouldn't do that to you again, but I just did. We're going to take our lunch break from 11:00 to 12:00 today with apologies.

Mr. Berl, if you wouldn't mind starting that question again, sir.

MR. BERL: This is the last time we'll do that in this trial.

BY MR. BERL:

Q. So I'd like to talk about the 98 percent native conformation limitation, Dr. Trout, with respect to this

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combination of Fraser plus Liu.

Did you hear Dr. Rabinow testify about the Liu reference?

A. Yes.

Q. Would Liu have informed whether formulations of aflibercept would meet the 98 percent native conformation limitation?

A. No.

Q. Why not?

A. Because Liu talks about different molecules, completely different molecules. It doesn't even tell -- or inform what those molecules are exactly, but they're different from aflibercept.

Q. Would the POSA conclude that, because Liu identified antibody formulations that met 98 percent native conformation for those molecules, aflibercept would perform the same way?

A. No, not at all.

Q. And let's -- again, what's the relevance of aflibercept's structure as a fusion protein to your opinion?

A. Well, first of all, as I've been emphasizing, I think it's clear aflibercept is a different molecule than the molecules in the Liu reference. And, furthermore -- I brought this up yesterday also to the Court -- these are -- well, the aflibercept is fusion protein. It's not a natural molecule. I used the term "Frankenstein molecule." And I even quoted some

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of the literature that would reflect the understanding of the skilled person that these molecules would tend to be less stable.

Q. Would the POSA have an expectation of success regarding the native conformation of aflibercept in view of Liu?

A. No.

Q. Let's talk about turbidity briefly. And we can look again -- this is recited in Claim 15 of the '865 patent. Does Dr. Rabinow rely again on Liu for this limitation?

A. Yes.

Q. Do you agree with Dr. Rabinow that the POSA would expect aflibercept formulations to have the claimed turbidity based on Liu?

A. No. Again, completely different molecule.

Q. Now, is the analysis you just provided with respect to native conformation the same with respect to the turbidity limitation?

A. Yes. That's correct.

Q. Now, I'd like to -- well, one final question on this combination.

Do you believe that the combination of Fraser and Liu render the asserted claims obvious?

A. No.

Q. Now, with that, I'd like to turn to Dix.

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Do you agree with Dr. Rabinow's opinion that the Dix '226 patent anticipates the asserted claims?

A. No.

Q. Now, Doctor, what priority date -- what priority dates did you assume in forming your opinions?

A. Well, I did the analysis with two different priority dates. One was June 16th, 2006, and the other was March 21st, 2006.

Q. Okay. Let's start with the first one.

If we could put on the screen parts of PTX 55.

This is part of the opening report of Dr. Rabinow. Is this the report you responded to for purposes of the prior art, invalidity, the obviousness, and anticipation arguments?

A. Yes, it looks like that report.

Q. And we've put up on page 164 of PTX 55 in paragraph 198 part of Dr. Rabinow's report entitled "The priority date for the '865 patent."

What priority date did you understand Dr. Rabinow was applying?

A. Well, as highlighted here, that was June 16th, 2006.

Q. Did you understand there to be any dispute as to whether the '865 patent was, as Dr. Rabinow puts it, entitled to a priority date of June 16th, 2006?

A. No. My understanding was there's no dispute.

Q. Let's take a look at Dr. MacMichael's report. That's

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PTX 53.

Did you also respond to that report?

A. Yes.

Q. And what priority date was applied in that report by Dr. MacMichael?

A. Well, again, as highlighted here in this excerpt, June 16th, 2006.

Q. Now, you said a moment ago, Doctor, that you also applied a date of March 21, 2006; is that right?

A. Correct.

Q. Did you reach a different conclusion with respect to validity based on that priority date?

A. No.

Q. Now, Dr. Graham discussed all of that a couple days ago with respect to the priority date; so we won't belabor that here. I want you to assume for the rest of my questioning on this topic that Dix is prior art to the '865 patent.

Can you make that assumption?

A. Okay.

MR. BERL: And, obviously, Regeneron disagrees with that, Your Honor, but we want to respond in the alternative.

BY MR. BERL:

Q. Do you agree with Dr. Rabinow that Dix anticipates or renders obvious the asserted claims?

A. No.

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Q. Let's go through the limitations, and let's first look at the 40 mg/mL. And we've seen that before. And let's look at page 4 of Dix. This is page 4 of Dix that we'll pull up, Doctor.

What does Dr. Rabinow rely on from Dix with respect to the 40 mg/mL limitation?

A. Well, he relies on this range that's here from Dix, the range of 10 to 50 mg/mL.

Q. Do you agree that the range of 10 to 50 mg/mL teaches 40 mg/mL?

A. No. There's no reason why that would point the POSA to 40 mg/mL.

Q. Do you understand that the disclosure of 10 to 50, do you believe that that discloses every number within that range?

A. No.

Q. Is 10 to 50 a small range?

A. No. It's a significant range.

Q. Is this range here of 10 to 50 in Dix being taught for intravitreal administration?

A. No.

Q. And is the concentration the POSA would understand should be used different for intravitreal administration compared to other kinds of administrations?

A. Yes.

Q. Now, if the POSA were choosing a concentration within

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the Dix range for intravitreal administration, what concentration would the POSA want to use?

A. Within Dix? Well, there's no real indication within Dix. But, again, as I talked about earlier from Gaudreault and other parts of the prior art, it would be on the lower end of the concentration, 10 mg/mL or perhaps even lower.

Q. And what would the POSA, in view of the prior art, have thought about using a 40 mg/mL concentration for intravitreal administration?

A. Well, as I discussed yesterday, the prior art teaches away from using the 40 mg/mL; so the POSA wouldn't want to do that.

Q. Does this disclosure of a concentration range on page 4 of Dix, is it teaching the aflibercept molecule with that range?

A. No. It just -- and I've highlighted the excerpt above. It just talks about a VEGF-specific fusion protein antagonist broadly. This is just a very broad disclosure here.

Q. And is aflibercept the only sequence that's taught in Dix?

A. No.

Q. How many sequences are taught in Dix?

A. Well, there are two sequences.

Q. And is this fusion protein antagonist language from Dix limited to those two fusion proteins or could it encompass

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others?

A. It could encompass others. In other words -- or again, I should say, as I discussed, this is just a very general disclosure towards the beginning part of Dix.

MR. BERL: With that, Your Honor, the next set of questions of a couple minutes are not in Dr. Trout's report. And the reason they're not in Dr. Trout's report is that they relate to an argument that was not in Dr. Rabinow's report, either the opening report or the reply report.

He said something about it at his deposition. He had it on one of his slides. We objected. That objection was overruled, and he said something very brief about it in cross-examination. So we'd like to respond to it, but it's obviously -- I just wanted to front that issue and not suggest that this was in Dr. Trout's report, because it's not.

THE COURT: Understood.

Any objection from Mylan?

MR. RAKOCZY: I'm not sure what the question --

THE COURT: Well, dust off your crystal ball, Mr. Rakoczy.

MR. RAKOCZY: I suspect I will be objecting, but I need to hear the question.

THE COURT: Understood. Well, let's see what the questions are. Thank you much, Counsel, for the preview, but go right ahead.

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BY MR. BERL:

Q. The first question actually is in your report; so the ones after that are not.

Doctor, I want to talk a little bit about lyophilized formulations. Are you familiar with that concept?

A. Yes, I am.

Q. Okay. What steps do lyophilized formulations require before the drug may be administered?

A. Well, first of all, you have to make the lyophilized formulation. So you go through various mixing processes, for example, make a prelyophilized solution, not a formulation, just a solution. And then you would go through the lyophilization process, so freeze-drying. That dried powder is also not an injectable or usable product as such until you add liquid -- generally, water for injection -- and reconstitute it. And so then you have a liquid finally -- a formulation that you can use, for example, for injection.

Q. And this prelyophilized solution that you describe, is that something that's to be administered to patients?

A. No. Not at all.

MR. RAKOCZY: Objection, Your Honor. Number one, not in the report. Number two, the witness isn't qualified to testify as to what is or is not properly administered to a patient.

THE COURT: Sustained on the second grounds. That's

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outside of the scope of his expertise as deemed qualified by this Court.

MR. BERL: Okay. So let me ask the question a little differently.

BY MR. BERL:

Q. From a formulator's perspective, is the prelyophilization solution that a formulator would make, is that intended to be administered to patients or is it intended to be freeze-dried as part of the manufacturing process?

MR. RAKOCZY: Same objection, Your Honor. I'm not aware of this being in the report, number one.

Number two, again, that's just repackaging the same question only putting formulator at the front.

MR. BERL: It wasn't. It was slightly different, if I may, Your Honor. I didn't ask him what's appropriate for injection, which I understood to be the subject of the objection, because that might involve some clinical judgment, but rather what is intended by a formulator? Is the formulator making it so that it can be injected as opposed to as a manufacturing process so it can be freeze-dried or lyophilized? That's what I was asking about.

THE COURT: Understood.

In light of the Court overruling the objection with respect to Dr. Rabinow, I'll overrule this one. But I don't think we need to delve too very deep on it.

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THE WITNESS: Yeah, as a formulator, again, someone who does pharmaceutical manufacturing, the prelyophilized solution is an intermediate. That's all. And then it would go through further processing.

BY MR. BERL:

Q. Now, I'd like briefly to bring up another section of Dix that Dr. Rabinow very briefly addressed. And it's on page 5 of Dix.

Doctor, we have on the screen part of page 5. And in part it talks about prelyophilized solutions and a 40 mg/mL prelyophilized solution is lyophilized and reconstituted to an 80 mg/mL solution.

Do you think, Dr. Trout, that this teaches the 40 mg/mL limitation of aflibercept for purposes of the claims of the '865 patent?

A. No. Again, it's just a manufacturing intermediate.

Q. Does Dix teach that this 40 mg/mL prelyophilized solution is for aflibercept?

A. No. This is part of a very general disclosure. It just mentions VEGF here. And this is part of a whole column of all kinds of different numbers and various, you know, discussions of prelyophilization and reconstitution.

Q. Would the POSA understand or expect that the 40 mg/mL prelyophilized solution would have 98 percent native conformation after two months at 5 degrees?

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THE COURT: One second, Doctor.

MR. RAKOCZY: Objection, Your Honor. That is not in the report.

MR. BERL: I agree completely that that's not in the report, but I'm addressing Dr. Rabinow -- again, I think he said one sentence about this on cross. What I don't want to happen is for them all the sudden to say that's an anticipation, and we can't respond.

MR. RAKOCZY: Your Honor, they did respond in the report. I think the witness took the position that lyophilized formulations are not even within the scope of the claim. So I'm not sure where this is going, but this is a completely new opinion.

THE COURT: I do recall Dr. Rabinow covering it. Subject to the Court's prior ruling on that, I'm going to overrule it at this point.

MR. BERL: I probably need to ask the question again.

THE COURT: Probably.

BY MR. BERL:

Q. Doctor, would the POSA expect or have any reason to believe that the 40 mg/mL prelyophilized solution that's the subject of this disclosure in Dix would meet the 98 percent native conformation as measured by SEC after two months at 5 degrees limitation?

A. No. And the way you would make this -- a formulator

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would make this wouldn't be to store it for nearly that long.

Q. In your view, Doctor, taken together, does Dix anticipate or render obvious the asserted claims?

A. No.

Q. And did Dr. Rabinow rely on the same disclosures of Dix for anticipation as he did for obviousness?

A. Yes.

Q. And do the opinions that you just expressed for anticipation apply for obviousness as well?

A. Yes. That's correct.

MR. BERL: And, again, Your Honor, Regeneron disputes that Dix is a proper obviousness reference, including the safe harbor of Section 103(c).

MR. RAKOCZY: We obviously disagree with the 103(c) arguments, which we briefed in summary judgment and we're happy to address again in the proposed findings, Your Honor.

THE COURT: Understood.

MR. BERL: I'm sure Your Honor will read more about that.

THE COURT: I'm looking forward to it.

BY MR. BERL:

Q. Doctor, did you also consider objective indicia of nonobviousness?

A. Yes, I did.

Q. What did you conclude?

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A. Well, I conclude that there's objective indicia, or I guess you call it secondary considerations. There are other evidence of nonobviousness.

Q. Did you consider industry skepticism regarding the use of VEGF Traps?

A. Yes, I did.

Q. Let's take a look at Ferrara 2004. Again, there are two Ferraras; this is the 2004 reference, PTX 1838. Let's take a look at page 7 of this article.

Can you explain what's disclosed here and how it relates to your concept and opinion about skepticism?

A. Yes. And, again, this is a review article; so it reflects the understanding in the literature. And, again, it talks about in this paragraph VEGF Trap and then says, "It is also possible that the junctions between the various structural elements in such multicomponent molecules can generate an immune response."

And, Your Honor, I showed you this yesterday also, but -- for the same excerpt but the same significance, but now for secondary considerations.

Q. And would the POSA have considered this warning important regarding immune responses?

A. Yes. Again, this is something that, as a formulator, is foremost in our mind of concern or one of the things that are of foremost concern.

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Q. There's been a lot of discussion about the lead author of this article, Dr. Ferrara.

Did researchers in the field consider the paper biased or misleading because Dr. Ferrara worked for Genentech?

A. No, not according to my understanding. As a matter of fact, I think there are over 3,000 citations of this paper.

Q. Is that lot?

A. That is a lot.

Q. Now, was this paper the only evidence of industry skepticism you considered?

A. No.

Q. Did you also consider the 2006 Ferrara review article that you discussed yesterday?

A. Yes.

Q. And we won't rehash that, but in your view, was the skepticism expressed in the prior art directed to the workability of the claimed invention of injecting VEGF Traps, such as aflibercept?

A. Yes, exactly.

Q. Did you also consider evidence of unexpected results, Dr. Trout?

A. Yes, I did.

Q. And let's take a look at the Thomas article. That's PTX 1155. Did you review this article for purposes of your objective indicia analysis?

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A. Yes, I did.

Q. And this is an article from 2013, after the priority date.

Let's take a look at page 4 of the article. What were the properties that ultimately were shown with Eylea? And were they expected in your view?

MR. RAKOCZY: Objection, Your Honor. Two grounds. Number one, they've admitted this is after the priority date; this is not prior art.

Number two, they're talking about the aflibercept molecule; they're not actually talking about the claimed formulations here. It's not relevant either.

THE COURT: How is it prior art?

MR. BERL: It's not prior art at all. That's why I pointed out, in fact, that it's from 2013, after the priority date.

The law is that postpriority evidence is relevant to unexpected properties. The Kroll v. Teva [sic] case is sort of the seminal case on this proposition, but other cases afterwards have reiterated that proposition down the line from the Federal Circuit.

THE COURT: Mr. Rakoczy.

MR. RAKOCZY: Your Honor, we obviously disagree. We will brief this. But beyond that, it still has to establish a nexus to claims. These are claims about formulations, not

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about the aflibercept molecule itself, which is what this is; so, again, no nexus, after the priority date.

THE COURT: Understood. It is after the priority date, obviously, but we need to tie this together, Mr. Berl, how it's related.

Objection overruled at this juncture.

BY MR. BERL:

Q. Were the properties of Eylea expected or unexpected as related by the Thomas article, PTX 1155?

A. So they were unexpected, as noted here. I'm going to read on the screen just because of my eyes.

On the upper left, "The most captivating aspect of aflibercept is its extended half-life, according to reviews of aflibercept by Stewart and Stewart, et al. The estimated serum half-life of intravitreal aflibercept is approximately 18 days versus ranibizumab and bevacizumab, which have half-lives of approximately 4.75 days and 8.25 days respectively."

So it's -- aflibercept -- or really the Eylea, which is an embodiment of the claims of the '865, has over double the half-life.

And then just to point to another excerpt from the same article on the right -- I think I can even read this -- "In conclusion, aflibercept dosed intravitreally each month or every two months after three initial monthly doses resulted in comparable efficacy and safety to monthly ranibizumab."

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Q. Can you explain how this relates to the formulation rather than just the molecule of aflibercept with respect to the properties you just relied on?

MR. RAKOCZY: Objection, Your Honor. He's now trying to tie something up that's actually not in the report anywhere.

MR. BERL: I don't agree with that. Let's look at paragraph 347, for example. Your Honor, I think this is in the binder. I believe it's styled as PTX 67, Dr. Trout's report. PTX 67.

THE COURT: 67.

MR. BERL: Not 367. Sorry.

THE COURT: What paragraph is that, Mr. Berl?

MR. BERL: 347. You'll see in that paragraph, Your Honor, he's discussing Eylea. He does not say aflibercept. I think -- he says aflibercept too because, of course, Eylea has aflibercept in it, but he says Eylea one, two, three, four times when providing his analysis of this article. This is the Thomas article that we're reviewing and the subject of this paragraph, and he's talking about how Eylea ultimately proved to be unexpectedly safe, how it compares to Lucentis.

And so that's what I'm asking him about is how -- what is Thomas disclosing about Eylea. That's the subject of the Thomas article and his opinion.

THE COURT: Mr. Rakoczy.

MR. RAKOCZY: That wasn't the question, Your Honor.

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The question was can you explain how this relates to the formulation other than just the molecule?

I agree that the report talks about the formulation Eylea. There is nothing in here attempting to give some explanation for why this unexpected result is not just about a molecule.

THE COURT: Understood.

Sustained. Reword your question.

MR. BERL: I'll reword the question.

BY MR. BERL:

Q. Doctor, can you explain how these properties relate to Eylea?

A. Yes. Well, again, these properties are discussion based on the use of Eylea, the whole formulation -- I don't know if I can say that, but Eylea is the formulation we've been talking about.

Q. Do you understand Eylea to be an embodiment of the claims of the '865 patent?

A. Yes.

Q. And can you administer aflibercept by itself without formulation?

MR. RAKOCZY: Objection, Your Honor. Again, new opinion. Nowhere in here.

MR. BERL: This has nothing to do with Thomas. This is just basic background.

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THE COURT: Overruled.

BY MR. BERL:

Q. Can you administer aflibercept without a formulation, such as Eylea?

A. No.

Q. Can you obtain the properties that Thomas is discussing by just administering aflibercept alone?

MR. RAKOCZY: Objection, Your Honor. This is well outside the scope.

THE COURT: That one's sustained.

MR. BERL: I'll withdraw that.

BY MR. BERL:

Q. Doctor, in your view -- let's look at another part of Thomas on page 4. Can you discuss what Thomas is disclosing here?

A. Yes. Again, just to read the excerpt here, "In conclusion, aflibercept dosed" -- and then it talks about the dosing I just read -- "side effects, either ocular or systemic, were similar across treatment groups with no differences between aflibercept administered every two months and monthly ranibizumab," again, referring to the Eylea.

Q. And was that expected or unexpected based on what the prior art disclosed about fusion proteins such as aflibercept?

A. That was unexpected for all the reasons that I mentioned.

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Q. Do you understand or consider ranibizumab to be the closest prior art?

A. Yes.

Q. Now, did you also consider evidence of copying?

A. Yes, I did.

Q. And in your view, did Mylan copy aspects of Eylea?

A. Yes.

Q. And what aspects of the claims, for example, did Mylan copy, in your view?

A. Well, it copied the aflibercept, of course, with the sequence ID, the polysorbate, the organic cosolvent, the buffer.

Q. Well, let's talk about a few of those. Let's talk about the polysorbate.

MR. BERL: Actually, if I may pause for a moment. I don't want to do anything that violates Mylan's perceived confidentiality. I think this was disclosed in open court, but I don't want to run afoul of any --

THE COURT: If you need to huddle and talk about that, go right ahead, please.

MR. BERL: I really don't want to seal the courtroom for one question; so maybe I'll just --

THE COURT: Why don't we save that one for last.

MR. BERL: Maybe we'll save that one for last. That's a good idea.

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BY MR. BERL:

Q. Did Mylan, in your view, copy the concentration of aflibercept that's in the claims?

A. Yes.

Q. Did Mylan -- I'll ask this generally. Did Mylan pursue formulations without polysorbate?

A. Well, in development, yes.

Q. And what was the result of that?

A. Mylan decided it had to include polysorbate to have an adequate formulation.

Q. In view of -- I just want to ask one final question about obviousness, Doctor.

In view of your analysis of motivation, expectation of success, and objective indicia, are the asserted claims of the '865 patent obvious?

A. No.

MR. BERL: So with that proviso that I might ask one more question at the end, I'm going to move to Section 112.

THE COURT: Someone put that last question on a sticky note.

MR. BERL: I won't remember; so please.

BY MR. BERL:

Q. Doctor, did you consider Dr. MacMichael's testimony on enablement?

A. Yes, I did.

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Q. Do you agree with his conclusions?
A. No, I do not.
Q. Dr. MacMichael talked about the simple *Wands* factors. Do you remember that?
A. Yes, I do.
Q. Let's put up the *Wands* factors on the screen.
Did you consider the *Wands* factors in conducting your enablement analysis?
A. Yes, I did.
Q. Let's start with the first one, the breadth of the claims. Do you agree with Dr. MacMichael's testimony that the breadth of the claims is very broad?
A. No. I think the claims are narrow.
Q. Let's take a closer look at that. Let's take a look at 1, 2, and 4 again.
Why, in your view, are the asserted claims not very broad?
A. Well, let's just start out with the -- where we usually start, with the VEGF antagonist and the specific sequence ID. So it's one specific biologic molecule, no others, with a very specific -- with a specific sequence ID, I should say. It's a vial. It's for intravitreal administration. It's got to have all these other components -- the organic cosolvent, the buffer, the stabilizing agent. And then it's got to be at 40 mg/mL. That's very -- I mean, that

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can't get more narrow than that in terms of concentration. And then it's got to -- this is just Claim 4 -- it's got to have the polysorbate 20. That's the only possible organic cosolvent and within this narrow range.

Q. Doctor, there's been some discussion for purposes of enablement about lyophilized or freeze-dried formulations. We're not going to repeat all of what we did a few moments ago, but in your view, did the specification also teach how to make lyophilized formulations?

A. Yes, it does.

Q. And is lyophilization just another way to make formulations?

A. It is another way of making formulations, yes.

Q. And there was also some discussion previously in the case about suspensions and emulsions.

In your view, would the claims be directed to suspensions and emulsions?

A. No. I don't think the claims would be directed, and I probably should have mentioned this before, but this other limitation, the 98 percent present in native conformation following storage at 5 degrees Celsius for two months as measured by size-exclusion chromatography, that's not an analytical technique that one would typically use for emulsions and suspensions.

Q. You discussed some of the structures in the claims.

Were the structures that are used in the claims known or unknown as of the priority date?

A. They were known as of the priority date.

Q. What about buffers? Were those structures known?

A. Yes.

Q. And what about polysorbate?

A. Yes.

Q. And what about aflibercept?

A. Yes.

Q. And what about stabilizing agents?

A. Yes.

Q. So, Doctor, what is your opinion regarding the *Wands* factor on the breadth of the claims? Does that support enablement or does it support nonenablement?

A. It's pretty narrow; so it supports enablement.

Q. Let's take a look at the nature of the invention, the second *Wands* factor.

What is the nature of the invention claimed here?

A. Well, the nature of the invention is a formulation, an ophthalmic formulation to be specific, suitable for intravitreal administration, with the various formulation components, including the aflibercept and with the 98 percent native after two months storage at 5 degrees Celsius and all the rest of the specifics.

Q. Did Dr. MacMichael identify any formulation with the

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structural elements recited in the claims that did not meet the 98 percent native conformation limitation?

A. No.

Q. Are you aware of any such formulations?

A. No.

Q. Now, let's go to the next *Wands* factors, the level of ordinary -- the level of ordinary skill.

Was the level of skill high or low?

A. High.

Q. How so?

A. Well, again, it would be a professional with a master's degree at least in a relevant field, so a technical field directly relevant to formulations here. I think Dr. MacMichael said even a PhD, higher, plus several years of skill. And I think I added in mine it could be a PhD with less experience than a master's degree but still considerable experience in formulation.

Q. Do you understand yourself to agree with Dr. MacMichael that the level of skill was high?

A. Yes.

Q. Now, did you hear Dr. MacMichael's testimony a few days ago regarding Regeneron's arguments during prosecution of different patents?

A. Yes.

Q. Do you agree with Dr. MacMichael's testimony about

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those documents?

A. No.

Q. Let's first take a look at DTX 5053, and this is on page 17.

Do you recall that this is a sentence that Dr. MacMichael relied on in his testimony?

A. Yes.

Q. And can you explain what this sentence means in your view.

A. Yes. It says, "One of ordinary skill in the art upon reading Remington's would expect to engage in significant nonroutine experimentation to develop a successful formulation as claimed herein."

Remington's is a general textbook, you could call it. It's a collection of different chapters, formulation and others, by experts; so it's a general textbook. And I agree with this statement, but Remington's doesn't disclose aflibercept; it doesn't disclose other aspects. Until you have that information, like the '865 patent discloses, you are in the situation discussed here.

Q. So to be clear, does Remington's disclose any formulations of aflibercept?

A. No.

Q. How about intravitreal formulations of aflibercept?

A. No.

Q. How about the concentrations to use for aflibercept intravitreal formulations?

A. Clearly not.

Q. Does Remington's disclose what pH to use for intravitreal formulations of aflibercept?

A. No.

Q. Now, Doctor, did you consider the Dix declaration cited by Dr. MacMichael from the prosecution of another patent?

A. Yes, I did.

Q. Let's take a look at the full context of Dr. Dix's statement. That's DTX 4430 at pages 3 through 4. It's paragraph 10. And Dr. MacMichael showed part of this paragraph.

Can you explain this paragraph and how it fits into your enablement analysis?

A. Yes. So, similarly here, Dr. Dix references now review articles, different from Remington's, but all of these are review articles that I'm familiar with. This is actually the same Wang that I talked about before but different review articles. Wei Wang likes to write review articles.

Dr. Dix says, "I am familiar with these literature articles, all in peer review journals, which all indicate that arriving at a stable formulation is not a straightforward matter and is not, for instance, possible to apply a formulation for one drug to another."

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So, again, in the absence of any information once you're starting out, this is the situation that the skilled person would be in.

Q. And, again, as we discussed with Remington's, do any of these articles disclose aflibercept formulations, intravitreal aflibercept formulations, the concentration to use for aflibercept intravitreal formulations, or the pH to use for aflibercept intravitreal formulations?

A. No, none of them disclose any of those.

MR. BERL: I'm sorry about that one. I'll be better.

THE COURT: I'll accept on behalf...

BY MR. BERL:

Q. Doctor, to practice the claims of the '865 patent with the specification in hand, would the POSA need to apply a formulation from one drug to another, as Dr. Dix talks about here?

A. Well, Dr. Dix says you don't do that, and I agree with that. That's not what we do.

Q. But if a POSA has the '865 patent in hand and wants to make formulations claimed in the '865 patent, does that require applying a formulation from one drug to another drug?

A. No. The '865 patent itself teaches how to do it.

Q. The '865 patent discloses formulations of aflibercept?

A. Yes, clearly. Yes.

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Q. And what formulations are claimed -- aflibercept or some other molecule?

A. Aflibercept.

Q. Now, let's turn next to the next *Wands* factor, the specification's guidance and then working examples. We can take those together.

How do the specification's guidance, if we could look at a demonstrative, compare to the prior art's guidance?

A. Well, the specification has significant guidance. It actually has eight examples. I've just put up three here. We wouldn't be able to see any of them -- you can hardly see it as it is -- if we put up all eight. Probably couldn't see anything.

And then it has several important disclosures within the specification, including this one, which is highlighted. And it talks about what the organic cosolvent might be, and it talks about different other agents, including the stabilizing agent and the buffering agent.

It also talks in this excerpt in the middle here about the pH range between about 5.8 and 7. And then it talks about more specific pH ranges, uses the terms more specifically, about 6.2 to 6.3.

Q. And for the record, the excerpts you're discussing are in Column 2 of the '865 patent, Exhibit 2; is that right?

A. Yes.

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Q. And you also have Tables 1, 3, and 5 shown on the screen in this discussion; is that right?

A. That's right. Actually, the whole examples including the tables, but yes.

Q. And, Doctor, you talked about some of the ingredients that are discussed in the '865 patent.

Do the claims for some categories narrow those structural requirements?

A. Yes.

Q. Now, we'll talk a little bit more about this in a moment, but the claims you said require a buffer.

What is a buffer?

A. Well, a buffer is a chemical compound that has a particular structure that leads to the formulation staying at a particular pH; so it resists pH changes.

Q. Would the POSA have known the structure of buffers that could be used to practice the claimed invention?

A. Yes.

Q. You noted that the patent teaches pH ranges, one of 5.8 to 7 and then more specifically 6.2 to 6.3, in Column 2.

How does that pertain to the buffer that the person of ordinary skill would use to practice the claim?

A. Well, one would want to select a buffer that its chemical structure is such that it can maintain the pH within a given range.

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Q. And is that a limited set of structures that could do that?

A. Yes.

Q. Does the patent provide an example of such a buffer that can be used?

A. Yes. The patent specifically -- again, that bottom left Column 2, it specifically says phosphate buffer.

Q. And, Doctor, in view of the specification's teachings, what buffers would the POSA use to practice the claims of the '865 patent?

A. Well, again, you could use buffers that would buffer within this range, like phosphate, could be succinate, for example, histidine.

Q. Let's turn to the next limitation, Dr. Trout, organic cosolvent. We've heard a lot about that. That's in Column 2.

And what does Claim 4 require with respect to the organic cosolvent?

A. Well, Claim 4 --

Q. What does Claim 4 require with respect to the organic cosolvent?

A. Claim 4 requires a specific one, polysorbate 20, and a specific range of that organic cosolvent.

Q. Do you understand all of the claims to require an organic cosolvent comprising polysorbate 20?

A. Yes. All the asserted claims, yes.

Q. Let's go back to the specification and address this limitation.

What does the specification teach with respect to organic cosolvent?

A. Well, it teaches various structures. Again, I'll look at the monitor here. Maybe polysorbate and, for example, polysorbate 20 or 80; polyethylene glycol, also abbreviated at PEG and then gives an example; or propylene glycol or a combination thereof.

Q. Would the POSA understand what those structures are?

A. Yes.

Q. Now, let's turn to the next limitation, stabilizing agents. And let's look at Column 2 there as well.

What does the patent teach about stabilizing agents?

A. Well, it teaches what it also calls sugars, sucrose, sorbitol, glycerol, trehalose, or mannitol specifically.

Q. Are those known structures?

A. Yes.

Q. Doctor, all of the asserted claims require some stability limitation as measured by SEC, the 98 percent native conformation; is that right?

A. Correct.

Q. And some of them say 99 percent, some of them have different time periods, but let's -- what does the patent teach with respect to formulations that meet the size-exclusion

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chromatography limitation?

A. Well, it teaches that, given the various formulations in the examples, if one encompasses the various structures that are described in the claims, one expects to meet the 98 percent limitation, or again the 99 under some circumstances with the different times.

Q. Let's take a look at Example 1. What does Example 1 teach, Dr. Trout?

A. Well, Example 1 teaches 50 mg/mL VEGF Trap, the exact one, because it references the sequence ID. It has a phosphate buffer. It has the polysorbate 20 organic cosolvent. And it has the sucrose stabilizing agent and pH 6.25 which can be rounded up to 6.3.

Q. Now, Doctor, you said -- well, how much aflibercept is in this formulation? What's the concentration?

A. Yes. I said 50 mg/mL.

Q. So is that within the asserted claims?

A. No.

Q. Does it nevertheless provide relevant guidance or teaching to the POSA with respect to 40 mg/mL?

MR. RAKOCZY: Objection, Your Honor. That's a new opinion not in the report.

MR. BERL: So, Your Honor, if we go to paragraph 387.

THE COURT: 387?

MR. BERL: Yes. Dr. Trout there addresses the

examples, including Example 1, that I'm taking him through. And he talks about the specification providing examples that meet this claimed property. That is the native conformation limitation. And I'm asking him how that pertains -- how the Example 1 pertains to the native conformation limitation.

THE COURT: Mr. Rakoczy.

MR. RAKOCZY: He does lay out the examples. I don't object to laying out the examples and identifying what they do and don't contain. But there's no opinion in here about somehow how 50 informs 40 or 40 informs 50, which I believe was the question.

THE COURT: Where is that specifically, Mr. Berl?

MR. BERL: Give me one moment.

THE COURT: Sure.

MR. BERL: Phone a friend.

If we go, Your Honor, to paragraph 395. And here he addresses more specifically the issue that I'm asking about, about whether the examples that are not within the scope of the claim because they have 50 are relevant or irrelevant to how the POSA would practice the claims. And later in the paragraph he talks in particular about Example 1, which is what I'm asking him about.

THE COURT: Overruled.

BY MR. BERL:

Q. Your Honor -- or Dr. Trout -- sorry.

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THE COURT: Don't ask me.

THE WITNESS: I think by now, Your Honor, you could probably answer all these questions.

MR. BERL: And more interested in the answers.

BY MR. BERL:

Q. Dr. Trout, how is this example of 50 mg/mL, Example 1, relevant to practicing the claim with 40 mg/mL?

A. Well, I think, given the teachings in the '865 patent and general understanding of the literature, the skilled person would understand that if this formulation with 50 mg/mL met that 98 percent or related limitations, then the similar formulation with 40 mg/mL would also meet those limitations, 98 percent, 99, and the different times.

Q. Is that always the case, that if you have a lower concentration of the same formulation, you'll have higher stability, or is it generally the case?

MR. RAKOCZY: That's a new opinion, Your Honor. That's not in this paragraph or the prior one.

MR. BERL: Well, I don't agree, Your Honor. It says "would expect." And so I'm trying to understand what would expect means. That's the language he uses. I'm reading in paragraph 395 of his report. And so I'm trying to understand -- it's a hard-and-fast 100 percent rule or something different than that.

MR. RAKOCZY: And now he's leading and telling the

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witness how to answer the question, Your Honor.

THE COURT: The first one's overruled. Let's rephrase the question and give it a try.

MR. BERL: Sure.

BY MR. BERL:

Q. Dr. Trout, can you explain your opinions with respect to the expectation from the same formulation going from 50 mg/mL of aflibercept to 40 mg/mL of aflibercept?

A. Certainly. So, generally speaking, as you increase the concentration of a protein, you have a higher propensity towards going to nonnative conformation. So that means that, generally, if you decrease the concentration, you're going to have a lower propensity.

In other words, if -- generally, if you meet the -- let's say, the 98 percent limitation and related ones we've been discussing at 50 mg/mL, it's most likely that you will meet that also at 40 mg/mL. It's not guaranteed, but I think in general the skilled person would expect that to be the case.

Q. Let's take a look at Example 3, Dr. Trout.

Can you explain what this example discloses?

A. Yes. So this example discloses 40 mg/mL VEGF Trap -- again, the molecule with that specific sequence ID Number 4 -- phosphate buffer, also the polysorbate 20 organic cosolvent, sucrose as a stabilizing agent, and a pH of 6.3.

Q. Is it your understanding that this is now called

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Eylea?

A. Yes, this is the formulation of Eylea. Yes.

Q. And what was the level of native conformation as measured by SEC after two months in this formulation?

A. Well, you can see right down here in the table, two months, again at 5 degrees Celsius. Going over, you can see it's 99.2, so greater than 99 percent.

Q. Let's take a look at Example 5.

What's Example 5?

A. Well, Example 5 is another formulation at 40 mg/mL of aflibercept. Again, phosphate buffer. Here it's got an organic cosolvent again, polysorbate 20, the same one. In this case it's got sodium chloride, but it doesn't have a stabilizing agent like the sugars that we've been talking about.

Q. And what is the level of native conformation for this one, Example 5, after two months?

A. Well, again, the native conformation is similar at 5 degrees, two months, and it's 99.2 percent, so greater than 98, greater than 99.

Q. Does the patent express any preference for Example 3 versus Example 5?

A. Well, yes, in the sense that Example 5 -- sorry -- Example 3 has the stabilizing agent.

Q. But in terms of the data or disclosure of the patent,

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does it say 3 is better than 5 or 5 is better than 3?

A. No. Actually, this data is very helpful in understanding what we call the robustness or how the structures in the claims should all meet that 98 or other limitations.

Q. Does the patent contain other examples too, Dr. Trout?

A. Yes, it does.

Q. What are Examples 4 and 6 of the patent?

A. Well, those are actually similar examples to 3 and 5, but they're in prefilled syringes instead of vials.

Q. So they're similar with respect to the formulations themselves?

A. Yes. That's right.

Q. And did they also achieve 98 percent native conformation after two months?

A. Yes. And, again, I think that's important for a general understanding of how these formulations work too.

Q. And what about Example 7 and 8?

A. Well, those are lyophilized formulations.

Q. We've discussed those already. We don't need to belabor any of that.

Doctor, let's -- so in view of your analysis of those factors, those *Wands* factors, in particular the guidance from the specification and working examples, does that weigh in favor or against enablement?

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A. In favor of enablement.

Q. Now, let's next turn to the state of the prior art. In your view, does the state -- well, did the prior art teach how to substitute one excipient in a category, such as a stabilizing agent or buffer, for another?

A. Yes.

Q. Did the prior art teach how to perform size-exclusion chromatography?

A. Yes.

Q. What about turbidity testing?

A. Yes.

Q. In your view, does this *Wands* factor, the state of the prior art view, weigh in favor of enablement or against enablement?

A. In favor.

Q. Let's finally turn to the last *Wands* factor, the quantity of experimentation. And let's discuss a couple background principles in that regard.

Let's take a look again at the Kaisheva reference. That's DTX 3610. Do you remember that this has been discussed by various experts in the case?

A. Yes.

Q. And if we go to paragraph 54 on page 16 of the Kaisheva reference, what is it disclosing?

A. Well, it talks about the formulation development

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approach, selecting optimal solution pH, selecting buffer type, concentration of the buffer, evaluating the effect of various excipients of the liquid and lyophilized stability, and optimizing the concentration of the screened excipients using a specific one, but an experimental design approach.

Q. Is that like the experimental design approach that Dr. MacMichael testified about, this design of experiments?

A. Yes, it is. And, actually, Dr. Rabinow also included this in his slides.

Q. So would the POSA test every possible combination of buffers and stabilizing agents in practicing this claim?

A. No. The POSA would test the various combinations and variations of those combinations as the '865 patent did and via experimental design as needed.

Q. How would the POSA practice the claims in view of the '865 patent's disclosure?

A. Well, the skilled person would practice the claims given the disclosures that we've been discussing, including the examples and in Column 2.

Q. Now, if the POSA -- well, what excipients or what buffers and stabilizing agents would the POSA want to use if the POSA wanted to vary from those used in the examples of the '865 patent?

A. Well, I'd say the POSA would use excipients that have the same structures, same structural characteristics as those

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discussed in the various categories in the patent, and would want to make sure that those are suitable for intravitreal administration by looking at the literature, for example, or, if need be, consulting an ophthalmologist.

Q. Doctor, did you hear Dr. MacMichael point to any examples that meet the claim limitations but would take undue experimentation to make and test, any formulations like that?

A. No.

MR. RAKOCZY: Objection, Your Honor. That's a new opinion. That's not in the report.

THE COURT: Mr. Berl?

MR. BERL: I just asked him something about Dr. MacMichael's testimony. Of course it wasn't in the report because Dr. MacMichael's testimony happened after the report.

THE COURT: It can still be a new opinion, correct. Is there any reference or discussion of this in the volley of reports?

MR. BERL: There's a lot of discussion about enablement and whether there's undue experimentation. He said that it's not undue experimentation to make and test the formulations in the claim, and I'm just asking him whether Dr. MacMichael identified anything to the contrary.

MR. RAKOCZY: That's trying to inject a new issue, Your Honor, this whole idea of did someone find a formulation that doesn't work. That's a new opinion, a new issue. And I

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don't believe it's in the report.

MR. BERL: I'll withdraw it, Your Honor. Dr. MacMichael's testimony is what it was. I don't need Dr. Trout to reiterate that.

BY MR. BERL:

Q. Doctor, in your view, does practicing the full scope of the claim require routine experimentation or undue experimentation?

A. Routine experimentation.

Q. And if we go back to all of the *Wands* factors, Dr. Trout, taken together in view of all the *Wands* factors, what is your opinion about whether the asserted claims are enabled?

A. That the asserted claims are enabled.

Q. I'd like to turn to a slightly different topic, written description.

Did you consider as part of your written description analysis whether the specification describes structural features common to the genus?

A. Yes.

Q. And what did you conclude?

A. Well, that each of those limitations that we've been discussing have common structural features.

Q. And what are the structural limitations of the claims?

A. Well, I mean, I guess the VEGF antagonist is one, but that is one very specific molecule. Categories, then, are the organic cosolvent, the buffer, and the stabilizing agent.

Q. Were these structures well known in the art?

A. Yes.

Q. Did you understand Mylan's experts to dispute that?

A. No.

Q. Do all of the formulations within the claims share those common structural features?

A. Yes.

Q. Can the POSA recognize the formulations that were claimed here?

A. Yes.

Q. And can the POSA visualize the formulations within the claims?

A. Yes.

Q. Can the POSA recognize from the specification that the inventors invented the claimed formulations?

A. Yes.

Q. And how and where in the specification would the POSA recognize that?

A. Well, again, from the examples and -- I mean, throughout, but specifically the examples, and then the disclosure on Column 2 that we've been discussing. Those are the key places.

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Q. Does the '865 patent provide species or examples representative of the genus?

A. Yes.

Q. Do all of the examples have at least 98 percent native conformation as measured by SEC after two months?

A. Yes.

Q. And do all the examples meet the turbidity limitation of Claim 15?

A. Yes.

Q. And are the formulations with 50 mg/mL, those examples, are those relevant to whether the claims are described?

A. Yes.

Q. Is that for the reason you discussed a moment ago?

A. Exactly.

Q. Doctor, is the patent here claiming simply by function or is it claiming structures?

A. These are all structures.

Q. Doctor, in your view, does the '865 patent provide adequate written description for the asserted claims or not?

A. For all the reasons I mentioned, yes, it does.

Q. Now I'd like to address indefiniteness.

Do you remember Dr. MacMichael's testimony about indefiniteness?

A. Yes.

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Q. Okay.

And let's put up the claims.

Do you understand him to have asserted that the claim -- the term "suitable for intravitreal administration" is indefinite?

A. Yes.

Q. Do you agree?

A. No.

Q. Would the POSA be able to interpret the phrase with reasonable certainty?

A. Yes.

Q. What does suitable for intravitreal administration refer to?

A. It means does it contain components as described in the claim that could be used for intravitreal administration, these structures, as we've been calling them.

Q. Is the term "suitable for intravitreal injection" subjective?

A. No.

Q. How would the POSA determine whether an ingredient or an excipient is suitable for intravitreal injection?

A. Well, first of all, the POSA would look to the teachings in the patent, again, the examples and those places in Column 2 that we've been looking at. And if a skilled person wanted to depart from those, a skilled person can go

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into the literature and find excipients or additives with the same structure or similar structures that had been used in intravitreal administration before and, if need be, could consult an ophthalmologist.

Q. Did your definition of a POSA include someone who could consult with an ophthalmologist or a clinician as needed?

A. Yes.

Q. Let's take a look at Chang, which is Exhibit 1832. Did you review this reference?

A. Yes.

Q. And if we go to page 16 --

THE COURT: Yes, Counsel?

MR. RAKOCZY: Objection, Your Honor. This is outside the scope of the report. The witness's response to this indefiniteness argument is about ten lines, one paragraph, and it doesn't cite anything.

THE COURT: What paragraph is that, Mr. Rakoczy?

MR. RAKOCZY: Paragraph 420 of the responsive expert report if Your Honor has it.

THE COURT: I do. It's PTX 67.

MR. BERL: And, Your Honor, in paragraph 83 Dr. Trout --

THE COURT: One second.

MR. BERL: Sorry to go back and forth.

THE COURT: Paragraph 83. Go ahead.

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MR. BERL: This is where Dr. Trout addresses the Chang reference that I was about to ask him about.

THE COURT: Overruled.

BY MR. BERL:

Q. If we could look at page 16 of Chang. Can you explain what Chang is saying here?

A. Yes. I've just highlighted the sentence.

"Generally, it is preferred to select excipients that have been used in marketed products with a relevant route of delivery."

Q. And is that -- can you explain how that relates to the practice of the '865 patent and whether the POSA would be able to know what is suitable for intravitreal injection?

A. Yes. It's just a reflection of what I've been saying and what the POSA would understand.

Q. And have you considered the Peyman reference? That's PTX 1758.

A. Yes.

Q. Okay.

And if we could put that on the screen.

MR. BERL: This, for the record, is page 4 of the Peyman reference.

THE COURT: Yes, Mr. Rakoczy?

MR. RAKOCZY: Objection, Your Honor. Again, I don't believe this is cited in the report on indefiniteness.

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MR. BERL: It's cited, Your Honor, at paragraph 175. And I'm going to ask him about an excerpt that is word for word in the report, paragraph 175.

THE COURT: Is it tied in the report in any way to indefiniteness?

MR. BERL: Well, it says "a formulation suitable for the treatment," and that's what indefiniteness is about now.

THE COURT: Yes, Mr. Rakoczy?

MR. RAKOCZY: It's actually not tied to the indefiniteness section, Your Honor, which, again, is paragraph 420. That is the extent of the response on indefiniteness.

THE COURT: Understood. It's in there, though. Overruled.

BY MR. BERL:

Q. So if we put up page 4 of Exhibit 1758, the Peyman reference, under "Summary of the Invention," what language is it using there?

A. Well, it specifically says "formulation suitable for the treatment of ocular and neovascularization."

Q. Is that a term that persons of ordinary skill or a person of ordinary skill would understand?

A. Yes.

Q. Did you understand Dr. Rabinow to conclude that the prior art taught formulations suitable for intravitreal

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injection?

A. Yes.

Q. Would the POSA understand the scope of the asserted claims, Dr. Trout?

A. Yes.

Q. What did you conclude as to whether the claims were indefinite?

A. That they are not indefinite.

Q. Now I'd like to shift to a new topic, the '572 patent.

A. Okay.

THE COURT: Mr. Berl, why don't we take ten before we shift topics. We'll take an actual 10-minute break and try to stay on the course today.

Doctor, you remain off limits for conversation during your testimony, but you can go ahead and step down. And we'll take a 10-minute recess. Thank you all very much.

(A recess was taken from 9:46 a.m. to 9:56 a.m.)

THE COURT: Mr. Berl, you were changing topics. Go right ahead.

MR. BERL: Yes. We're in the home stretch, Your Honor.

BY MR. BERL:

Q. Dr. Trout, I'd like to shift to the '572 patent and

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the disclosure there in the claim of isotonic solution. Do you understand that the priority date has now shifted? Before, we were talking about 2006. The priority date for the '572 patent is later, right?

A. Yes.

Q. Doctor, does any prior art disclose that aflibercept was formulated as an isotonic solution?

A. No.

Q. Does Dixon, PTX 204, disclose an isotonic formulation of aflibercept to the POSA?

A. No.

Q. Did the Hecht reference, DTX 3588, teach an isotonic solution of aflibercept?

A. No. It doesn't even teach intravitreal administration.

Q. Doctor, did you review the prior art that Dr. Rabinow asserted with respect to the isotonic limitation?

A. Yes.

Q. And is that the Hecht and Dixon references?

A. Yes.

Q. In your view based on your analysis, what is your opinion about whether it was obvious to use an isotonic solution of aflibercept to treat diseases?

A. It was not obvious.

Q. Now, let's take a look at the written description

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analysis of Dr. MacMichael with respect to the isotonic solution of the '572 patent. Do you recall Dr. MacMichael testifying that isotonic solution lacked written description?

A. Yes.

Q. Do you agree?

A. No.

Q. Let's take a look at the '572 patent. And we'll look at Column 6 here. And we've put up lines 18 to 35.

What does the '572 patent disclose with respect to isotonic solution?

A. Well, right here in Column 6 it says "isotonic solution."

Q. And what does it say about isotonic solutions?

A. Well, it says that it may be used in combination with appropriate agents and continues that.

MR. RAKOCZY: Objection, Your Honor. I've no objection to the first two lines, 22 to 25, but that is the extent of the opinion in citation in his report, which, again, is ten lines long. He doesn't say anything else about all this other language, solely those first two highlighted lines.

THE COURT: That's paragraph 420, right, Mr. Rakoczy?

MR. RAKOCZY: This is now paragraph 430.

THE COURT: I'm sorry.

MR. RAKOCZY: 430, entitled "Formulated as an isotonic solution." And the fourth line down, you see it's --

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'572 patent at 6, lines 22 to 25, that is the only material cited in this entire report.

MR. BERL: With respect to breadth, I mean, the opinions that he was responding to were very brief too. And he responded in kind. And I'm simply asking him about the description here of isotonic solution. This is what everyone was talking about and addressing is whether this description of isotonic solution here is or is not sufficient. That's the entire issue here.

THE COURT: Yes, Mr. Rakoczy?

MR. RAKOCZY: Your Honor, whether that's the entire issue I guess is open to debate. The fact of the matter is the witness cited lines 22 to 25, and that is it. One line.

THE COURT: Understood. And you're certainly free to cross Dr. Trout extensively on that if you believe his -- the grounds for his opinions have been augmented, but I will find they have been sufficiently disclosed in particular relying upon this section of the '572 patent.

Objection overruled.

BY MR. BERL:

Q. Dr. Trout, I forgot exactly the question I asked; so I'll ask this one.

What is the '572 patent disclosing here with respect to the isotonic solution?

A. Well, again, it's disclosing isotonic solution

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containing glucose and other auxiliary agents, et cetera. And then it talks about what those auxiliary agents, et cetera, are -- solubilizing agent, polyalcohols, nonionic surfactants, et cetera.

Q. Would the POSA understand what an isotonic solution is?

A. Yes.

Q. Is that a well-understood concept by formulators?

A. Yes.

Q. Was the patent's disclosure sufficient for the POSA to visualize or recognize what an isotonic solution is?

A. Yes.

Q. Would the POSA need more detail to understand what an isotonic solution is than what is provided in the '572 patent?

A. No.

Q. Doctor, what is your conclusion about whether the '572 patent adequately described isotonic solutions?

A. That it does adequately describe isotonic solutions.

MR. BERL: Your Honor, with that, I'm to the end of my outline. There was one question. Honestly, it's probably ten seconds, but -- I hate to do this, but they --

THE COURT: That's all right. We haven't gotten any steps in yet, Mr. Berl.

I assume Mylan would request the courtroom be sealed, given the subject area Mr. Berl indicates his next question

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relates to.

MR. RAKOCZY: Yes, Your Honor.

THE COURT: The Court will enforce its prior protective order.

Ladies and gentlemen in the gallery, if you are not specifically permitted to be in the courtroom as we discuss the materials covered by the Court's protective order, I'm going to kindly ask you to step out. Thank you very much.

I'll also ask Court security to seal our courtroom, please.

(The following proceedings (2121/11 to 2122/8) were had under seal, and are filed under separate cover.)

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THE COURT: Thank you, everyone. Mr. Rakoczy, I'll just remind you for flow purposes, we do have to break at 11:00, just as an FYI.

MR. RAKOCZY: Thank you, Your Honor.

THE COURT: Thank you. But if you're ready, you may proceed, sir.

MR. RAKOCZY: I am ready. William Rakoczy for Mylan and Biocon.

CROSS-EXAMINATION

BY MR. RAKOCZY:

Q. Good morning still, Dr. Trout.

A. Yes, sir. Good morning.

Q. Good to see you again.

A. You too.

Q. All right. Yesterday and today you discussed the aflibercept molecule or fusion protein quite a bit; so I just want to make one thing clear. The '865 patent is not about the discovery of the aflibercept molecule, correct?

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A. Right. It's about formulations of aflibercept.

Q. So the inventors of the '865 patent did not discover or invent the aflibercept molecule, correct?

A. That's my understanding.

Q. Aflibercept was known and invented before the '865 formulation patent, right?

A. Again, yes, that's my understanding. Yes.

Q. And you understand the aflibercept molecule is subject to other patents that were filed years before the '865 formulation patent, right?

A. Again, yes, that's my understanding.

Q. Now, you discussed some of the properties of the aflibercept. I just want to be clear, and we can go through some of these.

For example, there's no affinity or binding data for the aflibercept molecule in the '865 patent, correct?

A. That's correct.

Q. There's no half-life data in the patent for aflibercept, correct?

A. In the patent. Again, some of these -- this information is in a prior art, but correct, in the patent itself.

Q. I'm just asking in the '865 patent itself, there's no binding data, no affinity data, no pharmacokinetics data, no half-life data, no side effect data. None of that's in the

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patent, correct?

A. Explicitly in the patent, that's not there, although the 98 percent can speak to some of that.

Q. But, for example, there's no pharmacokinetics data in humans or animals, correct?

A. In the '865, that's correct.

Q. As a matter of fact, there's no testing or data on using aflibercept in humans or animals at all in the '865 patent, correct?

A. Explicitly, again -- there are references in prior art, but explicitly in the '865, that's correct.

Q. There's no retinal penetration data in the '865 patent, correct?

A. Again, with the same proviso, that's correct.

Q. And the asserted claims themselves don't have any limitations regarding efficacy, pharmacokinetics profiles, retinal penetration, binding, or half-life of aflibercept, correct?

A. That specific data is not there, that's correct.

Q. So the claims of the patent are all directed to ophthalmic formulations, I think you said, correct?

A. Yes.

Q. The asserted claims are taking the aflibercept known molecule and putting that in a formulation suitable for an intravitreal administration using known excipients and then

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testing that for native conformation and turbidity. Is that fair?

A. I think that's basically fair. I would say that the native conformation and, depending on the claim, the turbidity is part of the invention. So that's part of it.

Q. Yeah. I'll restate it.

So the asserted claims are about taking the aflibercept molecule, putting it into a formulation suitable for intravitreal administration, using known excipients, I think you called it, and then the formulation must meet certain native conformation and turbidity requirements. Is that fair?

A. Depending on the claims, yes, I think that's fair.

Q. All right. I'd like to start, then, talking about some of those excipients.

So you would agree the excipients used in the claimed ophthalmic formulations were known in the prior art, correct?

A. Yes.

Q. And the inventors did not invent any new excipients or classes of excipients, correct?

A. Correct.

Q. So let's start with buffers. I think you mentioned buffers. Buffers were known excipients and have been used for decades to stabilize the pH of solutions, including in formulations, correct?

A. Yes. With other molecules, yes.

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Q. And the skilled person would have understood that the role of a buffer in a formulation is to maintain a stable pH; is that right?

A. Yes. To maintain a pH at a certain desired range, yes.

Q. And the skilled person would have understood that buffers have suitable pH ranges at which they function, correct?

A. Generally, correct.

Q. And phosphate was a known buffer, correct?

A. Yes.

Q. And, in fact, the inventors selected phosphate as a buffer for Eylea precisely because it's a natural substance, it was one of the most common buffers, and would have a reasonable probability of being tolerated in the eye; isn't that right?

A. I'm sorry. You're getting that from a document? I don't think that's in the '865 patent.

Q. I can show you your report.

A. Okay.

Q. Let's pull up DTX 7066. It's your responsive report, paragraph 372. And here you see you're citing to Dr. Furfine. He's one of the inventors, right?

A. Yes.

Q. And you say, "Dr. Furfine explained that the inventors selected phosphate for the ultimate formulation used

in Eylea (and described in the '865 patent) because 'phosphate is a natural substance' and 'one of the most common buffers,' and thus 'seemed like something that would have a reasonable probability of being tolerated in the eye,' correct?

A. Yes. Again, that's from Furfine's deposition, not in the '865. But, yes, that's correct.

Q. And you agree with that, correct?

A. Yes.

Q. And the skilled person would have known all of that, correct?

A. Yes.

Q. Now, other intravitreal-administered products like Macugen have also used a phosphate buffer, correct?

A. I believe so.

Q. And prior to 2006, then, you'd agree that the skilled person would have expected that a phosphate buffer was safe to use in an ophthalmic formulation, correct?

A. I think generally that's correct. Again, there are other limitations.

Q. And they could have tested that, correct?

A. Tested what, Counsel?

Q. They could have tested whether phosphate was an appropriate buffer for an ophthalmic formulation, correct?

A. I think I would say it a little different. The skilled person would understand that the phosphate buffer would

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be appropriate for an ophthalmic formulation, and then they could test whether it would be -- certain other parameters, like the 98 percent native conformation.

Q. And that testing would have been within the capabilities of our skilled person, correct?

A. Correct.

Q. Now, histidine, I think you said, was also a well-known buffer at the time.

A. Yes.

Q. For example, you mentioned several formulations, but I believe you said the Shams reference at DTX 726, which is already in evidence, disclosed the use of a histidine buffer in a formulation for intravitreal administration. Isn't that right?

A. I think so, but could we just pull that up to make sure.

Q. Sure. We can pull up DTX 726. Go to page 32, bottom of the page. And you see the ranibizumab injection here using a histidine buffer for intravitreal administration, correct?

A. Yes. Thank you.

Q. And I believe you mentioned that Gaudreault reference. You recall that?

A. Yes.

Q. That was DTX 2256, already in evidence.

And I think you mentioned that uses a succinate

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buffer for ranibizumab formulation. Is that right?

A. Correct. I know it does, but do we want to pull it up just to make absolutely sure?

Q. You're not sure if it uses --

A. I am sure. I am sure.

Q. That's my only question, it uses succinate.

A. All right.

Q. So based on at least the Shams reference, we can agree the skilled person would have understood that other buffers could be used in an ophthalmic formulation that were suitable for intravitreal administration, such as histidine, correct?

A. Correct.

Q. Now, let's talk about stabilizing agents.

Stabilizing agents, like sugars and sugar alcohols, have been known for over four decades to provide thermal stability to proteins, correct?

A. That sounds like a correct statement.

Q. And trehalose, if I'm saying that correctly, trehalose is a commonly used thermal stabilizer known in the art, correct?

A. I think that's fair. And, yes, Counsel, I believe you're pronouncing it correctly.

Q. And the ranibizumab formulation from Gaudreault at DTX 2265, that used trehalose, correct?

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A. Yes.

Q. Now, the skilled person would have expected that 10 percent trehalose, such as that used in the Gaudreault formulation, would be suitable for intravitreal administration, correct?

A. Yes. And, again, I should be clear. I'm interpreting all of your question as with respect to the priority date of the '865 patent. I assume that was the case.

Q. Yes.

A. Yes. So yes.

Q. Yes. And I'm not aware of any dispute of Gaudreault being prior art. I didn't hear you testify to that effect.

A. Correct.

Q. All right. And if the skilled person would have been capable of testing whether trehalose was an appropriate stabilizer in a protein formulation, correct?

A. Again, that's a very broad question. I assume you mean for intravitreal administration, or are you just asking --

Q. Yeah, for intravitreal administration. They could have tested whether that was an appropriate stabilizer, trehalose, correct?

A. I would just say that they would understand that it would be suitable and could test whether it meets other parameters, like the 98 percent.

Q. And that testing would have been within the

capabilities of our skilled person, correct?

A. Correct.

Q. Now, sucrose was another stabilizer known in the art, correct?

A. Yes.

Q. And prior to 2006, the skilled person would have had an expectation that sucrose was safe to use in an ophthalmic formulation, correct?

A. Yes.

Q. Now, let's talk about surfactants like polysorbate. I believe I heard you say polysorbate 20 was a known excipient in protein formulations, correct?

A. Correct.

Q. And the skilled person would have known that other intravitreal formulations in the art also used polysorbate 20, correct?

A. Correct.

Q. The Lucentis, or ranibizumab formulation, from Shams at DTX 726, that used polysorbate 20, correct?

A. Correct.

Q. And I believe the VEGF antagonist Avastin, or bevacizumab formulation, used polysorbate 20 as well, correct?

A. That's what I recall, yes.

Q. And so prior to 2006, the skilled person would have had an expectation that polysorbate was safe to use in an

ophthalmic formulation, correct?

A. Correct.

Q. Now, to the extent the skilled person did not use excipients from the examples in the '865 patent, she could have turned to other excipients that would have been considered suitable for ophthalmic formulations, correct?

A. Yes. With related structures, yes.

Q. So the skilled person could have turned to excipients that were tested or contemplated in other intravitreal drug products, correct?

A. Yes. I think generally, yes.

Q. And they could have used -- they -- strike that.

For example, a skilled person, again, they would have known about the Lucentis intravitreal products from Shams, correct?

A. Yes. They would have known Shams, yes.

Q. And the skilled person would have known that that Lucentis intravitreal product used histidine, trehalose, and polysorbate 20, correct?

A. Yes.

Q. And the skilled person would have understood that the concentration of excipients could be decreased or increased to maintain a desired osmolarity, correct?

A. If one were to target that desired one, yes, it could have been adjusted.

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Q. Now, let's talk briefly -- I think you answered some of these, but let's hit the degradation products for protein formulations and how they're measured.

You would agree that techniques were known long before 2006 for how to detect, measure, and elucidate the various types of degradation products in protein samples, correct?

A. There were multiple techniques, yes.

Q. And size-exclusion chromatography, or SEC -- can I call it SEC?

A. Yes.

Q. And SEC was a known and routine method to measure native conformation of a protein, correct?

A. Yes.

Q. The skilled person could have readily performed an SEC test on a protein formulation, correct?

A. Generally. It depends on the formulation and whether it would be applicable, but the person would know SEC.

Q. It wouldn't take undue experimentation for the skilled person to run an SEC test on a formulation, correct?

A. Correct.

Q. Now, the skilled person could have also used other techniques in addition to SEC for assessing protein stability as well, correct?

A. Yes.

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Q. All right. Let's switch gears and talk a little bit about the specification.

I believe you testified that the claims are defined by common structural features. Do you recall that?

A. Yes.

Q. And I think you identified some of those common structural features in the claims and the examples.

Do you recall that?

A. Yes.

Q. And some of those structures were the known aflibercept, correct?

A. Correct.

Q. The known buffer, correct?

A. The buffers, yeah.

Q. I think you said the known polysorbate 20, correct?

A. Right.

Q. And I think you said known stabilizing agents, correct?

A. Correct.

Q. So I'd like to pull up a table you created in your expert report. Let's go to demonstrative DDX 9, Slide 1, and I've reproduced it here.

And you recognize this table, Dr. Trout, from your response report?

A. Yes.

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Q. And so in this table you laid out kind of in summary fashion all the examples from the '865 patent, correct?

A. Yes.

Q. And I think in your testimony, your direct testimony, you said that these examples are all species representative of the genus. Is that fair?

A. I'm not -- I'm not sure if I said that.

Q. Let's go back to Slide 1, DDX Slide 1.

And could we blow that up, please, Mr. Gibson.

You actually say that right above the table, right? "The '865 patent also describes species representative of the genus," and then you laid out those formulations in the examples, correct?

A. Yes. Yeah. I mean, I'm not saying that each of the examples are representative of the genus of the claims specifically. I'm saying that the tables incorporate species representative of the genus of the various components that we've been talking about, the structural components.

Q. Right.

Let's go back to DDX 9, Slide 2, where we have a bigger table. And I believe all of these examples, they all contain the aflibercept, correct?

A. Correct.

Q. They all contain polysorbate 20, correct?

A. Correct.

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Q. They all contain phosphate, correct?
A. Correct.
Q. And then they all contain sucrose except for two of them. So most of them have sucrose, correct?
A. Correct. And we should say that the different components are different concentrations, yes.
Q. Yes. I wasn't trying to mislead you. They're different concentrations for some of these, correct?
A. Correct.
Q. All right. So -- and I believe you testified that each of these examples with these common structural features all achieve the 98 percent native conformation requirement in the claims, correct?
A. Yes.
Q. All right. Now, many of these common structural features or known components are also found in a lot of the other formulations you've discussed today and yesterday, correct?
A. Yes.
Q. Let's look at some of those. On screen we have DDX 9.

Slide 3, please, Mr. Gibson.

And what I've done is -- let's go to Slide 3. And I have added a column to the right.

We can go to the next one, please.

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Here, I've added a column on the right for the Shams reference. Do you see that?

A. Yes.

Q. And so we see the Shams reference also contains a VEGF antagonist, correct?

A. Well, it's a different one.

Q. Yeah, it's a different one. It's ranibizumab, correct?

A. Correct.

Q. And to be fair, we've got 6 mg/mL and 10 mg/mL ranibizumab, correct?

A. Correct.

Q. And then Shams' formulation also has 0.01 percent polysorbate 20, correct?

A. Correct.

Q. And then we see it also has the 10-millimolar histidine, correct?

A. Correct.

Q. And then it's got that trehalose stabilizer, 100 mg/mL, right?

A. Yes.

Q. All right. Let's go to DDX 9, Slide 5, and let's add to our table. You see on the right I've added a column for Gaudreault now.

You recall that reference, right?

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A. Yes.

Q. And that's at DTX 2265. And the Gaudreault reference also contains ranibizumab, correct?

A. Yes.

Q. But that formulation had slightly different concentrations of the ranibizumab. It was 10 mg/mL and 40 mg/mL, correct?

A. Correct. And I explained why the skilled person would be turned away from the 40.

Q. We're going to get there. I promise you, we're going to get there.

But we can all agree now in my table, the Gaudreault column, that the Gaudreault formulation had 10 and 40 mg/mL ranibizumab formulations, correct?

A. Correct.

Q. And the Gaudreault formulation also had 0.05 percent polysorbate 20, right?

A. Yes.

Q. And it also had 10-millimolar succinate that we just mentioned, correct?

A. Yes.

Q. Lastly, it had 10 percent -- I don't want to butcher it -- 10 percent trehalose.

A. Yes. You're doing great with that pronunciation, Counsel.

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Q. All right. Let's go to DDX 9, Slide 7, and let's add another column. Here we've got Fraser's formulation.

Do you see that on the right?

A. Yes.

Q. Now, Fraser had 24.3 mg/mL of a VEGF antagonist called VEGF Trap R1R2, correct?

A. Yes.

Q. All right. We'll get to that more in a moment, but let's go to the next component.

Fraser also had 0.01 polysorbate 20, correct?

A. Yes.

Q. And Fraser also had 5-millimolar phosphate and 5-millimolar citrate, right?

A. Yes.

Q. And then lastly we see that sucrose stabilizer at 20 percent in Fraser, correct?

A. Yes. And I should have added, Counsel, you didn't mention the pHs, but those are also rightly included in your table.

Q. We're going to get to those.

A. Okay.

Q. All right. Let's see if we have any room to add any more. Let's check out DDX 9, Slide 9. Can we squeeze in one more?

All right. There we have Dix '226 and the last

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column on the right. I think we're out of room. You see Dix '226?

A. Yes.

Q. Dix '226 at DTX 13. Now, this formulation had 50 mg/mL of VEGF Trap Sequence ID Number 4, correct?

A. Correct.

Q. That's obviously the sequence for aflibercept, correct?

A. Correct.

Q. And Dix '226, the formulation also had 0.1 percent polysorbate 20, correct?

A. Correct.

Q. At 10-millimolar phosphate, correct?

A. Correct.

Q. And 20 percent sucrose, correct?

A. Correct.

Q. And then just to wind all this up, then, we've got the pHs in the bottom row. So Dix '226 had a pH of 6.25, correct?

A. Correct.

Q. Fraser was 6.0 pH?

A. Yes.

Q. And then Gaudreault was 5.0 pH?

A. Yes.

Q. And Shams was 5.5 pH, correct?

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A. Correct.

Q. All right. Now, looking at this table on DDX 9, Slide 9, can we agree that we see the common or known structural features from the examples of the '865 patent running throughout all of the Shams, Gaudreault, Fraser, and Dix formulations, correct?

A. Yes. That's correct.

Q. Shams, Gaudreault, Fraser, and Dix '226, those formulations and the species of the '865 patent all contain polysorbate 20, correct?

A. I'm sorry. Could you repeat the question.

Q. Yes.

The Shams, Gaudreault, Fraser, and Dix '226 formulations and the species of the '865 patent examples that we see here all contain polysorbate 20, correct?

A. Well, that's why I paused. And sorry if I didn't say this before, but Example 2 has the PEG. So it's not polysorbate 20 --

Q. I'm sorry.

A. -- just to be clear.

Q. I'm sorry. I'll rephrase. And thank you for catching that.

A. Okay.

Q. So to make sure our record's clear, Shams, Gaudreault, Fraser, and Dix '226 formulations, and most of the

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species in the examples of the '865 patent, use polysorbate 20, correct?

A. Yes. I think you might want to say most of the examples, but I think we understand, yes.

Q. Most. All except one, correct?

A. Yes.

Q. And Shams, Gaudreault, Fraser, and Dix '226 formulations and the species of the '865 patent examples all contain a buffer, either phosphate, histidine, or succinate, correct?

A. Yes.

Q. And Shams, Gaudreault, Fraser, and the Dix '226 formulations, and most of the species of the '865 patent examples all contain a stabilizer, either sugar or trehalose, correct?

A. Yes.

Q. Now, I want to stay on this slide and ask you, the skilled person could have easily made the formulations from Shams, Gaudreault, Fraser, and Dix '226, correct?

A. Counsel, you mean given the teachings of those respective references?

Q. Yes. They could have made these. That's within the skilled person's capabilities, correct?

A. Well, I think there's some issue with the Fraser, because it's unclear what the VEGF Trap is; but I think the

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others, they could have made.

Q. Well, let's assume the skilled person knew what was in Fraser, what that VEGF Trap was. The skilled person, it was within their skill set or capabilities to just make those formulations, correct?

A. Yes.

Q. And the order of addition of the excipients, the VEGF antagonist, the mixing time, the concentrations, and the temperatures, those are all basic steps that would have been routine in the art, correct?

A. I agree.

Q. Now, the skilled person also, after they made those formulations from Shams, Gaudreault, Fraser, and Dix '226, they could have tested them for native conformation and turbidity, correct?

A. They could have tested them, yes.

Q. That testing would have been within our skilled person's capabilities, correct?

A. The actual performance of the test, yes.

Q. Now, for my next few questions I'm going to ask you to make an assumption. Okay?

A. Okay.

Q. All right. I want you to assume for my next few questions that the skilled person would have been motivated to make a formulation with 40 mg/mL aflibercept. I know you

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disagree with that, but I want you to assume the skilled person would have been motivated to do that.

Are you with me?

A. Yes.

Q. Now, with that assumption, the skilled person could have made the formulation from Shams, except they could have substituted in 40 mg/mL aflibercept as the VEGF antagonist, correct?

A. I'm sorry. Just to be clear, I'm supposed to assume that they're going to substitute 40 mg/mL aflibercept?

Q. Yes.

A. That's part of the assumption?

Q. Yes.

A. Okay. Yes.

Q. So you agree the skilled person could have made that formulation, correct?

A. Yes.

Q. And the skilled person could have tested that formulation for native conformation and turbidity, correct?

A. Yes.

Q. So same questions for the rest of these formulations, Gaudreault, Fraser, and Dix '226. The skilled person could have made those formulations except substituted in 40 mg/mL aflibercept, correct?

A. Yes.

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Q. And they could have tested those formulations for native conformation and turbidity, correct?

A. They could have with some, again, proviso on what they might expect the results might be.

Q. But they could have -- they could have made the formulation with 40 mg/mL aflibercept from Shams, Gaudreault, Fraser, Dix, and they could have tested it for turbidity and native conformation, correct?

A. They could have done the test, yes.

Q. That's well within the capabilities of our skilled person, right?

A. Yes.

Q. In fact, I believe you testified about the Kaisheva -- and I may be butchering that as well -- Kaisheva 2013 reference.

Do you remember that?

A. I do. And I cannot speak to the pronunciation. I'm sorry.

Q. And let's say -- I'm going to continue saying Kaisheva.

Kaisheva actually laid out a formulation development approach, correct?

A. In, I mean, very broad terms.

Q. So let's go back to my examples on Slide 9.

If the skilled person substituted in 40 mg/mL

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aflibercept into each of those Shams, Gaudreault, Fraser, and Dix '226 formulations, they could have then optimized those formulations for stability, correct?

MR. BERL: Your Honor, I just want the record to be clear. Is the assumption still in play? I assume it is, but I just don't want any confusion about this.

THE COURT: Mr. Rakoczy, that was my impression.

MR. RAKOCZY: The assumption is still in play.

THE COURT: Doctor, you understand that, sir?

THE WITNESS: Yes, Your Honor. And that was my assumption too.

BY MR. RAKOCZY:

Q. Do you want me to rephrase it?

A. Please.

Q. So my question is the skilled person, having made the Shams, Gaudreault, Fraser, and Dix '226 formulations, except substituting in 40 mg/mL aflibercept with my assumption, they then could have optimized those formulations for stability, correct?

A. Well, there, there's somewhat of an issue because the skilled person wouldn't, a priori given your hypothetical, have an understanding of what the optimized target might be. So "optimization" is a very broad term, and the question is what the target might be.

Q. You are clairvoyant on my next question. Let's

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assume -- let's add to my assumption. Let's assume the target is 98 percent or better native conformation.

Can you assume that?

A. Okay.

Q. All right. So with that assumption, the skilled person could have made the Shams, Gaudreault, Fraser, and Dix '226 formulations using 40 mg/mL aflibercept and then optimized those formulations to meet that 98 percent native conformation requirement, correct?

A. Well, that's correct given the teachings of the '865 patent. But before the '865 patent, the skilled person wouldn't expect what that optimal might be.

Q. No, I'm asking you to assume that they want to hit 98 percent native conformation. Okay? That's part of my assumption. Can you assume that?

A. Okay. Yes.

Q. So my question is -- I'm sorry.

A. No, I did understand that.

Q. Assuming that that's the target the skilled person wants to hit, the skilled person could have optimized Shams, Gaudreault, Fraser, and Dix with 40 mg/mL aflibercept to reach that 98 percent native conformation, correct?

A. Not -- no, Counsel. Before the teachings of the '865 patent, the person wouldn't have expected they could reach that. Given the teachings, in hindsight, I would say yes, they

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would have. But they wouldn't have known that, and they could have failed.

Q. They could have failed. But they don't have blinders on, right? They can do screening studies for these excipients. They can vary the concentrations until they reach 98 percent native conformation, correct?

A. First of all, I know we made those assumptions. But I think we're adding an additional assumption of that formulation works in a certain way in which this doesn't. So I already said that you don't substitute one formulation for another. And I think there's literature for that.

But the other thing is now we're just talking about a formulation development; so the formulator may not reach the 98 percent.

Q. So your testimony is, for example, we can take Dix '226 -- let's look at that formulation. Okay?

Your testimony is that taking 40 mg/mL VEGF Trap Sequence ID Number 4, combining that with 0.1 percent polysorbate 20, 10-millimolar phosphate, 20 percent sucrose, and 50-millimolar NaCl, your testimony is that that's not going to achieve 98 percent or better native conformation?

A. No, Counsel, that's not my testimony.

The Dix actually says that this formulation does achieve the 98 percent. And given that, I think the skilled person would think it most likely that going to 40, for all the

reasons I mentioned in my direct, would also achieve that with all of the things being the same.

Q. Okay. So they would have known about the Dix '226 teachings and that that 50 mg was stable in 98 percent native conformation, correct?

A. They would have -- assuming the Dix is prior art, making those assumptions, they would have known that that reaches the 98 percent, the formulation on your slide, yes.

Q. And our skilled person is assumed to know all of this art, correct?

A. Well, again, there's this technical legal issue with the Dix. So if you want to make that assumption, I will --

Q. Well, I'm asking you. Is it your understanding that the skilled person is supposed to have a handle and a familiarity with all of the prior art or just some of the prior art?

A. Well, again, my understanding is the relevant prior art. But, again, that's the legal question perhaps.

Q. Well, let's assume Dix '226 is relevant prior art. You would agree the skilled person would know about all of these formulations, correct -- Shams, Gaudreault, Fraser, Dix '226, right?

A. With that assumption, yes.

Q. And if the skilled person is looking at Dix, 50 mg/mL aflibercept, and they see that that is stable and meets

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98 percent native conformation, that's going to assist the skilled person in making a formulation with 40 mg that meets the 98 percent native conformation, correct?

A. Yes. I think I keep saying I agree the skilled person would think it most likely.

Q. All right. Let's move on to aflibercept. Obviously, you've testified quite a bit about the molecule.

Can we agree aflibercept is glycosylated, correct?

A. Yes.

Q. And you mentioned the Holash publication at DTX 3549, I believe, yesterday.

Do you recall that?

A. Yes.

Q. You're familiar with Holash, correct?

A. Yes.

Q. Now, Holash -- strike that.

Aflibercept is described in Holash as VEGF Trap R1R2, correct?

A. I don't think that's an accurate statement.

Q. All right. Let's see what Regeneron told the Patent Office.

Let's pull up DTX 3501, and I want to look at page 1 first.

You see this is an application for extension of patent term. Do you see that?

A. Let me look on my screen. Yes, I see that it says that.

Q. And it's for U.S. Patent Number 7,070,959. Do you see that?

A. Yes.

Q. You're familiar with the '959 patent, correct?

A. I think so. I've reviewed a lot of documents, Counsel.

Q. Let's go -- we'll come back to that.

Let's go to -- sorry, Dr. Trout. Let me start over.

A. Certainly.

Q. Let's go to page 5 of this same exhibit, DTX 3501.

All right. And you see there in the second paragraph, starting around the fifth line, Regeneron said, "Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and is glycosylated, with the glycosylation constituting an additional 15 percent of the total molecular mass, resulting in a total molecular weight of 115 kilodaltons."

Do you see that?

A. Yes.

Q. And you agree with it. That's aflibercept, correct?

A. Yes. That sounds right.

Q. Now, let's look at the very next paragraph starting on the fifth line. Here Regeneron told the Patent Office,

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"Aflibercept is also described in Holash et al., Proc. Natl. Acad. Sci. USA, August 20th, 2002, Volume 99, number 17, pages 11393 through 11398 ('Holash,' Attachment G) as VEGF Trap R1R2."

You see that?

A. Yes.

Q. So Regeneron told the Patent Office that aflibercept is VEGF Trap R1R2 from Holash, correct?

A. Yeah, again, the VEGF Trap R1R2 in Holash is a skeletal disclosure in a general -- or a category, I should say. But I guess that's what they're telling the Patent Office now.

Q. They're not telling the Patent Office it's a category or a catchall or a genus. They said aflibercept is VEGF Trap R1R2, right?

A. Right. But I believe this is after the priority date.

Q. This is Regeneron's representation of Holash, correct?

A. Yes.

Q. Do you have any reason to dispute Regeneron wasn't being honest with the Patent Office when they said aflibercept is described in Holash as VEGF Trap R1R2?

A. No.

Q. So whenever we have VEGF Trap R1R2 in the prior art,

that's aflibercept, correct?

A. Not when you look at the prior art itself as of the priority date of the '865 patent.

Q. If VEGF Trap R1R2 is aflibercept, it's always going to be aflibercept, in the prior art or otherwise, correct?

A. But we don't -- I mean, yes after the fact, but we don't know that as of the priority date.

Q. Well, after the fact or not, VEGF Trap R1R2 is not going to sometimes be aflibercept and sometimes not be aflibercept, right?

A. It may be, Counsel. Right here, I guess Regeneron is describing Holash.

Q. So Holash describes VEGF Trap R1R2. We can agree on that, correct?

A. Yes.

Q. And Regeneron told the Patent Office that's aflibercept, right?

A. Yes again, but you don't get that from Holash.

Q. We don't get that from Holash. So Regeneron was misrepresenting what Holash says in their own article to the Patent Office?

A. No. I don't think that's correct.

Q. So we can agree, according to Regeneron, that aflibercept is VEGF Trap R1R2 in Holash, correct?

A. As they're telling the Patent Office after the

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priority date, yes.

Q. And your testimony is that VEGF Trap R1R2, despite Regeneron's representations, could mean something else in the prior art?

A. I don't think that's quite accurate. My testimony, for the reasons that I went through earlier this morning, is that VEGF Trap R1R2 as disclosed in Holash could be different molecules, could be a category.

Q. Could mean lots of things, right?

A. Well, I think if one traces it back to Papadopoulos, there are two options.

Q. Two options, but not according to Regeneron. Regeneron, one option, it's aflibercept, it's glycosylated, correct?

A. Yes. I think we talked about that earlier, but yes.

Q. Now, you haven't offered any opinions on the '959 patent that's the subject of this patent term extension application, have you?

A. I would have to go back. My report's pretty long, but it wasn't the main patents that I opined upon.

Q. Well, I didn't hear you talk about it yesterday or today, correct?

A. Correct.

Q. So you don't know whether the '959 patent discloses the aflibercept molecule itself and all of its properties. Do

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you know that?

A. I'm not sure.

Q. All right. Let's move on to some of the testimony you gave on teaching away. Do you recall that?

A. Yes.

Q. So let's talk about the size of aflibercept. If I understood you correctly, you testified the skilled person might be taught away from using aflibercept because of its large size; is that right?

A. Yes.

Q. Now, to be clear, the '865 patent doesn't contain any data or testing on the size of aflibercept, correct?

A. Again, it doesn't explicitly include that; there are references to the prior art.

Q. The '865 patent, you think there are references to the prior art in the '865 patent that talk about the size of aflibercept?

A. Well, I'd have to check exactly the references in the '865, but there are references, as I discussed, in the prior art.

Q. The '865 patent does not teach that only VEGF antagonists of a certain size can penetrate the retina, correct?

A. It doesn't explicitly speak about those issues, correct.

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Q. It doesn't have any retinal penetration data in it, correct?

A. Not explicitly, correct.

Q. It doesn't teach that aflibercept is better than any other VEGF antagonist in terms of getting into the eye, correct?

A. It doesn't talk about those issues explicitly, correct.

Q. The '865 patent doesn't teach the skilled person that somehow big molecules won't get into the eye, correct?

A. Not explicitly.

Q. All right. So there was a bigger molecule in the art that got into the -- penetrated the retina, correct?

A. Well, I'm not sure that that was the understanding as of the priority date.

Q. All right.

Let's pull up DDX 2, Slide 1.

Here we have aflibercept, 115 kilodaltons, right?

A. Yes.

Q. All right. Let's pull up the big molecule, bevacizumab. You remember this one. You testified about that yesterday, correct?

A. Yes.

Q. This one's bigger in terms of molecular weight, right?

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A. Yes.

Q. So bevacizumab, or Avastin, is 149 kilodaltons, correct?

A. Yes. And, again, I agree that these weights are guides. It's the volume or the radius that's what's most important. But yes.

Q. It looks big. Looks big, doesn't it?

A. Yeah. It's about the same size as aflibercept. Agreed.

Q. Well, in terms of molecular weight, it's actually over 20 percent larger than aflibercept, correct?

A. Yes. Again, I think I said this yesterday. The glycosylation groups in aflibercept make its volume probably a bit bigger.

Q. Help me with my math. It's -- bevacizumab is actually almost -- is it almost 30 percent larger than aflibercept in terms of molecular weight?

A. Almost. And just so you understand, I'm trying to make the point that this is a good guide. It's the volume that's important. This is -- it's related, but it's not exactly the same.

But yes, I grant that these are both large molecules, about the same size.

Q. And you're well aware that by 2006 multiple publications had discussed the effective administration of

bevacizumab injected intravitreally into human patients, correct?

A. Well, I think I testified about that. There was some debate. And I think the consensus before 2006 was that it's unclear that there would be penetration as such.

Q. Well, let's see what actual workers in the field were saying.

Let's pull up DTX 3058, already in evidence.

And I think you're aware or you've seen this, right, the Rosenfeld and colleagues publication?

A. I think so.

Q. Dated July-August 2005 entitled "Optimal Coherence Tomography Findings After an Intravitreal Injection."

Do you see that?

A. Yes.

Q. All right. Let's go to page 1 and look at the abstract.

And you see there it states that "An intravitreal injection of bevacizumab 1.0 mg was given. Within one week, optical coherence tomography revealed resolution of the subretinal fluid, resulting in a normal-appearing macular contour. The improved macular appearance was maintained for at least four weeks, and visual acuity remained stable."

Do you see that?

A. Yes, Counsel. Which exhibit is this in my binder?

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Q. This is DTX 3058, already in evidence, I believe.

Now, you would agree that actual workers in the field, Rosenfeld -- or Dr. Rosenfeld and his colleagues, they clearly weren't dissuaded or taught away from using a big molecule like bevacizumab, correct?

Is that correct, Dr. Trout?

A. Well, I think that's correct that they decided to test it. It doesn't mean that the skilled person would do that. This is a research study. And they say on page 333, "This is the first report of injection of bevacizumab into a human eye." So this is part of a research investigation.

Q. But this is an actual worker in the field, an actual researcher in the prior art, who was not dissuaded from using bevacizumab because of its large size, correct?

A. Researcher was testing it, yes.

Q. And Dr. Rosenfeld and colleagues, they would have been aware of the same prior art that you testified about, correct?

Can we assume Dr. Rosenfeld and colleagues would have been aware of all that art back in the day, but yet they were not discouraged from using a big molecule like bevacizumab, correct?

A. Well, I'm not sure if they'd be familiar with all of the art that I mentioned, just certainly familiar with some art and, again, performed the research study.

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Q. So he was not discouraged to use bevacizumab by intravitreal injection, correct?

A. He was not discouraged to test it, to investigate it as a research project.

Q. Let's take a look at another one. Let's pull up DTX 9036 and look at page 1 first. And you see this is *Ophthalmology.*

Do you see that?

A. One second, please.

Q. It's on screen as well.

A. Yes.

Q. You see it's *Ophthalmology*, Volume 113, Number 3, from 2006, correct?

A. Yes.

Q. Now, let's go to page 3 and look at the exact date on this.

And you see at the top we have a received stamp?

A. Yes.

Q. You see it says, "Received March 3rd, 2006, Library of Health Sciences, University of Illinois, College of Medicine, Peoria," correct?

A. Yes.

Q. You don't have any reason to doubt that date, do you?

A. Not sitting here.

Q. I think yesterday you said you weren't sure or maybe

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your counsel said wasn't sure when the Avery publication came out.

Do you recall that?

A. Yes. Which exact date it came out, yes.

Q. Well, we've got an exact date now, right? March 3rd, 2006?

A. If that stamp is correct, yes.

Q. And that's before the date that you used as an earlier priority date, correct? That's before March 21st, 2006, correct?

THE COURT: One second, Doctor.

Yes, Mr. Berl.

MR. BERL: Yes, Your Honor. They've never asserted this before. This is a new document with a new date stamp, never asserted it as prior art before. We haven't had an opportunity to assess this or its veracity or anything else. Doesn't seem like the time to be asserting the new prior art.

MR. RAKOCZY: It's the exact same -- oh, I'm sorry.

THE COURT: I understand.

Can we unzoom, if that's a word.

MR. RAKOCZY: This is the same Avery document, Your Honor. We just got one with the date on it because yesterday for the first time I hear counsel saying, "I don't know when this came out in March." So I thought I'd give him a date.

THE COURT: How about a proffer of where this copy

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with that stamp came from.

MR. RAKOCZY: This proffer -- could we blow it back up, Judge?

THE COURT: Sure, yes, yes. Now that -- I just lost track of which reference material this was. I'm sorry.

MR. RAKOCZY: This came, I believe, from the University of Illinois, College of Medicine in Peoria.

THE COURT: Anything further on this one, Mr. Berl?

MR. BERL: It's not -- it did not just come up yesterday. They asked us to stipulate, as part of the pretrial order, that this was prior art. We said no. We said no. And all they provided was a different copy of Avery without a date stamp. They have no declaration from the librarian. We've had no opportunity to connect the veracity of this Bates stamp or conduct any discovery to assess when it was received or whether this is, in fact, prior art. It doesn't look that way. Last day of trial, they all of a sudden say here's the date of the publication. We've been doing this for nine months.

MR. RAKOCZY: Your Honor, nobody even disputed Avery's prior art. This is the first time hearing it. They never gave a date of Avery.

THE COURT: I'm going to overrule the objection and receive it for what it's worth, which is a -- with all due respect to the University of Illinois, College of Media in Peoria -- a random stamp of some kind that says March 3rd,

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2006. It'll be received for what it's worth and afforded weight accordingly.

Objection overruled.

MR. RAKOCZY: Thank you, Judge.

BY MR. RAKOCZY:

Q. Let's flip to page 5 of DTX 9036, and this is the Avery article.

You recognize this, correct, Dr. Trout? You testified about this yesterday?

A. Yes, it looks to be the article.

Q. This is Dr. Avery and colleagues, their publication entitled "Intravitreal Bevacizumab (Avastin) for Neovascular Age-Related Macular Degeneration," correct?

A. Yes, that's the title.

Q. And let's look at the methods section if we could.

And you see here in the methods that Dr. Avery and colleagues said that patients received intravitreal bevacizumab 1.25 milligrams on a monthly basis, correct?

A. Yes.

Q. Let's jump to their conclusions if we could.

Here we see in "Conclusions" Dr. Avery and colleagues reported that "Short-term results suggest that intravitreal bevacizumab, 1.25 milligrams, is well-tolerated and associated with improvement in VA, decreased retinal thickness by OCT, and reduction in angiographic leakage in most patients," correct?

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Is that the correct conclusion, Dr. Trout?

A. I'm trying to -- I see. Yeah, but it continues.

Q. Yes, it continues, but that's the conclusion, correct?

A. That's part of the conclusion, yes.

Q. Now, my question is Dr. Avery and colleagues, they were not dissuaded or discouraged from using bevacizumab intravitreally, correct?

A. Well, again, they are attempting to do -- or they are doing a research study, and what you left out was the last sentence of the conclusion: "Further evaluation of intravitreal bevacizumab for the treatment of choroidal neovascularization is warranted."

So this is just an invitation to do an experiment. And if you remember from other parts of the paper, it talks about potential issues with using bevacizumab. And, really, the conclusions and the discussion throughout is tentative at best.

Q. Now, Dr. Trout, these are actual experts working in the field at the time, correct?

A. Yes. I have no reason to doubt that. Yes.

Q. Now, today you're saying the skilled person would be discouraged or taught away from using a big molecule, but people actually working in the field at the time were not discouraged. They used bevacizumab in the eye, despite its

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size, correct?

A. I mean, they -- I think they could have been discouraged. They're doing research studies. That's often what I do in my lab, is I do things that the art teaches away from to see if I can advance the field.

And again, the text, partly what I read but also on page 364, talks about the potential of thromboembolic events, and then the discussion on page 370 talks -- basically indicates the tentative results, the tentative nature of the results here.

Q. But that's your view after the fact. Back in the day, these researchers actually used bevacizumab in the eye despite its large size?

A. It's not my view after the fact. I agree they did this research study, but it's also Dr. Ferrara's conclusion, as I quoted this morning and yesterday, I guess.

Q. And these researchers went on to recommend full-blown clinical trials, correct?

A. Well, it says further evaluation is warranted and could be a hope, maybe, for a clinical trial.

Q. And because of the groundbreaking work of Dr. Avery and colleagues and Dr. Rosenfeld and colleagues, bevacizumab, even to this day, is one of the most prescribed VEGF antagonists, correct?

A. I don't have that data in terms of prescription

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percentages.

Q. You don't know that? You didn't hear that from the clinicians at trial?

A. I heard that it's used, but I'm not sure what's the most prescribed.

MR. RAKOCZY: All right. Your Honor, I'm about ready to switch topics. Would you like to break, or should we --

THE COURT: Yeah, let's go ahead and do that. It's the last day of volleyball camp. Sometimes that breaks a little early. I'm under strict orders to not be late. I'll leave it at that. Those orders came.

Doctor, one last quiet lunch for you. You're welcome. Counsel is under orders to feed you, but they also can't talk to you, as you well know by this point, sir, but you can go ahead and step down.

THE WITNESS: Thank you, Your Honor.

THE COURT: Thank you.

We'll take our lunch break at this point. We'll pick up at 12:00 with the doctor's cross-examination.

Thank you all very much.

(A recess was taken from 11:00 a.m. to 12:05 p.m.)

THE COURT: Thank you, Doctor.

Mr. Rakoczy, if you're ready to proceed, you may.

MR. RAKOCZY: Good afternoon, Your Honor.

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BY MR. RAKOCZY:

Q. Good afternoon, Dr. Trout.

A. Good afternoon, Mr. Rakoczy.

Q. Ready to go?

A. Yes, sir.

Q. I want to return real quick to the big-molecule issue. A couple questions I forgot to ask.

The '865 patent does not teach that the claim formulations were the first to ever get a VEGF antagonist to penetrate the retina, correct?

A. I'm sorry. The first what?

Q. Let me back up.

The patent does not teach that the claim formulations were the first formulations to get a VEGF antagonist to penetrate the retina, right?

A. I think those words as such are not explicitly in the patent.

Q. And, again, there's nothing in the patent about penetrating the retina, correct?

A. I believe that term's not explicitly in the patent, correct.

Q. And the patent doesn't say that it somehow resolved skepticism in the art about getting a big molecule into the retina, correct?

A. Again, those words are not there. I agree.

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Q. So I want to make sure we're clear here, then, for the record.

So you're relying on a teaching away that somehow the skilled person would have been taught away from using a big molecule to get into the retina and that teaching or that skepticism is not addressed or resolved in the '865 patent, correct?

A. The skepticism is resolved because of the formulations of the '865 patent. The skepticism, though, I agree is based on reviewing the relevant prior art.

Q. But you just told me that the formulations in the '865 patent were not the first formulations to get a VEGF antagonist into the retina, right?

A. I don't think that's what I said. I think what I said was, in response to your question, the '865 patent doesn't explicitly use those words. And I certainly discussed throughout today and yesterday the relevant art related to that.

Q. But the patent itself does not address this penetration into the retina at all, correct?

A. It doesn't use those specific words.

Q. All right. Now, another teaching away you mentioned was inflammation caused by 40 mg/mL.

Do you remember that?

A. That was part of it. There was other parts too.

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Q. You cited the Gaudreault reference for that, I believe?

A. Correct. There was that and the issue of maximum inhibition.

Q. Now, the Gaudreault study, that was the monkey study that showed inflammation with the 40 mg/mL concentration, right?

A. Moderate to severe, yes.

Q. Now, you are not an ophthalmologist, I think we established, correct?

A. That is correct.

Q. You're not an expert in ophthalmology or in treating diseases of the eye, correct?

A. Correct.

Q. Now -- so to be fair, you have no basis to say whether moderate to severe inflammation in a monkey that resolved itself by day eight would have discouraged a clinician from using 40 mg/mL of aflibercept, correct?

A. Correct. I can't speak to what a clinician would say per se; but as a formulator, I look at that. And that would bring serious doubts as to the applicability of the 40 mg/mL formulation. And, remember, as you pointed, this is for seven days at least out of a month.

Q. But you're not the one that's going to be using this to treat an eye disease, correct?

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A. Correct.

Q. Now, there's no data in the '865 patent about inflammation, correct?

A. There's no data about inflammation, that's correct.

Q. There's no data or testing in the '865 patent showing that the claim formulations somehow result in less inflammation than the prior art, correct?

A. There's not inflammation data. There's the SEC data that we've been talking about, which is a good indication of -- for a formulator again of having a lower risk of inflammation.

Q. So your testimony is that SEC data is inflammation data?

A. No, Counsel, that's not what I said. I can --

Q. So my question is there's no data in this patent showing that these claim formulations somehow result in less inflammation than prior art formulations, correct?

A. There's no -- you're correct there's no direct inflammation data. Again, from the standpoint of the skilled person, the SEC data, I should say all the stability data in the patent, would tell me that -- would indicate to the skilled person that there's a relatively lower risk of inflammation.

Q. I'm asking about inflammation data. You testified about inflammation data in Gaudreault. There's no such data like that in the patent, correct?

A. There's no direct inflammation data in the patent;

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there's other data.

Q. So, again, you're relying on a teaching away of supposed inflammation that the '865 patent itself does not address, correct?

A. The '865 doesn't explicitly discuss inflammation, I agree.

By the way, it's not just Gaudreault that I'm relying on.

Q. I understand. I understand.

And in Gaudreault, they actually concluded that ranibizumab was well tolerated, correct?

A. Yes. And indicated to use the 10 milligrams per mole.

Q. But they said it was well tolerated. That was their first conclusion, correct?

A. They do use those terms. And I apologize, Counsel, I gave the wrong units. 10 mg/mL. Sorry about that.

Q. We can pull up Gaudreault. Let's just confirm. It's DTX 2265. On page 2 we have the clinical findings.

The first finding from Gaudreault is that ranibizumab was well tolerated, correct?

A. That's what's listed here. And then it goes and discusses the relative differences in inflammation.

Q. And it says transient. That's how it characterizes the inflammation. You left that out. It says transient,

correct?

A. Yes. It wasn't an intention to leave it out. It lasted two to eight -- from day two to eight, so at least seven days out of a month.

Q. Okay.

Let's go to page 3, please, Mr. Gibson.

This is what you're referring to, right? The inflammation was present at day two, but it completely resolved by day eight, correct?

A. Correct.

Q. And you haven't heard any clinician in this trial testify that that would dissuade the use of 40 mg/mL, correct?

I haven't heard anyone.

A. I wasn't here for all of the clinicians' testimony; but from what I heard, I didn't hear that specifically. I'm telling you how a formulator would view this.

Q. But you didn't hear any testimony from a clinician, right?

A. Again, I wasn't here the whole time. I did hear testimony about having to be careful in injections, about how the injections are done, and general concerns about issues with injections, medical issues.

Q. Now, this is a POSA teaching away you testified about. That didn't prevent others in the art like Dr. Dan Dix from filing patents on even higher concentrations of

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aflibercept, correct?

A. Correct. Again, that's how invention works is to go against the prevailing art.

Q. Okay.

Let's put DTX 13 at page 7 on screen.

And this is the Dix '226 we've been talking about, correct?

A. I presume so. I didn't see the cover, but this looks like the example.

Q. You recognize Example 1, Dr. Dix and his team, they used a 50 mg/mL formulation here, correct?

A. 50 mg/mL, correct.

Q. So assuming this is prior art -- and I know you and your counsel dispute that. But assuming this is prior art, Dix and colleagues clearly weren't dissuaded or discouraged from high concentrations of aflibercept, correct?

A. Well, I think -- I'm sorry. I don't want to get confused here.

You're talking about after Dix or before Dix?

Q. This is Dix '226.

A. Yes. I understand.

Q. And Example 1, which is VEGF Trap Sequence ID Number 4, which is aflibercept. And they used 50 mg/mL, correct?

A. Yes.

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Q. Higher than 40?

A. That's right.

Q. So they weren't dissuaded from or taught away from using high concentrations of aflibercept, correct?

A. I don't know about the inventive process. Again, that's how inventions work is going against the prevailing views.

Q. Just like Rosenfeld and Avery and colleagues used a big molecule to get into the retina, Dix and his colleagues used high concentration, contrary to what you said the teaching away was, correct?

A. I think that the use of the 50 mg/mL of VEGF Trap is contrary to teaching away in the prior art, again, depending on the date we're talking about.

Q. But if this is prior art, then it's teaching 50 mg, higher than 40, correct?

A. Well, if it's prior art, it's teaching 50. And we talked about what the significance of that for 40 is, and we talked about the fact that this is not intravitreal. And you can look at the sucrose concentration, which is very high.

Q. My question is high concentration, Dix used 50 mg aflibercept, correct?

A. Correct.

Q. All right. Let's talk about the skepticism you mentioned. And I believe you cited a Ferrara paper.

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Do you recall that?

A. Yes.

Q. Okay.

Let's pull up PTX 1838 at page 7. And I believe this is the Ferrara 2004 paper. I saw it cited several times during your direct testimony, this exact same paragraph.

Do you recall that?

A. Yes.

Q. And there's something I wanted to ask you about. So in the highlighted part, that's what you cited during your direct, at least three times to my recollection.

You recall testifying about that, right, this immune response sentence?

A. Yes.

Q. So Ferrara doesn't actually cite any data or support for that sentence, does he?

A. No. This is what would have generally been understood in the art.

Q. So he cites no data; he just says it.

A. Well, I agree there's no citation after the last sentence, because this is what would be generally understood in the art.

Q. And he says it's just possible, right?

A. Correct.

Q. So he must not have had any data that it had actually

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happened, right?

A. It's unlikely that he had data. I agree with that.

Q. Now, if we look at the preceding sentence right above that, you see Ferrara says that these fusion proteins "represent an advantage over antibodies because they can result in higher binding affinity."

Do you see that?

A. Yes.

Q. So he's actually promoting the use of the fusion protein here, saying it could be better, right?

A. Right. But, therefore, at lower concentrations, correct.

Q. He's saying this makes the fusion protein a better route, correct?

A. Yes, because it could be formulated at lower concentrations than, for example, ranibizumab.

Q. Now, regardless of this teaching away that you mentioned in Ferrara, we can agree again there's no binding or affinity or immunogenicity data in the '865 patent, correct?

A. Not explicitly, correct.

Q. There's nothing in the '865 patent teaching that somehow those formulations are safer or result in less immunogenicity than other formulations, correct?

A. No, Counsel, that's not correct. As I said, the formulator -- I'm speaking from the standpoint of a formulator,

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which I am. The high stability, particularly with respect to SEC and the other data, would give the formulator the idea that there was relatively lower risk.

Q. I'm asking immunogenicity data, this immune response issue. Where is that data in the '865 patent?

A. I think I agreed several times, Counsel, there's no direct immune data explicitly in the '865, correct.

Q. All right. Let's move back to your table. I love that table, DDX 9, Slide 2.

Remember this table?

A. Yes.

Q. All right. Hopefully I can make quick work of this.

I'd like to just go back and talk a little bit about what these examples use and don't use. Is that all right?

A. Of course.

Q. Now, just so the record's clear, all of the examples in the patent use a phosphate buffer, correct?

A. Yes.

Q. No other buffers are even mentioned in the specification, correct?

A. Explicitly, correct. There's the structural category.

Q. But histidine, for example, is not mentioned in the patent, correct?

A. Not explicitly, correct.

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Q. Succinate is not mentioned in the patent?
A. Not explicitly, correct.
Q. And there's no stability data in the patent for a histidine or succinate-buffered composition, correct?
A. Not explicitly, correct.
Q. The only stabilizer -- sugar stabilizer used in the patent examples is sucrose, correct?
A. That's the only sugar in the examples. But in Column 2, there are other sugars explicitly mentioned.
Q. Yeah. They mention sorbitol, glycerol, trehalose, and mannitol, correct? Does that sound right?
A. Yes. And sucrose, I guess.
Q. But there's no data or examples on any of those stabilizers except sucrose, correct?
A. Correct. Again, the skilled person would understand, because of the common structure, that they should work in a similar way.
Q. So the skilled person would know that they would all work and expect them to work?
A. I think the skilled person would expect them to work.
Q. Okay. And they would expect them all to be suitable for intravitreal administration, correct?
A. I think that's correct, but I would want to be sure. I would want to go back to the literature for intravitreal injection just to make sure.

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Q. And all those stabilizers you told me, they were all known in the art, correct? Those aren't new?

A. Correct.

Q. All right. Let's stay on screen here. And real quick, Examples 1 and 2 are 50 mg/mL, correct?

A. Yes.

Q. So those are not covered by the asserted claims; is that right40?

A. Correct.

Q. And Example 7 and 8 are 20 mg/mL; is that right?

A. Yes.

Q. So those would not be covered by the asserted claims either?

A. Well, again, the 20 mg/mL is the pre-lyo solution. That isn't the formulation. The formulation is the 40 mg/mL. But I agree, because they're reconstituted lyo solution, they would not be covered by the asserted claims.

Q. And Examples 4 and 6 are prefilled syringes, correct?

A. Yes, that's correct.

Q. So those wouldn't be covered by the asserted claims either?

A. That's correct.

Q. And Examples 5 and 6 don't contain a sugar stabilizer, correct?

A. Correct.

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Q. So those would not be covered by the asserted claims; is that right?

A. Correct.

Q. Now, Examples 7 and 8, those actually don't contain any data showing percent native conformation following storage of a liquid formulation at 5 degrees C for two months, correct?

A. Yes, that's correct. It was the lyo formulation. That's correct.

Q. Now, let's talk quickly about the breadth of the claims. You testified -- I believe the word you used was that the asserted claims are narrow.

Do you remember that?

A. Yes, sir.

Q. So -- but you didn't attempt to estimate or calculate how many formulations are actually covered by the asserted claims, correct?

A. That's correct.

Q. I apologize. I meant to ask you before. Going a little out of order here.

A. That's okay.

Q. I asked you before, you're not an expert in ophthalmology or treating eye diseases. You told me you weren't, correct?

A. I am not an ophthalmologist, that's correct.

Q. And you're not an expert in the retina or the anatomy

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of the eye, correct?

A. That's correct.

Q. And you are not an expert in ocular pharmacokinetics; is that correct?

A. I think that's correct except from the standpoint of formulation, we often deal with pharmacokinetics. I can read the literature on that.

Q. You wouldn't consider yourself an actual expert in it, correct?

A. I would consider myself an expert in ocular pharmacokinetics related to formulation.

Q. Okay. Let's move to a different topic.

MR. RAKOCZY: May I have one moment, Your Honor?

THE COURT: You may.

BY MR. RAKOCZY:

Q. I want to ask you about the Rudge reference.

Do you recall that?

A. Yes.

Q. And I want to pull up your expert report, DTX 7066, at page 184. This is your materials considered where you cite the Rudge paper.

Do you see that?

A. Yes.

Q. And you --

If we could blow that up, Mr. Gibson.

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And you have a 2005 publication on Rudge here on your report, correct?

A. Well, that's what's written, but again -- I think we talked about this earlier in the trial -- that doesn't seem to be the date in which it was published.

Q. That's the date you wrote, though, correct?

A. Well, that's the date I reproduced from the cover; but again, there are references which postdate that; so...

Q. So you didn't go and check that? I guess I'm asking. I didn't see you dispute the publication date of Rudge in your report anywhere.

A. Well, I think I did. I can -- remind me which --

Q. I can represent to you there's no dispute about Rudge in your report. And I'm just asking, did you list a 2005 date on Rudge?

A. Well, I listed a date from the cover, again, noting that there are publications from 2006 that are referenced so the Rudge has to be -- has to postdate 2005.

Q. Let's confirm that. Let's pull up PTX 3209 at page 1.

A. I'm sorry, Counsel. Could you give me the --

Q. I'm sorry. PTX 3209.

A. Oh, so is that in your notebook or --

Q. That's in the big binder in front of you. Volume 2. Small binder.

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A. The small binder. The other --

Q. Yeah. This is the CV of one of the Rudge coauthors. Do you see that? George Yancopoulos.

A. Yes.

Q. Let's go to page 22 of the Yancopoulos CV, one of the coauthors of Rudge, and you see he also lists a publication date of 2005 for Rudge, correct? It's on screen. Publication 285.

A. Again, first of all, I should say I have not seen Dr. Yancopoulos's CV before; so I haven't seen this document before. But again, I think as we discussed earlier in the week, the 2005 is what's listed on the cover, but there were references from 2006.

Q. Well, he authored it, right?

A. He was one of the authors, I believe.

Q. And he listed 2005 on his CV, correct?

A. As the date that is on the first page of the -- of the article, I should say, publication.

Q. All right. Let's switch gears again, and I want to talk about this Dix '226 issue of whether it's prior art or not.

A. Okay.

Q. I believe you were told by Regeneron's counsel that Dix '226 can't be used as prior art because it's assigned to Regeneron.

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Do you recall that?

A. I do recall that. I don't know if those are the exact words, but that sounds like the general point.

Q. Let's pull up DTX 4956, please, page 1.

This is a Regeneron 10-K for the fiscal year ended December 31st, 2004.

A. I'm sorry, Counsel. I think this is in the other binder.

Q. That may be in the big binder in front of you.

MR. BERL: While we're finding that, Your Honor, if I may interpose an objection. This is not disclosed as prior art. I'm not sure what purpose counsel is using it for, but Mylan was required by statute to give us notice of what prior art they would be relying on a month before the trial. They violated that. It's under 35 U.S.C. 282. They sent us, for the '865 patent alone, 35 pages listing prior art, 15 or 20 per page, hundreds. This is not on it. And so --

MR. RAKOCZY: I'm not citing it as prior art, Your Honor. I merely want to explore with the witness whether he looked at some of the agreements referenced in here relative to the 103(c)(1) issue that Regeneron has briefed and argued repeatedly.

THE COURT: Understood. Overruled. I understand in the context of -- what's the date on this 10-K again, Mr. Rakoczy? I'm sorry.

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MR. RAKOCZY: This is a Regeneron 10-K dated December 31, 2004.

THE COURT: The information highlighted on the big screen. Yes. Thank you. Thank you, sir. Sorry.

MR. RAKOCZY: Thank you, Your Honor.

BY MR. RAKOCZY:

Q. I'd like to go to page 4, fourth full paragraph. And here, you see -- I want to lay a little foundation, Dr. Trout, and then just ask if you looked at a few things.

It says here, "In September 2003 we entered into a collaboration agreement with Aventis Pharmaceuticals (now part of the Sanofi-Aventis group) to joint development and commercialize the VEGF Trap throughout the world."

Do you see that?

A. Yes.

Q. Did you look at that collaboration agreement?

A. No, not that I recall.

Q. So you didn't review that collaboration agreement in any way, shape, or form to see what the intellectual property rights and licenses were that were part of that collaboration?

A. As far as I recall, I didn't, and from the standpoint of the POSA, I don't even think -- I've never even seen a document like this before, except I think you may have shown something earlier this week. But I've never seen anything like this in my years as a scientist.

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Q. That's okay. My only question is you haven't reviewed that, correct?

A. I do not think I've reviewed that, no.

Q. Let's look at page 4, same page, third sentence. You see here it says, "In January 2005 we at Sanofi-Aventis amended our collaboration agreement to exclude rights to develop and commercialize the VEGF Trap for eye diseases through locally -- local delivery systems. We now have the exclusive right to develop and commercialize the VEGF Trap for eye diseases through local administration to the eye."

Do you see that?

A. I'm sorry, Counsel. I didn't want to interrupt you, but I think you went too fast. I didn't see -- could you point me again to where you're reading.

Q. Yes. So it's page 4, halfway down.

A. DTX page 4.

Q. VEGF Trap-Eye diseases, third line down.

A. The bold VEGF Trap-Eye disease.

Q. Yes. And third line down, it references in January 2005 that Regeneron and Sanofi-Aventis amended their collaboration agreement.

Do you see that?

A. Yes. Thank you. Now I see it.

Q. And it says that Regeneron now has the exclusive right to develop and commercialize the VEGF Trap for eye

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diseases. Do you see that?

A. Yes.

Q. Did you review the amendment to the collaboration agreement?

A. Not as far as I recall.

Q. Did you review any licenses or any other documents regarding intellectual property or patent rights in connection with the collaboration agreement or the amendment to the collaboration agreement with Sanofi?

A. Again, not as far as I recall, no.

Q. All right. I'd like to pull up -- sorry. I apologize, Dr. Trout. One more question on this.

A. Of course.

Q. Could we please pull up DTX 4986 at page 1. And I think I know the answer to this. I just want to confirm.

This is the second amendment to the collaboration agreement I just referenced. My question is, again, you have not reviewed this second amendment to the collaboration agreement, correct?

A. Okay. Just to be clear, this is another document.

Q. Yes. This is DTX 4986.

A. Have not reviewed this, no.

Q. I'd like to go back to the patent now.

If we could, Mr. Gibson, please go back to the '865 patent, at the top of Column 2, which is PTX 4 -- sorry --

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PTX 2 at page 4.

And it's on screen as well, Dr. Trout.

A. Okay.

Q. And you see here at the top of Column 2 it says, "Ophthalmic formulations are known." Do you see that?

A. Yes.

Q. You agree with that, correct?

A. Yes. As a general statement, yes.

Q. And it goes on to say, "An ophthalmic formulation of a VEGF antibody is described in U.S. Patent Number 6,676,941."

Do you see that?

A. Yes.

Q. I'd like to show you the '941 patent here referenced in the '865 patent.

MR. RAKOCZY: Your Honor, may I approach? It's a loose exhibit.

THE COURT: You may.

MR. RAKOCZY: It's DTX 8171 for the record, a very large --

BY MR. RAKOCZY:

Q. So for the record, I have just handed you, Dr. Trout, DTX 8171, and you see it is U.S. Patent 6,676,941, which is the same patent referenced in the specification of the '865 patent that I just referenced, correct?

A. Yes.

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MR. BERL: For the record, Your Honor, this likewise was not disclosed in the 35 pages of prior art references. I don't know if he's using this as prior art or not, but he shouldn't be able to.

MR. RAKOCZY: Your Honor, it's admitted prior art in the actual patent specification, which is why I laid the foundation for it.

THE COURT: Overruled.

BY MR. RAKOCZY:

Q. I only want to ask you about a quick part of this. Let's go to page 58 of the patent, please, Dr. Trout, and I'll put it on screen as well.

And in the left-hand column, starting at line 9, should be Column 100.

THE COURT: Column 100, line 9, Counsel?

MR. RAKOCZY: Yes.

Mr. Gibson, could you please pull up Column 100. There it is. Starting at line 8.

BY MR. RAKOCZY:

Q. You see, Dr. Trout, this '941 patent, which is identified in the '865 patent, discloses that "The ophthalmic preparation will preferably be in the form of a sterile aqueous exclusion containing, if desired, additional ingredients, for example, preservatives, buffers, tonicity agents, antioxidants and stabilizers, nonionic wetting or clarifying agents,

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viscosity increasing agents, and the like."

Do you see that?

A. Yes, I see that.

Q. And these would have all been known excipients or structures, in your words, correct?

A. Counsel?

Q. Yes.

A. I think broadly speaking, but I have not, that I recall, reviewed this entire document. This is a general disclosure and however many hundreds of columns. So I would want to go and make sure that my general understanding of these terms is also the way it's being used in this document.

Q. My question is simple. You don't see any new classes of excipients here, correct?

A. Again, just in high level, these don't seem new. Again, I don't know what the authors are disclosing throughout this document, but this seems to be just a very general, high-level discussion.

Q. All right. Just a couple more questions, Dr. Trout.

Did I hear you correctly during your direct examination that you said ranibizumab is the closest prior art? Is that your view?

A. Well, ranibizumab and the formulations. So ranibizumab would be the closest prior art to aflibercept in the formulations that we discussed, for example, Gaudreault and

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Shams.

Q. So you didn't pick an aflibercept reference as your closest prior art, correct?

A. Correct.

Q. Last question. You mentioned copying. And I just want the record to be clear.

MR. RAKOCZY: And I don't think we need to close the courtroom for this, Your Honor.

BY MR. RAKOCZY:

Q. But you agree -- and I think we established this earlier -- that the Mylan and Biocon formulation, Yesafili, it doesn't copy Eylea, correct? It uses a different buffer, different stabilizer. As a matter of fact, it's patterned after the Lucentis formulation, correct?

A. No. I think it's -- I mean, again, I don't want to get into any specifics, but it copies for the reasons I mentioned.

Q. But Eylea uses a phosphate buffer, correct?

A. Yes.

Q. Yesafili does not use a phosphate buffer, correct?

A. Correct. It has common structure.

Q. Eylea uses a sucrose stabilizer, correct?

A. Correct.

Q. The Mylan/Biocon Yesafili product does not use a sucrose stabilizer, correct?

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A. No. One with a common structure, though.

MR. RAKOCZY: Subject to the redirect, Your Honor pass the witness.

THE COURT: Thank you, Counsel.

Mr. Berl.

MR. BERL: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. BERL:

Q. Good afternoon, Dr. Trout.

A. Good afternoon, Mr. Berl.

Q. I just want to go through a few items about which Mr. Rakoczy examined you.

Do you recall that he asked you various questions about intravitreal administration of bevacizumab?

A. I do, yes.

Q. And he first showed you the Rosenfeld article; is that right?

A. Yes, I think so.

Q. And is that a -- was that article about administration in one patient?

A. Yes. It specifically said one patient, yes.

Q. Okay. And then he showed you the Avery reference.

Do you recall that?

A. I do.

Q. And he asked you various questions about whether it

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was disputed that it was prior art.

Do you remember that?

A. Yes.

Q. Let's take a look at your expert report, if we could, Dr. Trout. That's PTX 67. And we'll try to put that on the screen on the first page.

What --

A. Counsel, just one minute here.

Q. Sure. It's PTX 67. It should be in the binder that we used for your direct examination. We'll also try our best to put the excerpts I'm going to ask you about on the screen.

A. Okay. Thank you.

Q. And my first question is what was the date of the expert report?

A. Oh, March 2nd, 2023.

Q. More than three months ago, right?

A. Yes.

Q. And did you hear counsel for Mylan say that yesterday was the first he heard about the idea that the Avery reference may not be prior art?

A. I think he said that, yes.

Q. Let's take a look at paragraph 170 of your report.

And, Dr. Trout, can you read the second sentence that was in your report on March 2nd, 2023.

A. Yes.

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"Dr. Rabinow fails to establish that Avery was published before the invention of the '865 patent" -- which was in parenthesis -- "no later than March 21st, 2006" -- in parenthesis -- "or the filing of the provisional patent on June 16th, 2006." And then it refers to a Section Roman numeral X.

MR. RAKOCZY: Your Honor, I'm going to lodge an objection. That's precisely why I showed the witness the document with an exact date on it prior to that.

THE COURT: Understood. The Court denied the motions for summary judgment in this case because of the factual issues. I'll add this one to that list as well.

Understood. Objection overruled. And I'll sort it out later, obviously, with the benefit of significant briefing from counsel, of course.

MR. BERL: Of course. No question.

BY MR. BERL:

Q. Doctor, he then asked you about Avery.

Do you recall that? That's DTX 2264.

A. I do.

Q. And let's pull that up, if we could.

A. Let me just also get it, Counsel. 2264, right?

Q. Yes. And let's first put up on the screen a slide of Avery. That's 2264 6.1.

Is this a part of the discussion in Avery from

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page 6?

A. Yes.

Q. And what is it communicating, Dr. Trout?

A. Well, it's an acknowledgement by the authors themselves of the shortcomings of this study. I was trying to answer some of this when Mr. Rakoczy was asking me. The retrospective design, limited number of patients, nonstandard visions, limited follow-up. And then a couple lines down it says, "However, the visual results of this study are difficult to interpret."

Q. Is that consistent with how the person of skill would have viewed Avery, difficult to interpret?

A. Yes.

Q. And Mr. Rakoczy was asking now about what people back in the day who were actually practicing in this field were saying and thinking.

Do you recall that?

A. Yes.

Q. And did you look at what Dr. Ferrara said about Avery?

A. I did, yes.

Q. Was Dr. Ferrara practicing in the field at the time?

A. Yes.

Q. So let's take a look at Dr. Ferrara's article. We'll do the other Ferrara article. That's 701.

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Is this Dr. Ferrara's 2006 article, Doctor?

A. I'm sorry.

MR. BERL: Why don't we go back, Mr. Schliesske, to the cover. And we're showing, for the record, PTX 706.

BY MR. BERL:

Q. And my question is is this Dr. Ferrara's article from 2006?

A. Yes. Thank you.

Q. Yes. And so now let's go to page 8 of Dr. Ferrara's article.

Does Dr. Ferrara cite and discuss Avery?

A. Yes, explicitly. 114.

Q. And is Dr. Ferrara saying that Avery has somehow changed the conventional wisdom you testified about with respect to larger molecules penetrating into the retina upon intravitreal injection?

A. No. The opposite. Dr. Ferrara says, "Although intriguing, these early findings are difficult to compare with data from rigorous double-masked Control 3 trials." And it talks about various of those. I mentioned this before.

"In addition, it is noteworthy that initial uncontrolled Phase I or II studies with pegaptanib or verteporfin photodynamic therapy suggested a considerably greater benefit in AMD patients than that eventually demonstrated in randomized Phase III studies, further

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emphasizing the difficulty of interpreting early clinical results."

And then -- in other words, the results are tentative at best.

Q. If we go back to page 4 of Dr. Ferrara's article. That is PTX 701. What does Dr. Ferrara say and ultimately conclude with respect to VEGF Trap-Eye?

A. Well, highlighted here, "Interestingly, these studies show that systemic administration of the VEGF Trap inhibits neovascularization by 75 percent; however, intravitreal administration of the same agent resulted in approximately 25 percent inhibition." It says, "The limited efficacy...may be due, at least in part, to the existence of a barrier to the transretinal penetration of large molecules, such as VEGF Trap."

Q. And is this consistent with what the POSA would have thought at the priority date in view of all the prior art?

A. Yes.

Q. Now, the bevacizumab injections that you were asked about, do those address any of the formulation concerns you raised with respect to formulating 40 mg/mL of aflibercept?

A. No, they do not.

Q. Do they address any of the concerns you raised relating to toxicity or immune reactions to 40 mg/mL of aflibercept injected intravitreally?

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A. Not at all.

Q. Now, let's take a look at the Dix patent, which is DTX 13. And if we could try to pull up Column 7 and 8, which Mr. Rakoczy asked you about, Example 1.

Do you recall questions about Example 1 in Dix?

A. Yes.

Q. Let's take a moment to pull that up.

If we could do the bottom of Column 7.

Do you see now shown on the screen is the bottom of Column 7 and the top of Column 8 of DTX 13, Dix?

A. Yes.

Q. And it was pointed out to you that this has 50 mg/mL of aflibercept?

A. That's correct.

Q. Is Dix teaching 50 mg/mL of aflibercept for intravitreal injection?

A. No.

Q. Does Dix thereby somehow address the concerns about high concentrations of intravitreal injections that you discussed from Gaudreault?

A. No, it doesn't.

Q. Did you hear Dr. Graham's testimony earlier this week about the dilution of the Dix formulation before administration?

A. Yes.

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MR. RAKOCZY: Objection, Your Honor. I didn't ask about Dr. Graham. Dr. Graham's been on and off the stand. I didn't ask a single question about his testimony.

MR. BERL: I was just asking if he heard it, if he was in the courtroom for it.

THE COURT: Sustained. It's redirect. I heard it.

MR. BERL: That's all that matters.

THE COURT: Thank you, Mr. Berl.

BY MR. BERL:

Q. Doctor, does Dix Example 1 or otherwise inform the person of ordinary skill regarding the moderate to severe inflammation that Gaudreault teaches upon administration of 40 mg/mL of ranibizumab?

A. Not at all.

Q. Now, finally, I want to go back to one of Mr. Rakoczy's slide. It was his Demonstrative 9.9. Do you recall him asking you various questions about this table?

A. I do.

Q. Do you recall that he asked you to make various assumptions regarding what the person of ordinary skill would have been motivated to do and what the person of ordinary skill would have known before the '865 patent?

A. Yes, I definitely do.

Q. Do you believe any of those assumptions are correct?

A. No.

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Q. Now, this chart, which combines Shams and Gaudreault and Fraser and Dix, have you seen any assertion in this case that those references would be combined?

A. No.

Q. Do you see that, in any of the reports from Dr. Rabinow, that he would combine all of these references as Mr. Rakoczy did in his slide?

A. No.

Q. Have you even heard, throughout the trial that you've observed, that the person of ordinary skill would have combined all of these references shown in Mr. Rakoczy's slide?

A. No.

Q. Do you believe that the person of ordinary skill -- well, I'll leave that one.

Have you heard, Doctor, with respect to Dix, any evidence or testimony that the Dix patent and the '865 patent are not commonly assigned to Regeneron?

A. No.

Q. Now, even combining all of these references -- and, again, we dispute that the last one is prior art at all or can be used for obviousness. But even if combining these references somehow, Dr. Trout, do they provide any basis to use 40 mg/mL of aflibercept?

A. No, not at all. And as I've said several times, the Shams and Gaudreault specifically teach away from that.

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Q. Do they provide any basis even to use 40 mg/mL of ranibizumab?

A. No. They teach away from that. And the Shams, in fact, goes forward with 6 and 10 mg/mL.

Q. Do they provide any basis to use 40 mg/mL of aflibercept intravitreally?

A. No, not at all.

Q. Do these references, even if combined as Mr. Rakoczy did, provide any data or information about 98 percent native conformation by size-exclusion chromatography even for ranibizumab?

A. No.

Q. Are there any data in these references for 98 percent native conformation of ranibizumab from Shams or Gaudreault, for example?

A. There's none in those articles.

Q. And what about turbidity? Any basis in Shams or Gaudreault for 98 percent -- sorry -- for meeting the turbidity limitation of Claim 15 of the '865 patent even for ranibizumab?

A. Nothing.

Q. Do you have any basis to believe that Lucentis -- sorry -- that Genentech continued to pursue 40 mg/mL even for ranibizumab after the data from Gaudreault?

A. I see no evidence.

Q. Even if all of these references were combined as

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Mr. Rakoczy did in his Demonstrative 9.9, do you see any disclosure of a pH range of 6.2 to 6.3 for Shams, Gaudreault, or Fraser as Claim 9 requires?

A. No.

MR. BERL: No more questions. Thank you very much, Dr. Trout.

THE WITNESS: Thank you.

THE COURT: Recross?

MR. RAKOCZY: May I have a quick moment, Your Honor?

THE COURT: You may.

MR. RAKOCZY: Your Honor, before we let the good doctor go, I'd like to move in a few exhibits if I could.

THE COURT: Understood.

Assuming that doesn't pose a problem for Madam Clerk, we can start with the defendants' exhibits. Go right ahead slowly, then, Mr. Rakoczy.

MR. RAKOCZY: Defendants move into evidence DTX 3501, DTX 4956, DTX 4986, DTX 9036, DTX 8171, and PTX 1838.

THE COURT: Any objection to any of those?

MR. BERL: Yes, Your Honor, I believe two of them. The first of them was DTX 4986.

THE COURT: Okay. And just -- what is 4986?

MR. BERL: That was, I think, the amendment to an agreement between Sanofi or Aventis and Regeneron. Dr. Trout said he never saw that before. There was no basis laid or

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foundation for any of that with any witness, including Dr. Trout.

THE COURT: Understood.

MR. RAKOCZY: Your Honor, that goes right to the 103(c)(1) theory. In fact, the witness who's disputing that it's prior art has not looked at the various intellectual property collaboration agreements is, in our view, admissible evidence because it goes directly to the fact that they can't show that Dix is a prior art. So we believe it's relevant and should be admissible. As a matter of fact, it was their burden to bring that out, not ours.

THE COURT: Mr. Berl?

MR. BERL: If they wanted to dispute that with agreements or otherwise, that's what their experts are for. They should have brought that up and addressed it then. Instead, they're trying to put it in through a witness who's never seen it before, and they didn't lay a foundation for it.

THE COURT: I'm going to overrule the objection and receive it to the limited extent it's information that Dr. Trout could have reviewed but did not. But I'll overrule the objection.

MR. RAKOCZY: I didn't hear the second one.

THE COURT: I think we're about to get there.

MR. BERL: I believe it's 9036, which was the Avery -- the new version of purportedly Avery with the date

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stamp.

THE COURT: The Court's already ruled on that. For the same reasons, I'll overrule that objection, understanding it's worth what it's worth.

MR. BERL: And, Your Honor, with your permission, we'd like to move in -- offer various exhibits used with Dr. Trout.

THE COURT: Let me just make sure we've closed the loop.

That was the entire list of exhibits for Mylan; is that correct, Mr. Rakoczy?

MR. RAKOCZY: That's correct, Your Honor, with this witness.

THE COURT: Understood.

MR. BERL: I'll now read ours slowly into the record.

THE COURT: One second.

Sir, if you need to confer, go ahead. The list Mr. Rakoczy identified are deemed admitted subject to the Court's rulings on the objection to two of them.

(DTX 3501, DTX 4956, DTX 4986, DTX 9036, DTX 8171, and PTX 1838 were admitted.)

THE COURT: With that, Mr. Berl, you may proceed slowly.

MR. BERL: PTX 1826, PTX 1835, PTX 1773, PTX 576, PTX 1842, PTX 701, PTX 1757, PTX 1838, PTX 1556, PTX 1155,

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PTX 1832, PTX 1758, PTX 753, PTX 53, and PTX 55.

MR. RAKOCZY: Your Honor, we may need a moment to go through that list.

While we're checking that list, Your Honor, I do have -- I promised you to follow up on the Dr. Graham exhibits. Would you like me to wait until the witness is out of the box?

THE COURT: Yeah. Let's do that.

Are there some for Dr. Stewart as well?

MR. BERL: I don't know if that has been tidied up yet.

MR. GREGORY: I think that was me, Your Honor. We had no more exhibits to move in through Dr. Stewart.

THE COURT: All right. Understood.

Don't try to save trees now, Mr. Rakoczy.

MR. RAKOCZY: I'm not. I want the whole thing in, Your Honor.

All right, then. Actually, I take back what I just said. We will not object to any of those.

THE COURT: All right. Without objection, then, the list Mr. Berl identified are hereby deemed admitted.

(PTX 1826, PTX 1835, PTX 1773, PTX 576, PTX 1842, PTX 701, PTX 1757, PTX 1838, PTX 1556, PTX 1155, PTX 1832, PTX 1758, PTX 753, PTX 53, and PTX 55 were admitted.)

THE COURT: Anything further we need the good Dr. Trout up here for?

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MR. BERL: Not from Regeneron.

MR. RAKOCZY: Nothing from Mylan and Biocon.

THE COURT: Sir, you may step down. Thank you so very much. Have a safe trip home.

THE WITNESS: Thank you.

MR. RAKOCZY: Your Honor, I apologize. I don't mean to make this difficult. So for Dr. Graham, do you recall I objected to the majority of those exhibits as nondisclosed, and Your Honor accepted them and indicated we should fight about that in posttrial briefing?

THE COURT: Yes.

MR. RAKOCZY: I would like to provisionally move to admit several exhibits conditioned on Your Honor's ruling, meaning if you end up not accepting those exhibits, then I wouldn't want these admitted either, if that makes sense.

THE COURT: It does make sense.

Any position on that, Mr. Berl?

MR. BERL: I don't know what they are.

THE COURT: There is that. There is that. In its conceptual framework, it sounds like an eminently reasonable proposal, Mr. Rakoczy. But let's put some guts to the framing, if you will.

MR. RAKOCZY: So we would move to provisionally admit from Dr. Graham PTX 2034, PTX 3312, PTX 3313, PTX 3314, and PTX 3266.

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And I believe they're all studies -- stability study documents from -- or covering those.

MR. BERL: Honestly, I don't have a clue what those are. This is the first time --

THE COURT: It's a contingent question. What I would anticipate doing, in all candor, is we receive those exhibits proffered by Regeneron. If the Court does rely upon any of those contested exhibits, then we would admit that list as well.

But as Mr. Rakoczy pointed out, if the Court does not rely upon those exhibits for any number of reasons, including whether or not they were disclosed, then those would not be considered part of the record nor addressed in the Court's final order.

(PTX 2034, PTX 3312, PTX 3313, PTX 3314, and PTX 3266 were admitted.)

MR. RAKOCZY: Thank you, Judge.

THE COURT: Thank you.

Yes, Mr. Berl? I think the floor's still yours.

MR. BERL: A few logistical questions. We've closed our case. That's our last witness.

THE COURT: Understood.

MR. BERL: So I just wanted -- there were three minor logistical issues I may want to raise.

THE COURT: You've rested that portion of your case.

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Anything further from Mylan, then, Mr. Rakoczy?

MR. McLAUGHLIN: A few last exhibits. We looked at the transcripts just trying to clean things up and trying to coordinate and make sure we've got everything in that we intended to move in.

So we would like to move to admit just a few more exhibits that we've been relying on the last couple weeks if that's okay.

THE COURT: Go right ahead slowly, sir.

MR. McLAUGHLIN: DTX 9038, DTX 9023, DTX 913, DTX 902, DTX 5082, DTX 6444.

THE COURT: Thank you. Is that the universe?

MR. McLAUGHLIN: That's it.

THE COURT: All right.

Regeneron?

MS. OBERWETTER: Your Honor, I don't know what those are. So we may need a moment to try to figure out what those are and whether they were used with a witness pursuant to the pretrial order.

THE COURT: Please do.

Counsel, if you wouldn't mind conferring with Ms. Oberwetter and identifying what those are, if anyone knows.

MR. RAKOCZY: I was about to speak, but can I check with my team before I misspeak?

THE COURT: Yes. Sorry. You may.

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MR. RAKOCZY: While we're waiting, Your Honor, should we put more witnesses in the box?

MR. BERL: Or there are a couple of logistical questions that I had.

THE COURT: Yeah, we'll take those up. I would ask, as the gaggle works through those loose-end exhibits, if anyone can identify which witness those exhibits were used with, that would certainly be of benefit to Madam Clerk. But I'll add that to their to-do list.

THE CLERK: I found mine, except one.

THE COURT: With that, Mr. Berl, your list of logistical issues.

MR. BERL: Yes, three issues, I think in descending order of complexity.

First, Your Honor, as you're aware, has directed the parties to address various evidentiary issues posttrial, in posttrial briefing. We just wanted clarification whether it's Your Honor's intention that those issues should be raised in the initial brief -- the initial posttrial brief. And our thinking was that, if so, the other side responding to those evidentiary points could respond to them in the proposed findings of fact and conclusions of law.

THE COURT: Yes, Mr. Rakoczy?

MR. RAKOCZY: Your Honor, because we have -- we have a lot of issues to brief in that opening 30-page, we would

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request that we address the evidentiary issues in the proposed findings of fact, conclusions of law. And that way, the parties can focus on the merits in their actual briefing.

MR. BERL: I'm fine with that, Your Honor, subject to one concern, which is that, as I understood Your Honor's rulings about when various submissions are due, there's only one round of proposed findings of fact, conclusions of law.

THE COURT: That's correct.

MR. BERL: So if we raise an evidentiary issue, they wouldn't really have an opportunity to respond to it if it were only in the proposed findings of fact and conclusions of law, and vice versa. And so that's why I thought there should be some opportunity for a response.

THE COURT: I've got quite a chart up here of looming decisions on that front to make. Let's reserve those two, proposed findings of fact and conclusions of law, which, against the request of everyone up here, I've not put page limits on. Let's leave it there so that you're using your real estate in the argumentative briefs more wisely.

I've got a good handle on what we still need to sort through, but I would certainly encourage everyone to address each of those in your proposed findings and conclusions.

MR. BERL: So when would Mylan then respond to our evidentiary issues raised?

THE COURT: You would not.

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MR. BERL: We would not. Okay.

THE COURT: No. No, because we treat those truly as proposed findings of fact and conclusions of law we've argued here. You're free to augment the argument with research and the rest in those, but we don't need a volley in the papers.

MR. BERL: Excellent. So the second issue relates to closings. It's been my perception that trial has gone very smoothly in person. And I would suggest that, given the complexity of the issues, we would at least prefer, if possible, for closings to occur in person. Obviously, we understand the issues with respect to the courtroom and the projects to clean up the asbestos, but wherever it would be convenient for the Court, whether it's in Wheeling or Elkins or my cocounsel Mr. Ruby suggested even maybe at the law school in Morgantown, anywhere. We're willing to go anywhere, but we'd like to be in person.

THE COURT: Why, Mr. Ruby, do you hate law students?

Any opposition to that suggestion?

MR. RAKOCZY: We have no objection to in person, Your Honor.

THE COURT: No. I would tend to agree, Mr. Berl, that in person is better. I was so tired of getting Court of Zoom during the early portion of the pandemic. We said Zoom just to get that on everyone's calendars. We don't know what our deal will be here.

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Our Elkins facility, which is not the easiest to get to for folks traveling from afar, is expansive compared to this, as is Wheeling, although Wheeling is not as big as Elkins. But in all candor, the law school would be easier for me because that's just across town.

Let us work on logistics on one of those venues, and we'll let the parties know what we might be able to pull off.

Like I said -- and if I didn't say that out loud when we set sort of the schedule for posttrial proceedings and briefing, I was more concerned with getting a date for that because we don't know -- like I've told every witness, we're a court without a country for a little while. And that is largely in the hands of the GSA. And for any former government employees, you understand what that means.

MR. RAKOCZY: May I raise one issue about the law school, Your Honor?

THE COURT: Yes.

MR. RAKOCZY: If it was held at the law school, would we have the benefit of courtroom security if we needed to seal the courtroom?

THE COURT: Yes, we would. But those are logistical issues that we will deal with on that front. The main courtroom at the law school would certainly be large enough to accommodate everyone who's been here. They have sufficient AV equipment available to us. I'm just thinking through it. But

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that is one of the logistical things we would have to work on, Mr. Rakoczy, but we will work through those.

Elkins is always available to us. And Judge Stamp in Wheeling has been quite gracious to let us use his courtroom at the Wheeling point of holding court, which is now named for him, for a couple criminal trials we have in July. So we have some options. We'll work through that.

MR. BERL: Thank you, Your Honor.

And, lastly, I'd just like to close by saying we understand that this case and the schedule that we have gone through and executed has imposed a substantial burden on the Court and its staff. And we thank the Court and its staff for dealing with us and for your hospitality over the last few weeks. It's been a pleasure to try the case before Your Honor.

And a special thank-you to Ms. Knecht for her daily transcripts, which have been invaluable and surprisingly accurate.

THE COURT: I'll let her address if she takes that as a criticism. Mr. Berl, that will be reflected as a premium in your invoice with the Court's blessing.

MR. RAKOCZY: For Mylan and Biocon, we thank the Court and staff as well. I can't say we appreciate the expedited schedule as much as Mr. Berl.

THE COURT: That objection is noted, Mr. Rakoczy.

Okay. Any other issues from Mylan? I know we do

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have the remaining exhibits.

Yes, Counsel -- yes, Ms. Oberwetter?

MS. OBERWETTER: We've gone through the list. We do not have an objection to DTX 9038, DTX 913, DTX 902, or DTX 5082.

DTX 903 [sic], insofar as it was used for impeachment only, as -- it was a disclosed exhibit; so we would ask that it be taken only for that purpose.

THE COURT: Any objection to that, Mr. McLaughlin?

MR. McLAUGHLIN: You're talking about DTX 9023?

MS. OBERWETTER: Correct.

THE COURT: 9023?

MS. OBERWETTER: Correct.

MR. McLAUGHLIN: And what's the proposal?

THE COURT: That it be received as impeachment material.

MR. McLAUGHLIN: That's fine.

MS. OBERWETTER: And then DTX 6444 was the summary judgment stipulation, which does not seem appropriate from our standpoint to be put into evidence. There's a stipulation on the docket. It was used with a witness.

THE COURT: It's part of the record, right? Understood.

MR. McLAUGHLIN: As long as it's on the record, that's fine.

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THE COURT: Is that -- that's all of them, then?

MS. OBERWETTER: That is all of them.

THE COURT: Those will be admitted. 9023, for the purpose identified, the stipulation with respect to summary judgment, it's part of the record. I recognize its use and purpose here at trial.

9038, does anyone know which witness that exhibit was used with?

MR. McLAUGHLIN: That came in with Dr. Albini.

THE COURT: And then 9023.

MR. McLAUGHLIN: That came in during Dr. Csaky's first cross-examination.

THE COURT: Okay.

Any others, Madam Clerk?

THE CLERK: That's it.

THE COURT: All right. Those will all be deemed admitted, then. Thank you.

(DTX 9038, DTX 9023, DTX 913, DTX 902, DTX 5082, and DTX 6444 were admitted.)

MR. McLAUGHLIN: Thank you, Your Honor.

THE COURT: Let me say this before everyone scatters to the ends of the earth. Please check with Madam Clerk to make sure she has copies of all the exhibits. I can't imagine that we don't, but we always do need to track one or two down. Please make sure that all those are checked off the list.

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Mr. Rakoczy, anything else from Mylan?

MR. RAKOCZY: Nothing from Mylan or Biocon, Your Honor.

THE COURT: Thank you.

Mr. Berl, anything else from Regeneron?

MR. BERL: Nothing from Regeneron. Thank you, Your Honor.

THE COURT: The Court's prior order with the briefing schedule and the rest we'll leave unchanged, with the caveat we added with respect to the proposed findings. Any of the evidentiary issues at trial that may have been held in abeyance or conditionally addressed, please feel free to address those therein.

Thank you all very much. We appreciate all of your hard work. And I know how difficult it is to try a lengthy and complicated case and even more so how difficult it is to be far from office and home to do so. So we appreciate everyone's hard work and preparation. And I really do mean that.

Thank you. Please thank all of your witnesses, in particular, your experts. I've learned a great deal over the last two weeks. I don't know what the heck I'll use it for in my day-to-day life going forward, but as I've regaled my bride and others with tales from this trial, they just looked at me quizzically.

The Fourth Circuit judicial conference is next week.

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I look forward to talking about hydrophilic and hydrophobic molecules and the rest with my judicial colleagues. And I'll be sure to thank you all for the reception topics.

With that, at 10 after 1:00, I'll consider this matter adjourned for trial purposes. Thank you all very, very much.

MR. BERL: Thank you, Your Honor.

MR. TRASK: Thank you, Your Honor.

(Proceedings concluded at 1:15 p.m.)

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CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 23, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 23rd day of June 2023.

/s/Cindy L. Knecht

_____

Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

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