

1 UNITED STATES DISTRICT COURT
2 NORTHERN DISTRICT OF WEST VIRGINIA

3 Regeneron Pharmaceuticals, Inc.

4 Plaintiff,

5 VS. CIVIL ACTION NO.

6 1:22-cv-61

7 Mylan Pharmaceuticals, Inc., and
8 Biocon Biologics,
9 Defendants.

9 - - -

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

12 - - -

13 APPEARANCES:

14 On behalf of the Plaintiff:

15 David I. Berl
16 Ellen E. Oberwetter
17 Kathryn S. Kayali
18 Williams & Connolly, LLP
19 680 Maine Avenue, SW
20 Washington, D.C. 20024
21 202.434.5000

22 APPEARANCES CONTINUED ON NEXT PAGE

23

24

25

26

27

28

On behalf of the Plaintiff, continued:

Steven Robert Ruby
Carey, Douglas, Kessler & Ruby, PLLC
797 Virginia Street, East, Suite 901
Charleston, WV 25301
304.345.1234

Petra Scamborova
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6717
914.847.7611

On behalf of the Defendant:

Deanne M. Mazzochi
William A. Rakoczy
Neil B. McLaughlin
Rakoczy, Molino, Mazzochi & Siwik, LLP
6 W. Hubbard Street, Suite 500
Chicago, IL 60654
312.527.2157

Gordon H. Copland
William J. O'Brien
Steptoe & Johnson
400 White Oaks Blvd.
Bridgeport, WV 26330
304.933.8162

Proceedings recorded utilizing realtime translation.
Transcript produced by computer-aided transcription.

1 Monday Morning Session,
2 June 12, 2023, 9:30 a.m.

3 - - -

4 THE COURT: Thank you. Please be seated.

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

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

9 Will counsel please note your appearance for the
10 record.

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

20 THE COURT: Welcome home, sir.

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

24 Also Petra Scamborova, James Evans, Andrew Deciare,
25 and Arun Bhounik, all from Regeneron.

1 THE COURT: Good morning, everyone.

2 Good morning, Counsel.

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

9 THE COURT: Good morning, everyone.

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

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

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

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

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

6 THE COURT: Understood.

7 Counsel?

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

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

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

15 THE COURT: Understood.

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

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

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

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

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

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

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

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

24 That's who the plaintiff is.

25 The defendants in this case are Mylan and Biocon.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24 THE COURT: Understood.

25 The Court would then seal our proceedings. Those not

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

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

5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 There were many VEGF inhibitors in the prior art. It

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

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

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

17 And what they said was penetration of their molecule,
18 ranibizumab, into the retina is critical for its credible use.
19 You've got to get to the retina. Or as people in the field
20 often say, the tissue is the issue. So you've got to get to
21 the right tissue. And why do they say their product gets to
22 the retina? Because of its small molecule size,
23 48 kilodaltons. Kilodaltons is just a measure of weight like
24 pounds or kilograms.

25 And they contrasted it with what they called a

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

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

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

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

25 And when you did this systemic administration, what

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

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

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

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

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

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

14 So Genentech, the leader in the field, ditched the
15 40 milligrams per milliliter idea and instead pursued lower
16 doses, 6 milligrams per milliliter or 10 milligrams per
17 milliliter, which is what they ultimately used in Lucentis.

18 The argument based on Fraser of obviousness fails for
19 this reason alone. Not only does it fail to disclose
20 aflibercept or intravitreal injection, it has only
21 24.3 milligrams per milliliter, and the claim requires 40. The
22 skilled artisan would have used less than 24, not more, and
23 certainly wouldn't have gone all the way up to 40 when
24 Genentech, the prior art, was teaching away from it.

25 Now, the second prior art reference for obviousness

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

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

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

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

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

1 40 milligrams per milliliter. And based on the prior art that
2 we've seen, the skilled artisan never would have used that high
3 a concentration. It would have used a much lower concentration
4 for the intravitreal injection, just as the prior art
5 repeatedly taught.

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

13 Now, Regeneron did not succeed because it had a
14 molecule that inhibited VEGF. Lots of companies had that. But
15 consider what happened with Genentech. They were the big
16 800-pound gorilla in the field, the leaders in the field of
17 biotechnology in general and VEGF in particular. They had a
18 big first mover advantage with their product, ranibizumab.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 can be used, the written description requirement is met.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 THE COURT: The solution itself? That's not

1 reflecting how much aflibercept is in the solution?

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

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

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

12 THE COURT: Thank you.

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

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

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

1 important.

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

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

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

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

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

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

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

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

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

15 Now, Mylan's anticipation theory is actually based on
16 the prn arm of this published trial, of this published regimen.
17 What they say is that with prn dosing, it's possible somehow
18 that someone could have gotten a fourth and fifth dose at weeks
19 12 and 16 and then possibly, magically, could then have gotten
20 doses every eight weeks pursuant to his pro re nata treatment
21 appropriate after UR-inspected regimen.

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

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

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

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

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

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

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

1 eight weeks.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 THE COURT: Understood. Thank you, Counsel.

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

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

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

1 So 15 minutes enough for you guys to switch?

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

4 (A recess was taken from 10:45 a.m. to
5 11:01 a.m.)

6 THE COURT: Counsel, are you ready to proceed?

7 MR. RAKOCZY: I am, Your Honor.

8 THE COURT: The floor is yours, then.

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

13 I'd like to start by hitting the reset button, Your
14 Honor. Suffice it to say you're going to hear quite a
15 different perspective from me than what you just heard. In
16 short, the evidence will show that the asserted claims of the
17 '865 patent are not infringed and they are invalid. Before I
18 preview that evidence, three quick introductory points.

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

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

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

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

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

18 Point three, I think we heard more accusations of
19 copying, that somehow Yesafili is a copy of the '865 patent, or
20 Eylea, in a word, nonsense. Regeneron's the me-too that copied
21 the prior art blueprint for a stable protein formulation in the
22 '865 patent. Yesafili practices that prior art blueprint as
23 well. It's not a copy of Eylea or the '865 patent.

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

1 As Your Honor can see here on DDX 1, Slide 4, protein
2 formulations go back many decades, to the late 1990s at least.
3 And in this area, Genentech was the trail blazer. They had
4 formulated a number of stable protein formulations, starting
5 with Herceptin in 1998, up to the VEGF antagonist formulations,
6 some of which you heard about -- Avastin in 2004, Lucentis in
7 2006.

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

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

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

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

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

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

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

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

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

25 So the art had evolved considerably before the '865

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 about and not about?

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

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

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

23 So let's get to it, then. What is the
24 noninfringement case? Just to recap, the asserted claims are
25 4, 7, 9, 11, and 14 to 17. They all depend in one fashion or

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 references.

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

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

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

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

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

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

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

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

25 Now, that decision was vacated pursuant to a

1 settlement of all things --

2 THE COURT: I may have heard about that.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11 THE COURT: Understood. Thank you, Counsel.

12 MS. MAZZOCHI: Thank you very much.

13 Good morning, Your Honor. Pleasure to see you again.
14 Deanne Mazzochi for Mylan and Biocon to discuss the '601 and
15 '572 dosing patents.

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

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

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

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

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

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

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

1 particularly in the relevant time periods here.

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

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

16 Now, when it comes to Claim 25 of the '572 patent,
17 Regeneron points to the method of using this single initial
18 dose followed by secondary doses, which Claim 25 specifies it
19 for, for a total of five doses before starting eight-week
20 dosing. And that's the identical issue that we see for the
21 '601 patent, Claim 11, and then for another disease state
22 called diabetic retinopathy that we see in Claim 19. Again,
23 all they're focusing on is the existence of five loading doses
24 in the regimen.

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

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

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

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

25 Because what the federal circuit has stated is that,

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

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

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

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

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

24 THE COURT: "Working" being the operative term.

25 MS. MAZZOCHI: I am not relying on that for

1 inherency.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 You can go to the next slide.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 THE COURT: Close enough, Counsel. Close enough.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 THE COURT: Understood, Counsel.

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

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

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

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

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

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

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

4 Thank you, Your Honor.

5 THE COURT: Thank you, Counsel.

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

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

16 (A recess was taken from 12:05 p.m. to
17 1:14 p.m.)

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

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

25 THE COURT: Any objection to that, Counsel?

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 MS. OBERWETTER: No, Your Honor.

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

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

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

8 THE COURT: I withdraw my question, then.

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

13 THE COURT: It does, absolutely.

14 MS. OBERWETTER: Thank you, Your Honor.

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

17 **GEORGE YANCOPOULOS, PLAINTIFF'S WITNESS, SWORN**

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

21 Counsel.

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

24 DIRECT EXAMINATION

25

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 BY MS. OBERWETTER:

2 Q. Good afternoon, Dr. Yancopoulos.

3 A. Good afternoon.

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

6 Could you please introduce yourself to the Court.

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

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

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

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

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

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

25 We had started over the years with this focus on

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

20 First, just briefly, where is Regeneron based?

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

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

24 A. We now have about 10,000.

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 company?

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

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

9 A. Yes, I am.

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

12 A. Over 150.

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

15 A. Yes, I do.

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

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

19 THE COURT: You may.

20 BY MS. OBERWETTER:

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

23 A. Do I take them out of these folders?

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 do you recognize --

2 A. This chair is --

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

5 Go right ahead.

6 BY MS. OBERWETTER:

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

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

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

13 A. Yes, I do.

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

19 A. PTX 001 and PTX 003.

20 Q. That's correct.

21 A. Yeah.

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 become a scientist.

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

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

7 Q. And what was your experience at Columbia?

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

10 Q. Did you graduate with any honors?

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

3 A. Yeah.

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

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

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

11 Q. What ultimately caused you to leave Columbia?

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 emotional for me.

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

11 Q. What happened after that conversation?

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

2 A. In the late '80s.

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

4 A. No. That's okay.

5 Sorry. This is ridiculous.

6 Q. All right. Families are emotional.

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

14 What is the name of the active molecule in Eylea?

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

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

22 A. Sure.

23 Q. How would you describe what aflibercept is?

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

4 If we can please pull up PTX 3333.

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

10 THE COURT: Understood. Overruled at this point.
11 Counsel.

12 MS. MAZZOCHI: Thank you.

13 MS. OBERWETTER: Thank you, Your Honor.

14 BY MS. OBERWETTER:

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

18 A. Well, it's much harder to consider treating directly
19 into the eye. In fact, I was the first person to consider
20 treating into the eye with growth factors back in the early
21 1990s. Those efforts actually failed, like all of our efforts
22 did in the 1990s.

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

6 Q. Thank you.

7 And we can take that slide down.

8 Approximately when did aflibercept enter into
9 preclinical development?

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

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

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

3 But what was the purpose of referring to Lucentis
4 here?

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 the doctors and so forth.

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

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

8 Do you see that bullet?

9 A. Yes.

10 Q. What were you referring to there?

11 A. This is exactly what I was talking about before.

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

22 Q. And if we just look briefly at the last bullet on
23 that page, what is that last bullet, "We can deliver
24 4 milligrams," in reference to?

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 leaking --

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

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

21 So let's stay on target, Counsel.

22 MS. OBERWETTER: Yes, Your Honor.

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 BY MS. OBERWETTER:

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

4 If you could please go ahead and finish your answer.

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

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

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

17 But this is done using a monthly regimen.

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

21 Can you describe what you were trying to convey here?

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

3 What were you trying to convey here?

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

16 A. Yes.

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

17 If we could pull up PDX 3.001.

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

20 A. Yes, I have.

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

4 Q. Okay.

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

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

8 THE WITNESS: Eight weeks. I'm sorry.

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

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

15 THE COURT: Sorry, Counsel.

16 MS. OBERWETTER: Thanks very much, Your Honor.

17 THE COURT: Hey, you're welcome.

18 BY MS. OBERWETTER:

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

22 A. Yeah. Once again, you know, Latin. I don't really
23 know what it means but q means every. 0.5 refers to the dose;
24 q means every four or first week. So 0.5 q4 means
25 0.5-milligram dose, q means every, four means four weeks, and

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

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

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

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

24 A. No.

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 VIEW trials mean that you expected that it would work?

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

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

6 THE COURT: State the objection.

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

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

13 Repeat your question, please, Counsel.

14 MS. OBERWETTER: Yes, Your Honor.

15 BY MS. OBERWETTER:

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 that, we would have been happy with that.

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

6 Q. Okay. We can take that slide down.

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

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

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

13 A. Yes.

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

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

25 This is nowhere in those discovery responses. So if

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

4 THE COURT: Understood.

5 MS. MAZZOCHI: Thank you, Your Honor.

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

9 BY MS. OBERWETTER:

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

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

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

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

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

23 If we can pull up PDX-3.002.

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 A. Yes, I have.

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

4 A. Yes, it does.

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

6 A. Yes.

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

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

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

19 A. No.

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

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

24 Q. And what was the strategy instead tested here after
25 12 weeks?

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

15 Q. Okay. We can take that slide down.

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

17 If we could please pull up DTX 212.

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

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

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

24 A. It's January 2006.

25 Q. Who is Neil Stahl?

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

6 Do you see that?

7 A. Yes, I do.

8 Q. And what was that a reference to?

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

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

20 Do you see that?

21 A. Yes.

22 Q. What is the VA data there?

23 A. The visual acuity data.

24 Q. What is this sentence a reference to?

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

13 Was that a perspective that you shared?

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

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

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

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

25 Q. Okay. We can take that document down.

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

12 A. Yes.

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

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

18 A. Yes, I do.

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

17 Q. What is the date of this document?

18 A. April 4th, 2007.

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

22 Do you see that line?

23 A. Yes, I do.

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

20 Do you see that?

21 A. Yes, I do.

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

8 A. Yes.

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 that says we should do this.

2 Q. Okay. We can take this document down.

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

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

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

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

13 A. Yes, I was.

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

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

18 Q. Did you participate in drafting this paper?

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 a little bit easier to read.

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

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

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

3 A. Right. So, basically, it's the forearms that were
4 described in the previous study. The blue line is Lucentis
5 monthly; the yellow line is 2 milligrams of aflibercept every
6 four weeks or every month; the green line is the 0.5 milligram
7 dose every month; and then the red line, this last line, is the
8 2-milligram arm after three loads given every eight weeks or
9 every two months. So that red one is the key arm, which you
10 can see is right on top of all the other lines.

11 Q. And we can take that document down.

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

14 A. I guess you could describe it as elation.

15 Q. And why is that?

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

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

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

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

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

12 THE COURT: Go right ahead.

13 BY MS. OBERWETTER:

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

17 Just briefly, what are those conditions?

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 angiogenic eye disorders other than AMD?

2 A. Yes.

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

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

10 A. Yes.

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

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

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

16 A. January 13th, 2011.

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 Do you see that?

2 A. Yes.

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

6 A. Yes.

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

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

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

19 Do you see that?

20 A. Yes.

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

25 Why did you call out diabetic macular edema and

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 diabetic retinopathy specifically?

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

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

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

13 A. We listed it here; so yes.

14 Q. And we can take that document down.

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

18 A. No.

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

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

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

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 relying on the wet AMD trials?

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

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

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

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

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

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

20 Do you see that?

21 A. Yes.

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

24 A. Yes.

25 Q. And were there sometimes slide decks sent around of

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 the meetings that were conducted with outside key opinion
2 leaders and the like?

3 A. Yes.

4 Q. Let's take a look at page -- the page that is marked
5 as 0005. The header at the top says "Impressions."

6 If we can pull out that middle couple of bullets on
7 this page, both of those.

8 There's a reference here to "Detailed discussion of
9 direct-to-Phase III plan not held."

10 Do you see that?

11 A. Yes.

12 Q. And some additional verbiage between that.

13 What was being conveyed about the DME program in this
14 section of this slide?

15 A. Well, there was some discussion that could we use
16 exactly the same treatment regimen for DME that we had used for
17 AMD? And basically everybody agreed that you couldn't
18 necessarily.

19 Q. Okay. And there's a reference in that second bullet
20 to possible safety concerns in diabetic population not seen in
21 AMD patients.

22 What is that a reference to?

23 A. Yeah. In some ways diabetic patients, they suffer
24 higher risks of heart attacks, strokes, problems like that.
25 And the concern was there was a possible link even at that time

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 between VEGF inhibitors and increasing the risks of heart
2 attacks and strokes and so forth.

3 And so the concern was too much dosing or too high a
4 dose might have a different kind of side effects, might cause
5 more problems either systemically, in terms of heart attacks
6 and strokes, or even maybe locally in the eye so that you
7 couldn't predict not only the efficacy but you also couldn't
8 predict the safety profile and whether the same regimen would
9 behave the same way for either safety or efficacy in DME
10 patients compared to AMD patients.

11 Q. I'd like to talk briefly about the Phase II study
12 that Regeneron conducted for DME.

13 And if we can pull up PDX 3.004.

14 Dr. Yancopoulos, is this another slide that you had
15 an opportunity to review for today's testimony?

16 A. Yes.

17 Q. And can you please walk us through, briefly, the
18 study arms that were used in the Phase II Da Vinci trial for
19 DME.

20 A. Well, in some ways they look very similar to what we
21 tried in AMD in that we had a monthly regimen for 2 milligrams,
22 a monthly regimen for 0.5 milligrams; then we had a three
23 loading doses followed by eight-week regimen for 2 milligrams;
24 and then we had three lowering doses followed by prn. And we
25 were comparing them to the fifth arm, which was the standard

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 laser control.

2 Q. Okay. In the Phase II trial for DME, did Regeneron
3 even test a regimen that had five loading doses?

4 A. No.

5 Q. Okay. Were you aware of any other VEGF drugs under
6 development at the time that were using five loading doses?

7 A. No.

8 Q. Okay. We can take that document down.

9 Do you recall approximately when the one-year data
10 for the Phase II Da Vinci trial became available to Regeneron?

11 A. No.

12 Q. And we'll take a look at a couple of documents that
13 may refresh your recollection.

14 Let's start first with a couple of documents in your
15 binder that are grouped together as PTX 3187 and PTX 3188.

16 A. Yes.

17 Q. And can you please identify what these documents are.

18 A. This is a email about an agenda and a presentation
19 for a Bayer-Regeneron joint steering committee meeting to
20 discuss utilization of VEGF Trap-Eye, or aflibercept, in
21 diabetic macular edema.

22 Q. And what is the date of the email here?

23 A. October 19, 2010.

24 MS. MAZZOCHI: Your Honor, I'd just like to renew our
25 objection as well that this is also to the extent they're

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 trying to do this to establish a prior conception type date.
2 This was also not disclosed in their discovery responses. We'd
3 like to brief that as well.

4 THE COURT: Understood. Posttrial briefing and
5 proposed findings and conclusions will be an outstanding avenue
6 for those arguments to be made. Understood.

7 Counsel, you may proceed.

8 BY MS. OBERWETTER:

9 Q. Dr. Yancopoulos, what is that? The PowerPoint is
10 titled "JDC Presentation for JSC October 21, 2010."

11 Can you explain just briefly, what is the JDC and the
12 JSC?

13 A. The JDC, joint development committee, is a collection
14 of the team members at lower levels who are directly working on
15 things. And they prepare things for these meetings, and they
16 prepare a lot of the -- they do a lot of the work.

17 And the joint steering committee are the senior-level
18 meetings that the -- senior-level individuals that JDC team
19 members report to.

20 Q. Okay. And were you on one of these committees?

21 A. Yes. I was on the joint steering committee.

22 Q. I'd like to advance through the document a little bit
23 to page 3, and there's a page called "Health Authority
24 Feedback" on PTX 3188.0003.

25 There's a part near the top of that page called

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 "Study Design," if we could please pull that out.

2 And there's a reference to "Study design proposed
3 dosing arms 2 milligrams q4, 2 milligrams q8 after three
4 loading doses," and then "Control: Acceptable."

5 Do you see that?

6 A. Yes.

7 Q. As of October 2010, what number of loading doses were
8 being contemplated for the forthcoming Phase III trial?

9 A. Three loading doses.

10 Q. There's a sentence right under that one that starts
11 with "final one-year data."

12 Do you see that one?

13 A. Yes.

14 Q. Can you please explain what that sentence is in
15 reference to.

16 A. That we were still awaiting some more data, and that
17 might provide additional guidance on number of loading doses.

18 The reason we were so concerned is the number of
19 loading doses is critical because you want to gain vision and
20 then maintain it when you shift to the every-two-month dosing
21 because you don't think you're going to be gained during the
22 two months. So if you're off by the number of loading doses,
23 you may never get to the same level, the equivalent level,
24 that, for example, monthly Lucentis gets to.

25 On the other hand, there's also enormous pushback

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 from a variety of people, including commercial. They want the
2 least number of doses. So you're playing a very tight --
3 you're walking a tightrope here.

4 Q. Okay. We can take this document down.

5 Did you eventually review the data that came out --
6 the one-year data that came out from the Da Vinci trial?

7 A. Yes.

8 Q. And let's look at two documents together. These are
9 PTX 80 and PTX 1028C.

10 MS. OBERWETTER: And, Your Honor, there's a third
11 exhibit that goes with this that we have in hard copy, if I may
12 approach the witness.

13 THE COURT: You may.

14 BY MS. OBERWETTER:

15 Q. Dr. Yancopoulos, if we go back to the email which we
16 have up as PTX 80, there's two attachments to this document,
17 correct?

18 A. Yes.

19 Q. Okay. And what was the date of this document?

20 A. December 8, 2010.

21 Q. All right. And you were one of the recipients of
22 this, correct?

23 A. Yes.

24 Q. There's an email from Caroline Saxton.

25 What is she referring to there in her email?

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 A. She's referring to the data that we now have in front
2 of us, which is the short presentation on the one-year data and
3 then the complete data set in this bigger binder.

4 Q. And why don't we take -- we'll walk through some of
5 this in order, and I assure everyone we're not going to get
6 through every page of PTX 1170 which we've handed up to the
7 witness.

8 But if we can start with PTX 1028C, what is this
9 document that we're looking at?

10 A. This is a summary of the results from the one-year
11 data from the Phase II trial in diabetic macular edema.

12 Q. And were these -- was this an internal presentation
13 or an external presentation?

14 A. Internal presentation.

15 Q. And if we advance forward just to page 3 of this
16 document briefly and pull out the upper left-hand.

17 This was marked, at least in part, with a
18 confidential ledger, correct?

19 A. Right.

20 Q. Had Regeneron published the details of its one-year
21 Phase II Da Vinci trial at this point in time?

22 A. No.

23 Q. And was it keeping that data confidential?

24 A. Yes.

25 Q. Did you have additional data above and beyond even

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 what was in this PowerPoint?

2 A. Yes.

3 Q. And if we just take a look for a moment at PTX 1170,
4 what is PTX 1170 that I have handed you?

5 A. Well, it's the full data set from the trial that's
6 summarized in this shorter PowerPoint.

7 Q. And at a high level, can you describe what kind of
8 data is contained in PTX 1170?

9 A. Well, it gives detail efficacy and safety results on
10 a group level as well as on a patient level.

11 Q. And did you have that data set available to you when
12 you were deciding what to do for the DME Phase III trial?

13 A. Evidently, from the email, yes.

14 Q. Yes. Okay.

15 And let's take a look at the PowerPoint for a moment.
16 If we can please take a look at page 11 of PTX 1028-C.

17 Can you please explain what kind of data is presented
18 on this page.

19 A. Once again, this is visual acuity data, as we said.
20 So on the vertical axis is gain or loss in vision. The white
21 line is the current standard of care at the time because,
22 remember, Lucentis hadn't been approved for this indication at
23 the time; so it was laser. And you see laser; they gain a
24 little vision, it goes up above the zero, and then by the end
25 they've lost vision. And then the four other curves are the

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 four arms, the experimental arms that are trying various dosing
2 schedules of -- dosing schedules and doses of aflibercept.

3 Q. Okay. And this data that we're looking at on this
4 page, if we zoom back out, this is, again, the Phase II
5 Da Vinci data, correct?

6 A. Right.

7 Q. Were there aspects of this data set in the visual
8 acuity data from Da Vinci that limited its utility to you?

9 A. Yeah. As one can see, this is why the experts, as we
10 talked about before, in the other slides that we went through,
11 agreed that you can't really count on Phase II data because the
12 data sets are so small and why the FDA doesn't accept this sort
13 of data.

14 If you just look up there, these top three curves,
15 see the dark green one, the light blue one, and this purplish
16 one. Okay. At least through 12 weeks, these groups are all
17 treated the same. So in a perfect world or if you had, for
18 example, hundreds or thousands of patients per arm, those three
19 groups would have been right on top of each other. They
20 literally should be identical.

21 And it just shows that you can't count on the
22 results. These things are bouncy. They're bouncing around.
23 They don't look like the Phase III data, and arms that should
24 be identical can look -- as you can see the green from the
25 other ones -- very different.

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 So even before you get the different treatments for
2 these three curves started at the 12-week time point, but you
3 can see by then they're already different.

4 So these are important directionally. We do these
5 studies -- first of all what you can see is every single one of
6 these arms definitely looks like it's better than laser. So it
7 made us feel that, frankly, many of these regimens would be
8 better than laser. But the question is which regimen might
9 actually be better -- or which regimen might actually work with
10 a lower treatment burden compared, for example, to monthly
11 Lucentis and so forth.

12 These are things that are, frankly, almost impossible
13 to tell from these small studies. So you incorporate -- as I
14 was saying before, those of us who have managed to figure out
15 how to get successful in the business, you incorporate millions
16 of points of data, including things like this, including data
17 that you're seeing there, and many other pieces of data to try
18 to make your best judgments as to which regimens are you going
19 to bet on in these Phase III trials.

20 Q. Okay. And was this data on this page of PTX 1028-C
21 sufficient to decide on a five loading dose regimen?

22 A. No. It would be very hard for anybody to
23 definitively come up with any definitive regimen based on this
24 data based on the noise that you're just seeing right here.

25 Q. And how is it that you decided ultimately on a five

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 loading dose regimen for DME?

2 A. Well, like I said, it's a matter of integrating a
3 million pieces of data. I mean, these are questions that
4 sometimes are unanswerable. I mean, how did I come up with the
5 idea to invent the VEGF Trap in the first place? It sort of
6 just came to me, but I incorporated a million pieces of
7 information that I had -- I had integrated over the years.

8 And the same thing here. I realized that we had to
9 maximize the -- so the whole notion -- the basic notion, the
10 basic thing that we described is you want intense dosing, and
11 then you back off to go to the every-other-month dosing.

12 And how long you do the intense dosing, we reasoned,
13 or I reasoned, should be different for diabetic macular edema
14 based on, like I said, many points of data. There were many
15 others who thought that VEGF signal was higher in DME than it
16 might be in AMD. We had reason to think that in dosing,
17 division continued to improve as you dosed with monthly
18 treatment.

19 So there was a lot of things that went into it. It's
20 impossible to point to one thing. But this is why some people
21 are successful in this business, because they guess right more
22 often than not.

23 Q. Okay. Thank you.

24 We can take that document down.

25 I want to turn to talking briefly about the results

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 of the Phase III VIVID and VISTA trials.

2 THE COURT: Counsel, before we transition topics, is
3 that a good point to take a brief break or --

4 MS. OBERWETTER: We could, Your Honor. I have a
5 little bit more; so yes.

6 THE COURT: Okay. Why don't we do that.

7 Doctor, we're going to take an afternoon break at
8 this point. We're going to take 15, given the crowd numbers we
9 have and our limited restroom facilities here in the building.

10 During this break, because you're midstream on your
11 testimony, no one can talk with you. I don't want you to think
12 anyone here is being rude or discourteous, but it's part of the
13 rules that govern this proceeding. So you're a little bit of a
14 man without a country, for lack of a better term, during the
15 next 15 minutes. So if you see folks turn and scatter from
16 you, that's why. It doesn't have anything to do with the
17 PowerPoints we talked about earlier.

18 But you can go ahead and step down if you'd like, and
19 you can leave all those materials there. We'll deal with
20 those. Thank you very much, sir.

21 Otherwise we'll take 15 and resume at that point.
22 Thank you all very much.

23 (A recess was taken from 3:04 p.m. to
24 3:19 p.m.)

25 THE COURT: Are you ready, Doctor?

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 Counsel?

2 BY MS. OBERWETTER:

3 Q. All right. Dr. Yancopoulos, we were turning to the
4 Phase III results for Regeneron's VIVID and VISTA trials. If
5 we take a look at PTX 932. And can you please identify this
6 document for us.

7 A. Yes. This is the published manuscript that describes
8 the two Phase III trials for aflibercept in diabetic macular
9 edema.

10 Q. And you are listed on this paper?

11 A. Yes, I am.

12 Q. Okay. If we take a look again -- if we go to the
13 data page of this document, which is at page -- advancing
14 forward to Figure 1A, which we've marked for convenience as
15 PDX 932-C, could you please describe the results that Regeneron
16 obtained from its Phase III VIVID and VISTA trials with
17 reference to this figure.

18 A. So once again, the vertical axis, the Y axis, is
19 vision gained or lost in letters. The red line is the standard
20 of care at the time, which was laser, which is keeping the
21 patients stable.

22 And what you can see here is that both of the
23 aflibercept treatment arms do almost identically in terms of
24 gaining and maintaining the vision. And once again, the key
25 thing about this is that the 2q8 arm -- that is after five

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 loads, then going on to every-other-month dosing -- maintains
2 the vision as well as monthly.

3 Once again, that was the big take-home message and
4 the big advance here that allowed Eylea to become such an
5 important drug for this disease.

6 Q. Okay. Going into these trials, the VIVID and VISTA
7 trials, did you have an expectation as to the five loading dose
8 eight-week arm would perform?

9 A. Did I have a what?

10 Q. An expectation.

11 A. I had hope, for sure. I mean, I was hoping that it
12 would work. But that's, of course, why we had the two arms
13 because we were, once again, taking the higher likelihood thing
14 which would be monthly, and then we were hoping beyond hope
15 that the every-other-month would behave as well as it did.

16 Q. Okay. After the completion of the VIVID and VISTA
17 trials, did Regeneron ask the FDA to approve this regimen for
18 patients?

19 A. Yes.

20 Q. And why?

21 A. Because, clearly, it was an advance over the standard
22 of care at the time which was laser, but the results resulted
23 in impressive safety and efficacy, and the regimen that the FDA
24 approved was the every-other-month regimen.

25 Q. We can take that document down.

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 Was Regeneron also ultimately able to get an
2 indication for diabetic retinopathy?

3 A. Yes, we were.

4 Q. And at a high level, how did that indication come
5 about?

6 A. Well, we had some evidence from this trial, but the
7 FDA felt that we hadn't prospectively identified all of our end
8 points and so forth, and so it wanted us to confirm it; so we
9 had to do a separate single Phase III trial.

10 Q. Okay. And that was the PANORAMA trial?

11 A. Yes.

12 Q. Have there been other significant -- I'm going to
13 change topics a little bit.

14 Have there been other significant treatments for wet
15 AMD that have come onto the market since Eylea?

16 A. Well, for those of us in the field, it almost seemed
17 like back to back to back. I mean, there was the big advance
18 of the Macugen, the first drug. Then that was rapidly
19 displaced by Lucentis. And then Eylea came along and became
20 the new gold standard of care. And it seemed like it was
21 really easy.

22 In the following ten years, the field was littered
23 with many, many failures, including our own. We had several
24 studies, several attempts to improve on Eylea.

25 So as I said, Lucentis had set a high bar, which we

GEORGE YANCOPOULOS, MD, PHD - DIRECT

1 were able to meet and exceed. But after that, the Eylea set
2 such a high bar that none of us, including for ten years our
3 own efforts, were able to exceed it. Only in the last year
4 there was an approval of another anti-VEGF agent, but it did
5 not seem to really distinguish itself or exceed in any way
6 Eylea. It was only as good more than ten years later.

7 And it just shows how hard this field is, how hard it
8 is to get everything right from the drug to the formulation to
9 the regimen and so forth, to get success, let alone success
10 that exceeds what the bar is in the field right now.

11 And so the whole field failed for more than ten
12 years, many, many, many failures, and the one recent success
13 just matched Eylea, did not in any way surpass it.

14 Q. And in your view, what has accounted for Eylea being
15 as successful as it has been for as long as it has been?

16 A. Well, the impressive safety and efficacy profile.
17 It's very hard. Some of the drugs that I talked about failed
18 because of safety problems. Some of them failed because of
19 efficacy problems. So having the safety and efficacy and what
20 is now acknowledged as the longer duration of action really
21 made such a difference, and it became adopted as the standard
22 of care.

23 MS. OBERWETTER: Thank you. No further questions.

24 And I pass the witness.

25 THE COURT: Thank you.

GEORGE YANCOPOLOUS - CROSS

1 Counsel.

2 MS. MAZZOCHI: Thank you, Your Honor. We have some
3 binders for the Court and for the witness.

4 THE COURT: Everyone may approach.

5 Counsel, go right ahead.

6 CROSS-EXAMINATION

7 BY MS. MAZZOCHI:

8 Q. Do you have your binders, Dr. Yancopoulos?

9 A. One binder.

10 Q. Yeah, one binder.

11 Dr. Yancopoulos, you talked quite a bit about some of
12 your patents in your direct examination.

13 Do you recall why you decided to file for these
14 patents?

15 A. Why I decided to file for these two patents?

16 Q. Right.

17 A. Because they were demonstrating a new approach to
18 treating angiogenic eye disorders that we thought could have
19 value that we wanted to protect.

20 Q. I'd like you to take a look in your binder at an
21 exhibit that is numbered DTX 3196. And these are going to be
22 exhibit pages 7 and 8. And I'm going to pull some information
23 from them up on the screen, specifically your deposition
24 transcript pages 25, line 24, through deposition transcript
25 page 26, line 2.

GEORGE YANCOPOLOUS - CROSS

1 If we could just pull that up on the screen, please.

2 A. Could you repeat the numbers again, please.

3 Q. Yes. DTX 3196. I'll put these specific lines up on
4 the page. They're on exhibit pages 7 and 8. If you see in the
5 lower right-hand corner 001, 002. And actually we're going to
6 take a look at line -- transcript page 25, line 24 and 25, over
7 to page 26, line 1.

8 Do you recall giving a deposition in this case?

9 A. Yes.

10 Q. All right. Can you confirm that at that deposition I
11 asked you the question, "Do you recall why you decided to file
12 for these patents?" and you gave the answer, "I don't recall"?

13 A. I may have said that. I don't recall.

14 Q. Do you know how many of your patents over the years
15 have been held invalid?

16 A. No, I do not.

17 Q. Do you know how many have been held unenforceable for
18 inequitable conduct?

19 A. No, I do not.

20 Q. Are you aware -- do you know that at least one of
21 your patents has been held invalid for inequitable conduct?

22 A. I guess 1 out of 150? I can understand that.

23 Q. You can understand that?

24 A. I can understand that. Sometimes something happens
25 that something invalidates a patent. I don't know much about

GEORGE YANCOPOLOUS - CROSS

1 the patent business. Sorry.

2 Q. Well, are you aware that one of the reasons why your
3 patent was held unenforceable for inequitable conduct is
4 because the court found that you made material
5 misrepresentations regarding unexpected results to the PTO that
6 were false?

7 A. I thought it was because we failed to cite what was
8 considered one citation that was prior art. So we missed one
9 citation. That was my understanding.

10 Q. Tell you what. Let me pull up for you.

11 MS. MAZZOCHI: Tom, this is in --

12 THE WITNESS: Are you trying to imply that I tried to
13 misrepresent something in one of my patents?

14 THE COURT: Doctor, your role here is simply to
15 answer questions.

16 Counsel, next question, please.

17 BY MS. MAZZOCHI:

18 Q. If it would be helpful to you, I can refresh your
19 recollection on some of the details. If we can turn to page --

20 MS. OBERWETTER: Objection, Your Honor. I don't
21 understand the relevance of this as it relates to any of the
22 patents at issue in this case, and there has been a prehearing
23 ruling on their motion to amend to add inequitable conduct.

24 THE COURT: Correct. But I assume this is aimed at
25 the witness's credibility. Is that correct?

GEORGE YANCOPOLOUS - CROSS

1 MS. MAZZOCHI: Correct.

2 THE COURT: Understood, but the exhibit that's
3 displayed currently on the Court's screen is a case. I can
4 barely read it. But we need to ask the witness about things he
5 has personal knowledge about, including -- and that includes
6 impeachment or credibility.

7 Objection overruled at this point.

8 BY MS. MAZZOCHI:

9 Q. And if we can -- we're going to page 1349.

10 A. Which document are we in?

11 Q. This is a court decision entitled "Regeneron
12 Pharmaceuticals Inc."

13 A. What number? What am I looking for?

14 Q. We're going to put it up on the screen because I have
15 to actually see if this is going to help refresh your
16 recollection. Then if it does, we can talk more about it.

17 A. Okay. Couldn't I just turn to it? Could you just
18 tell me which document it is?

19 THE COURT: It's not in the binder, Doctor.

20 THE WITNESS: It's not in the binder.

21 THE COURT: Use the screen there. Thank you.

22 Go ahead, Counsel.

23 BY MS. MAZZOCHI:

24 Q. Dr. Yancopoulos, you indicated that you thought that
25 all that was at issue was that you didn't cite a reference.

GEORGE YANCOPOLOUS - CROSS

1 According to the court decision, one of the things it said
2 Regeneron did was that "Regeneron sent -- also sent a
3 presentation to the PTO with the reply. In that presentation,
4 Regeneron asserted that it had developed a commercial
5 embodiment of the claimed mouse with surprising results. It is
6 undisputed that that assertion was false. Regeneron had not
7 developed any such mouse at the time."

8 Does that help to refresh your recollection as to one
9 of the reasons why one of your patents was held unenforceable
10 for inequitable conduct?

11 A. You know, I am not involved in these sorts of patent
12 disputes and I was not present. I didn't testify in that case.
13 I know very little about it. And I somehow had thought that it
14 had to do with citations. I don't know exactly what this is
15 referring to.

16 Q. Okay. Well, Dr. Yancopoulos, given the fact that
17 Regeneron had been -- had one of their patents, one that you
18 were on, held invalid for inequitable conduct based on -- based
19 on a false statement to the PTO, did you after that point make
20 sure that your scientific representations and specifications
21 were reviewed for scientific truth and accuracy?

22 MS. OBERWETTER: Objection, Your Honor. The question
23 is lacking foundation in multiple respects at this point, both
24 with respect to what the ultimate conclusion of the court was,
25 the reasons for it, and this witness's lack of knowledge.

GEORGE YANCOPOLOUS - CROSS

1 THE COURT: The witness indicated he's not familiar
2 with this background, Counsel. I think if you want to ask
3 about any changes in business practices, that's appropriate,
4 but he's not expressed any personal knowledge about this at
5 this point.

6 MS. MAZZOCHI: Right. And that was exactly what I
7 believe I just asked, is that given --

8 THE COURT: I disagree. Objection sustained.
9 Rephrase.

10 MS. MAZZOCHI: Okay.

11 BY MS. MAZZOCHI:

12 Q. Did you implement any business practices to ensure
13 that the accuracy of all of the scientific representations that
14 your patent applications were making were truthful and
15 accurate?

16 A. I don't really know how to answer that question. I
17 think that we always endeavor to do everything truthfully and
18 correctly. And I'm sure on occasion some things get missed, no
19 matter how good our due diligence.

20 So I don't know the details about this. I don't know
21 how -- clearly, we did develop a commercial embodiment of the
22 claimed mouse that was very successful. I don't know whether
23 the timing is what was at issue. I don't know whether that was
24 done deliberately or was somehow a mistake. But I'm sure that
25 we have practices that try to ensure that things happen

GEORGE YANCOPOLOUS - CROSS

1 correctly and truthfully all the time. Not to say that
2 sometimes mistakes don't happen.

3 Q. Let's put up on the screen DTX 2745, exhibit page 1.
4 A copy of this should be in your binder.

5 THE COURT: What number was that, Counsel?

6 MS. MAZZOCHI: 2745.

7 THE COURT: Understood. Thank you.

8 BY MS. MAZZOCHI:

9 Q. Can you confirm this is a publication by Jocelyn
10 Holash, you, and others, titled "VEGF Trap: A VEGF Blocker
11 with Potent Antitumor Effects," which I believe was published
12 in the proceedings of the National Academy of Sciences in 2002?

13 A. Yes.

14 MS. MAZZOCHI: Your Honor, we'll move DTX 2745 into
15 evidence.

16 THE COURT: Any objection?

17 MS. OBERWETTER: No, Your Honor.

18 THE COURT: Without objection, so admitted.

19 (DTX 2745 was admitted.)

20 MS. MAZZOCHI: Thank you, Your Honor.

21 BY MS. MAZZOCHI:

22 Q. Dr. Yancopoulos, in DTX 2745, pages 1 to 2, I'd like
23 to direct your attention to the "Materials and Methods" section
24 that appears under the subheading "Engineering VEGF Traps."
25 Let me pull that up on the screen for you.

GEORGE YANCOPOLOUS - CROSS

1 Do you see those on the screen?

2 A. Yes.

3 Q. If we look at the last sentence, which appears on the
4 top of exhibit page 2, you reported in your papers that all of
5 your VEGF Trap variants were produced and purified from Chinese
6 hamster ovary cells. True?

7 A. I know that we produced them using Chinese hamster
8 ovary cells. I assume that this statement is true.

9 Q. And using CHO cells will cause your VEGF Trap
10 proteins to be glycosylated, right?

11 A. It depends on which Chinese hamster ovary cells you
12 use. There's some that cause glycosylation, some that don't.

13 Q. And let's go to the second page of DTX 2745,
14 right-hand column, where you are discussing your injections
15 into mice. It's the text that starts "obtained from
16 American-type culture collection."

17 Do you have that there on the screen?

18 A. Yes.

19 Q. And roughly in the middle of the text we have up on
20 the screen, there's a reference to a vehicle that states PBS
21 plus 0.5 percent glycerol.

22 PBS stands for phosphate-buffered saline, right?

23 A. Yes.

24 Q. And it's an isotonic solution?

25 A. I'm not sure, actually.

GEORGE YANCOPOLOUS - CROSS

1 Q. Dr. Yancopoulos, let me call up DTX 8180, exhibit
2 page 1, which is an article titled "The one-year results of the
3 CLEAR-IT 2, a Phase II study of vascular endothelial growth
4 factor Trap-Eye dosed as-needed after 12-week fixed-dosing,"
5 from the journal *Ophthalmology*, June 2011, Volume 18,
6 pages 1098 to 1106.

7 You were a coauthor on this publication, yes?

8 A. Yes.

9 MS. MAZZOCHI: Your Honor, we move DTX 8180 into
10 evidence.

11 THE COURT: Any objection.

12 MS. OBERWETTER: No objection.

13 THE COURT: Without objection, so admitted.

14 (DTX 8180 was admitted.)

15 MS. MAZZOCHI: Thank you, Your Honor.

16 BY MS. MAZZOCHI:

17 Q. Let's go to the second page of DTX 8180, the second
18 full paragraph that starts off "vascular endothelial growth
19 factor Trap-Eye."

20 Do you have that on the screen?

21 A. Yes.

22 Q. I'd like to direct your attention to the second
23 sentence in that paragraph that's talking about VEGF Trap-Eye
24 that says, "It was developed specifically as an ultrapurified
25 iso-osmotic solution for ophthalmologic use."

GEORGE YANCOPOLOUS - CROSS

1 Do you see that?

2 A. Yes.

3 Q. And as support for that statement, do you have a
4 notation there, a citation number 25?

5 A. Yes.

6 Q. If we can turn to the DTX 8180, exhibit page 8, can
7 you confirm that citation number 25 in the right-hand column is
8 to Holash, et al., VEGF Trap, a VEGF blocker with potent
9 antitumor effect, proceedings of the National Academy of
10 Sciences USA, 2002, Volume 99, 11393-8, which we were just
11 looking at before as DTX 2745?

12 A. Can we go back to the previous paragraph that we were
13 looking at?

14 Q. I'm not sure. Let's start first. Can you just
15 confirm this is the citation, that I read it correctly?

16 A. It's just that, clearly, a mistake was made in the
17 position of the reference. It should have been after the first
18 sentence of that paragraph as opposed to the second sentence
19 because there was nothing about that point in that reference.
20 So it was -- that reference refers to the wrong sentence.

21 Q. Let me be clear. It's your testimony here today that
22 the citation support in a journal with your name on it in
23 peer-reviewed literature is wrong?

24 A. No. I'm saying it was inappropriately moved one
25 sentence. It should have been one sentence earlier.

GEORGE YANCOPOLOUS - CROSS

1 These things happen. It could have been done in --
2 at the editorial stage or somebody could have missed it. But
3 clearly the paper is not referring to anything about ophthalmic
4 use, but the previous sentence is the one that describes what
5 the VEGF Trap is.

6 Q. Again, I just want to be clear. It's your testimony
7 today that you believe that there is a mistake in your
8 journal -- in this journal publication?

9 A. There was a mistake in the position of -- how many
10 footnotes are in here? Yeah. It was a mistake in the position
11 of one in 50 or so footnotes. I'm sorry. By one position.

12 Q. Dr. Yancopoulos, I believe we've heard a lot from you
13 earlier today that you believe it was the properties of
14 aflibercept itself that allowed for your eight-week dosing
15 regimen to work where you believe it had failed with other
16 molecules, right?

17 A. For sure, part of the reason for the success was the
18 molecule. Without a molecule, you have nothing. On the other
19 hand, if it hadn't been delivered to that concentration and
20 purity and so forth, it quite possibly would not have worked
21 either. So it's a combination of many factors that allowed it
22 to actually work. Obviously, if we had given a tiny amount of
23 it, it would never have worked, so -- no matter how good the
24 molecule was.

25 Q. But ultimately, you believe your eight-week dosing

GEORGE YANCOPOLOUS - CROSS

1 regimen worked because you had a molecule you thought was a
2 better molecule, which was aflibercept?

3 A. And for many other reasons as well, including the
4 fact that we were able to concentrate and deliver enough of it
5 so we could last longer. If we gave one molecule of the
6 greatest blocker in the world, it obviously would not have
7 worked for two months.

8 Q. All right. Now, even though you had found this
9 extremely potent VEGF inhibitor, I believe, in late 1990s, you
10 said you were having some difficulty finding big pharma
11 partners to fund you?

12 A. Yes.

13 Q. And the lack of target validation in the clinic,
14 together with that lack of recognition of commercial
15 opportunities, also contributed to that difficult partnering
16 environment for Regeneron, fair?

17 A. Could you just repeat that.

18 Q. Sure. The lack of target validation in the clinic,
19 together with a lack of recognition of commercial
20 opportunities, initially led to a difficult partnering
21 environment for Regeneron, right?

22 A. Yes. Yes.

23 Q. Now, when it came to finding partners, one of the
24 first game changers, when it came to using VEGF inhibitors for
25 cancer indication, were the Avastin cancer results, right?

GEORGE YANCOPOLOUS - CROSS

1 A. Yes.

2 Q. And those came out around 2003?

3 A. Yes.

4 Q. And then the next game changer for Regeneron was the
5 clinical trial data that came out for Lucentis. That's what
6 allowed you to partner with Bayer, right?

7 A. That contributed to the partnership.

8 Q. That was a game changer, right, the Phase III
9 Lucentis data?

10 A. It contributed to the interest in the field, yes.

11 Q. Do you recall whether you called it a game -- the
12 Phase III Lucentis data a game changer that led to the global
13 collaboration with Bayer HealthCare for VEGF Trap-Eye?

14 A. It would not surprise me if I called the Lucentis
15 results a game changer. I think I referred to them that way
16 today. I don't know if I necessarily publicly linked them to
17 our deal. I couldn't remember whether I did that or not.

18 Q. Whether you said that publicly, internally you
19 understand that, right? That was what was -- that's what
20 incentivized or enticed Bayer to want to partner with you,
21 true?

22 A. Well, it was a major reason that the fact that, as
23 you said, it was now clinical validation in the field
24 contributed to somebody wanting to partner with us.

25 Q. Right. And it was the Phase III Lucentis data that

GEORGE YANCOPOLOUS - CROSS

1 was the driver on that for Bayer, right, in terms of wanting to
2 come to you?

3 A. Like I said, it was one of several things that
4 contributed. You have to ask Bayer if it was the major driver.

5 Q. By 2010 Lucentis was a 2 to \$3 billion market,
6 correct?

7 A. I don't remember the timing of when it became an
8 important drug in the revenues, but if you say so.

9 Q. If it would help you out, let's pull up DTX 2053.
10 And do you see that this is titled "RBC Capital Markets,
11 Moderator Phil Rosenfeld, October 1st, 9:00 a.m. Central Time"?

12 A. Yes.

13 Q. Do you recall receiving a copy of this transcript?

14 A. I don't recall. I may have.

15 Q. If it will help you out, I can give you the document
16 showing that this was attached to your email. Let's go ahead
17 and pull up what I'll designate as DTX 2053A.

18 Can you confirm that this is an email dated Tuesday,
19 October 19, 2020, from Murray Goldberg to Len Schleifer as well
20 as you and others? It says, "Attachments, transcript.doc."

21 A. That's what it says.

22 Q. It says, "Attached is the transcript of the
23 conference call that RBC hosted with Phil Rosenfeld and Quan
24 Nguyen re: Lucentis, Avastin, and VEGF Trap-Eye. Lots of
25 interesting observation."

GEORGE YANCOPOLOUS - CROSS

1 Do you see that?

2 A. Just trying to find the document in my book here.

3 What was the question?

4 Q. Sure. Just do you see what I just read out from the
5 highlighting?

6 A. I see it. I see the highlighting here.

7 Q. So does this help to refresh your recollection that
8 you probably did, in fact, receive a copy of the RBC
9 transcript?

10 A. This implies that I received it. Whether I read it
11 or not, this doesn't help me.

12 Q. But, nevertheless, you received a copy of it as part
13 of your ordinary customary business activities at Regeneron,
14 right? Through your email?

15 A. Yeah, looks like I received an email of this.

16 MS. MAZZOCHI: Your Honor, we move DTX 2053 into
17 evidence.

18 THE COURT: Any objection?

19 MS. OBERWETTER: Depends on the purpose for which it
20 is offered, Your Honor.

21 THE COURT: Fair enough.

22 Purpose?

23 MS. MAZZOCHI: Sure. The relevance is that there's
24 some information in there that they thought was interesting
25 about Lucentis and Avastin. It relates to some of the issues

GEORGE YANCOPOLOUS - CROSS

1 in the case that we're going to get into in terms of what
2 people were thinking at the time in 2010, which is shortly
3 before the patents were filed in this case.

4 THE COURT: What specific issues?

5 MS. MAZZOCHI: I don't know if you want me to say it
6 in front of the witness, Your Honor, but there are certain
7 things in there relating to, as stated here in the covering
8 email, hospital academic centers, Avastin, and private
9 practice, physician reimbursement, as well as -- I was actually
10 going to use it initially just to point out that they
11 acknowledge that the Lucentis market was over \$3 billion.

12 THE COURT: Any objection?

13 MS. OBERWETTER: Your Honor, it's a long document.
14 So I will reserve on further hearsay objections, but subject to
15 that, no, Your Honor.

16 THE COURT: So admitted.

17 (DTX 2053 was admitted.)

18 MS. MAZZOCHI: Thank you.

19 BY MS. MAZZOCHI:

20 Q. Dr. Yancopoulos, let's go back now to DTX 2053, and
21 let's look at the exhibits page 2, sixth paragraph down. And
22 can you confirm that in this transcript that was attached to
23 your email, it says, "Lucentis dominates the branded-approved
24 market with about 3 billion in sales"?

25 A. I see that.

GEORGE YANCOPOLOUS - CROSS

1 Q. Was that consistent with your recollection in that
2 time frame of 2010 that Lucentis had a market that was billions
3 in sales?

4 A. I probably knew that Lucentis had lots of sales. I
5 probably did not know the exact number.

6 Q. And did you also have an understanding that Avastin,
7 even though -- let me take a step back.

8 You understood that physicians in this 2010 time
9 frame were using Avastin off-label to treat wet AMD, right?

10 A. Yes.

11 Q. And the formulation that was being injected into
12 patients' eyes was a formulation that had been developed for
13 intravenous cancer use, right?

14 A. Yes.

15 Q. And physicians were, to your knowledge, still being
16 reimbursed by CMS, the federal government, in connection with
17 those uses, right?

18 A. Yes.

19 Q. All right. Now, one of the other things that this
20 conference call mentions is that in 2010 Lucentis was charging
21 about \$2,000 per injection.

22 Do you recall whether that price point also guided
23 your decision on how to price Eylea?

24 A. Yes, it did.

25 Q. Let's move on to DTX 913, exhibit page 1.

GEORGE YANCOPOLOUS - CROSS

1 Can you confirm that DTX 913 is an email thread that
2 was forwarded to you, your CEO Leonard Schleifer, and others on
3 Monday, February 5th, 2007, from Avner Ingerman about Lucentis
4 labeling that had been approved in Europe?

5 A. Yes.

6 Q. And one of the things Mr. Ingerman was forwarding to
7 you by this February 2007 date was the Lucentis labeling that
8 was approved in Europe?

9 A. Yes.

10 Q. And one of the things that the European regulatory
11 authorities did do is they approved Lucentis for both monthly
12 dosing in AMD as well as for use with a loading dose of one
13 injection per month for three consecutive months, followed by a
14 maintenance phase or monitoring that was described as being
15 given on a prn basis.

16 A. This was a highly controversial decision because it
17 was based on absolutely no data. And what we know in Europe,
18 they tend to do things because of cost as opposed to patient
19 benefit. And as has now been largely validated by subsequent
20 studies, that was a really inferior regimen that resulted in
21 lots of vision loss.

22 So it was a controversial decision for them to
23 approve a regimen that was never tested or studied in Phase III
24 trials and which resulted in worse vision outcome for patients.

25 Q. Dr. Yancopoulos, let's start first with you don't

GEORGE YANCOPOLOUS - CROSS

1 dispute that one of the things that the dosing instructions for
2 Lucentis included in the European Lucentis label was a loading
3 phase of one injection per month for three consecutive months?

4 A. Followed by prn dosing, which I just want to point
5 out was a very controversial decision at the time. It was
6 subsequently realized to be very inferior regimen that led to
7 poor visual outcomes for patients.

8 Q. I just want -- Dr. Yancopoulos, I just want a clear
9 yes or no. I understand you're going to say you don't like prn
10 dosing regimens. I just want to be clear that your
11 understanding, as of February 2007, is that the European
12 regulatory authorities approved a dosing regimen that had three
13 monthly loading doses followed by a maintenance phase that
14 would allow for an extended dosing interval beyond one month.

15 A. It was followed by prn dosing, which was a highly
16 controversial decision at that point in time, which resulted in
17 worse visual outcomes.

18 Q. Prn dosing allows for a regimen or a dosing interval
19 to go beyond one month, right?

20 A. Prn dosing is dosing as needed. That's what it
21 stands for.

22 Q. Right. And if the patient does not need the dose at
23 the next month, they can extend until the next office visit,
24 right?

25 A. The problem is, is how do you determine "as needed"?

GEORGE YANCOPOLOUS - CROSS

1 And the problem with prn dosing is it depends. "As needed"
2 means the patient starts to fail and that you treat them when
3 the patient fails. And what that has resulted in is in
4 systematic underdosing of patients and poor visual outcomes,
5 which is why it is no longer used.

6 Q. Well, with the DME data that you saw that was coming
7 out of Phase II when the doctors were allowed to dose the
8 patients as needed in a prn regimen, they actually got better
9 letter gains relative to what happened for the three loading
10 doses followed by the fixed eight-week dosing interval, right?

11 A. Well, as you said, in Phase II studies, prn at times
12 appeared like an attractive dosing regimen. When prn was
13 studied in large Phase III trials, such as CATT and HARBOR, it
14 resulted in the realization that the prn dosing regimen was a
15 very inferior regimen that resulted in worse visual outcomes,
16 which is why sophisticated drug developers don't focus and
17 count all their data just on Phase II. That's why you need
18 large Phase III trials, which have invalidated prn, which is
19 why prn is no longer utilized.

20 Q. That's your opinion, right? You haven't done any
21 surveys or anything in that regard that you've presented in
22 court today?

23 A. Well, I can tell you that prn is no longer utilized
24 by the community.

25 MS. MAZZOCHI: Your Honor, I'd just like a very, what

GEORGE YANCOPOLOUS - CROSS

1 I think, is a yes-or-no answer. Did he know that the European
2 labeling would allow for three loading doses followed by a
3 maintenance phase that would permit an extended dosing
4 interval? It either did or it didn't.

5 A. I think I've answered that question.

6 THE COURT: Try one more time, Doctor. Were you
7 aware that's what the label says?

8 THE WITNESS: Well, I think a yes-or-no answer can be
9 used in a misleading way, and I don't want to mislead anybody.
10 I think that there was -- as I described it, the full answer is
11 that this was a controversial decision, which has subsequently
12 been realized to have resulted in poor vision outcomes and is a
13 regimen that's no longer utilized.

14 BY MS. MAZZOCHI:

15 Q. But it's a regimen that you utilized in your own
16 clinical studies, right?

17 A. It was one of the many regimens that we included in
18 our various clinical trials.

19 Q. You were also, in the 2006 to 2007 time period,
20 tracking what was happening with Lucentis for the DME
21 indication, true?

22 A. State that again.

23 Q. You, in the 2006 to 2007 time period, were tracking
24 what was happening with Lucentis for the DME indication, true?

25 A. Yes.

GEORGE YANCOPOLOUS - CROSS

1 Q. Let's take a look at DTX 4070, a publication titled
2 "Vascular Endothelial Growth Factor is a Critical Stimulus for
3 Diabetic Macular Edema" by Quan Dong Nguyen, et al., from 2006.

4 You've seen this paper before, haven't you?

5 A. Folder just completely fell apart.

6 THE COURT: It's 4070.

7 MS. MAZZOCHI: The title is up on the screen for you
8 as well, Dr. Yancopoulos.

9 THE COURT: Just one second, Counsel. We're
10 reassembling the exhibit notebook.

11 THE WITNESS: Yes.

12 MS. MAZZOCHI: Your Honor, we move DTX 4070 into
13 evidence.

14 THE COURT: Any objection?

15 MS. OBERWETTER: No objection, Your Honor.

16 THE COURT: Without objection, so admitted.

17 (DTX 4070 was admitted.)

18 BY MS. MAZZOCHI:

19 Q. Now, Dr. Yancopoulos, back in 2006 when you first
20 reviewed this paper directed to the use of Lucentis for
21 diabetic macular edema, you believed that this study had a lot
22 of important implications, right?

23 A. Yes, I did.

24 Q. And one of the reasons why you believed the study had
25 very important implications is because it showed patients had

GEORGE YANCOPOLOUS - CROSS

1 substantial visual gain, right?

2 A. Can you keep going?

3 Q. I'm just saying, do you recall stating --

4 A. I actually showed Figure 4 from this paper in the
5 Bayer presentation. That was what we spent time on in the
6 previous discussion, and that figure summarized why I thought
7 this paper important because in Figure 4 it clearly shows that
8 Lucentis did not appear to last for two months. It only lasts
9 for one month. That's why I thought this paper was important,
10 as we summarized in the Bayer presentation that I showed, if
11 you want to go to Figure 4.

12 Q. I'm asking a different question, sir, and I'd
13 appreciate it if you just try focusing on what I'm asking you.

14 You characterized the results of this paper as
15 showing that these patients have substantial visual gain,
16 right?

17 A. I don't know if I characterized, but I would
18 characterize that they had substantial vision gain, yes.

19 Q. Let's pull up DTX 8127, exhibit page number 1.

20 Can you confirm that this is an email from you to
21 Peter Powchik and Neil Stahl and others dated Thursday,
22 December 7, 2006, subject line, "Lucentis pH 1 in DME and
23 implications, attachments, read Lucentis pH 1 DME."

24 Is that your email?

25 A. Yes.

GEORGE YANCOPOLOUS - CROSS

1 Q. And if you take a look at the second point that you
2 put in your email, did you indicate that these patients have
3 substantial visual gain?

4 A. Yes.

5 Q. Okay. Did you say yes?

6 A. Yes.

7 Q. Thank you.

8 All right. Attached to this particular exhibit -- so
9 let's just stay in this one since you had the paper -- a
10 version of the article attached.

11 A. What was the DTX for that email?

12 Q. 8127.

13 A. Could you put that back up for a second?

14 Q. We've got your -- oh, you want the email back up?

15 A. Yeah.

16 Q. Sure.

17 A. Because like I said, the most important point is
18 Point 1, which says that "Lucentis clearly does not last past
19 four weeks, according to this study."

20 So as I said, that was the major point to me of this
21 paper, Point 1, as I summarized in this email, and as was
22 detailed in the Bayer presentation that we showed before. That
23 was the major take-home message from this paper.

24 Q. Let's go to DTX 8127, the actual paper itself, and
25 let's go to the "Methods" section that appears on the second

GEORGE YANCOPOLOUS - CROSS

1 page of the exhibit.

2 Can we agree that ten patients with chronic DME
3 received, as of this publication date, intraocular injections
4 of 0.5 milligrams of ranibizumab at baseline, and at one, two,
5 four, and six months.

6 A. That's what it says.

7 Q. And if they -- the patients received a dose at
8 baseline and at one, two months, those would be three loading
9 doses spaced a month apart, right?

10 A. Yes.

11 Q. And then the next dosing interval was eight weeks
12 later at month four?

13 A. Where does it say that here?

14 Q. Where it says at baseline and at one, two, four, and
15 six months, right?

16 A. Yes.

17 Q. All right. So the fourth dose in the regimen would
18 have been eight weeks after the third dose in the regimen,
19 right?

20 A. This is exactly the data that we went over, which
21 actually showed that Lucentis at eight weeks didn't last, the
22 one with the red arrows and the bracket that said Lucentis
23 doesn't last eight weeks.

24 MS. MAZZOCHI: Your Honor, I'm really trying to move
25 things along here. It's not going to go very well if the

GEORGE YANCOPOLOUS - CROSS

1 witness argues with me at every single opportunity.

2 THE COURT: Repeat your question, Counsel.

3 MS. MAZZOCHI: Sure.

4 BY MS. MAZZOCHI:

5 Q. My question, Dr. Yancopoulos, is was there an
6 eight-week, or two-month, separation between the third dose in
7 the regimen and the fourth dose in the regimen? Yes or no.

8 A. There was an eight-week separation that resulted in
9 lack of vision gain.

10 Q. I'm just -- I'm not asking for additional commentary.
11 I just want to know --

12 A. I'm providing useful context. I don't want to say
13 something out of context.

14 THE COURT: Everybody, questions are asked, Doctor.
15 You may answer them and provide context within reason.

16 Next question.

17 BY MS. MAZZOCHI:

18 Q. Can you confirm that the next -- that the -- there
19 were then also -- there was a second eight-week dosing interval
20 between four and six months?

21 A. Yes. There was another eight-week interval that also
22 failed to result in visual gain.

23 Q. Dr. Yancopoulos, nevertheless, in your covering
24 email, you did note that, overall, at the end of this regimen,
25 patients did, in fact, experience gains in visual acuity and

GEORGE YANCOPOLOUS - CROSS

1 improvements -- I'm sorry -- gains in visual acuity.

2 A. Well, we had a context, because the most important
3 point was Point 1 which says, "Lucentis, which clearly does not
4 last past four weeks, according to the study." That's the
5 take-home message. That was why I made that whole figure for
6 the Bayer presentation, not what you're trying to seemingly
7 imply, that eight-week dosing worked. The whole point of my
8 email says Lucentis clearly does not last past four weeks.
9 Clearly, eight-week intervals did not work.

10 Q. I am asking at the conclusion of the study, did the
11 patients experience an improvement in visual acuity?

12 A. From their baseline levels.

13 Q. Yes. And --

14 A. That's not what Point 2 says, though, in the email.

15 Q. And compared to their baseline levels, by the end of
16 the dosing regimen, patients did, in fact, experience an
17 improvement in macular volume?

18 A. I'm really confused here because, if what you're
19 trying to imply is that Lucentis every two months would have
20 worked, clearly, that's not the case.

21 So is that what you're trying to imply?

22 Q. All I'm asking, Dr. Yancopoulos, is did patients
23 overall at the end of the regimen experience an improvement in
24 their vision compared to baseline?

25 A. As they did in the PIER regimen, which is

GEORGE YANCOPOLOUS - CROSS

1 every-three-month dosing.

2 Q. And they also experienced an improvement in macular
3 volume at the end of the dosing regimen compared to baseline,
4 right?

5 A. The question is were they achieved as good --

6 THE COURT: Doctor, Doctor, you need to answer the
7 question that's asked.

8 Will you repeat that question, Counsel.

9 BY MS. MAZZOCHI:

10 Q. Yes. Dr. Yancopoulos, can you confirm that the
11 patients in this study at the end of the regimen did, in fact,
12 experience an improvement in macular volume?

13 A. For context, they achieved improvements. Nowhere in
14 this study does it show that they improved -- achieved
15 improvements that would be equivalent to that to monthly
16 ranibizumab.

17 Q. I wasn't asking you that question, sir.

18 A. That is the relevant question.

19 THE COURT: Doctor, with all due respect, that's my
20 decision as to what questions are relevant or not.

21 The question was answered. Move on, Counsel.

22 BY MS. MAZZOCHI:

23 Q. Let's take a look at Example 5 of your '572 patent,
24 which is in PTX 3. I believe it's around page 22 of the
25 exhibit in Column 14.

GEORGE YANCOPOLOUS - CROSS

1 A. Is this in your book or in my prior book?

2 Q. It's in your prior book, PTX 3. Lawyers kill a lot
3 of trees, but we do try to not repeat exhibits if we don't have
4 to.

5 THE COURT: What page in that exhibit, Counsel?

6 MS. MAZZOCHI: It is exhibit page 20, Column 14,
7 starting at lines -- around 30 to 50. We've got it up here on
8 the screen for you as well.

9 BY MS. MAZZOCHI:

10 Q. Dr. Yancopoulos, can you confirm that the dosing
11 regimen set forth in Example 5 of your '572 patent is
12 described -- one of the arms is described as giving three
13 initial doses of 2 milligrams VEGFT once every four weeks,
14 i.e., at baseline and weeks 4 to 8, followed through week 52 by
15 either once every eight weeks dosing or as-needed dosing with a
16 very strict repeat dosing criteria, prn.

17 A. Yes.

18 Q. And the dosing regimen that was described as three
19 initial doses, i.e., at baseline and weeks four and eight,
20 every four weeks, followed by every eight weeks dosing, at
21 least for the first six months, tracked the Lucentis DME study
22 we were just looking at in terms of the steps of the regimen
23 being the same?

24 A. The steps of the regimen but not the visual acuity
25 outcomes, which track very differently.

GEORGE YANCOPOLOUS - CROSS

1 Q. Dr. Yancopoulos, the name that Regeneron gave to the
2 clinical trial that corresponds to your patent's Example 5 was
3 the Da Vinci trial, right?

4 A. Yes.

5 Q. Do you recall who made the decision to use three
6 monthly loading doses?

7 A. The ultimate decision would have probably been on me,
8 after consultation with our team, though I can't specifically
9 remember that at this point in time, 10 to 15 years later.

10 Q. Well, you do remember it or you don't remember it.
11 Do you not remember?

12 A. I don't specifically remember it, but I assume that
13 that was probably the case.

14 Q. Let's go with what you actually do or don't remember.

15 Now, even though -- well, you were not listed as a
16 coauthor for the publication about this clinical trial, right?

17 A. If you can point me to the paper.

18 Q. Sure. Let's pull up PTX 686, first page. This is
19 the Diana Do, reporting on the outcomes of the Da Vinci study.

20 Can you confirm that you are not even listed as a
21 coauthor on the article reporting on this study?

22 A. I can see that I'm not listed on the list.

23 Q. Now, you talked a bit about this decision to move
24 from three to five loading doses for the Phase III clinical
25 trials. Is there data that you put into your '572 and '601

GEORGE YANCOPOLOUS - CROSS

1 patent specifications for any rationale, such as about reaching
2 a plateau in the context of DME therapy, that would justify
3 increasing the number of loading doses before switching to the
4 eight-week dosing?

5 A. I can't say right now without reading the patent
6 whether there's anything in there; but as I said before, that
7 decision was based on a million points of data, as we saw
8 before in this book and in the presentations and so forth. How
9 much of it might be in the patent, I couldn't tell you without
10 reading the whole patent right now.

11 Q. All right. Again, do you remember that I asked you
12 this question at your deposition?

13 A. Do I remember that you asked me this specific
14 question at the deposition?

15 Q. Right.

16 A. No.

17 Q. All right. Well, let's put up DTX 3196, exhibit
18 page 11, which is your deposition transcript.

19 THE COURT: I'm sorry, Counsel. What exhibit number
20 is that again?

21 MS. MAZZOCHI: 3196.

22 THE COURT: Thank you.

23 MS. MAZZOCHI: Exhibit page 11, transcript lines
24 40:24 through 41:14.

25

GEORGE YANCOPOLOUS - CROSS

1 BY MS. MAZZOCHI:

2 Q. Dr. Yancopoulos, did I ask you, "Well, is there any
3 data that you put in your '601 patent or any rationale about
4 reaching this plateau in the context of DME's therapy that
5 would justify increasing the number of loading doses before
6 switching to the eight-week dosing?"

7 And did you give the answer, "In my attempt to read
8 the whole patent very quickly earlier, I'm not aware of seeing
9 that data shown, though it could well be in some of the many
10 references that are included."

11 Was that the question you were asked and the answer
12 you gave?

13 A. If that's what the transcript says, I guess that's
14 what I said.

15 Q. Okay. Let me take you back to your -- well,
16 actually, let's try to move along.

17 Let's actually switch gears for a minute and talk a
18 little bit more about some of these formulation issues.

19 If you could take a look -- we'll go back to PTX 3
20 again, and now we're going to go to exhibit page 16, which
21 corresponds to Column 5. And I'd like to direct your attention
22 to lines 64 to 67 in your '572 patent.

23 Do you have those lines on the screen?

24 A. This is Column 6?

25 Q. Column 5, lines 64 to 67 in your '572 patent.

GEORGE YANCOPOLOUS - CROSS

1 A. Yes.

2 Q. Did you state there, "A multitude of appropriate
3 formulations can be found in the formulary known to all
4 pharmaceutical chemists, Remington's Pharmaceutical Sciences,"
5 and then gives the citation.

6 A. Yes.

7 Q. Was this a true statement you made in your patent
8 there?

9 I'm just asking if it's a true statement,
10 Dr. Yancopoulos, that you put in your patent.

11 A. Right. It's caveated right below, "Provided that the
12 VEGF antagonist is not inactivated by the formulation, the
13 formulation is physiologically compatible and tolerable with
14 the route of administration." Yes.

15 Q. Dr. Yancopoulos, I'd like to now direct your
16 attention to one of your other VEGF patents, which is DTX 2730,
17 and we'll start with exhibit page 1. U.S. Patent Number
18 7,303,747, which issued on December 4th, 2007.

19 Do you see that?

20 A. Yes.

21 Q. And you're a named inventor on this patent?

22 A. Yes.

23 Q. Do you remember if this patent actually covers your
24 aflibercept molecule?

25 A. I'd have to look at this patent. Was it in my --

GEORGE YANCOPOLOUS - CROSS

1 your book?

2 Q. Oh, yeah. You've got a copy of it in the binder that
3 we gave you.

4 A. Under --

5 THE COURT: 2730.

6 MS. MAZZOCHI: 2730.

7 Your Honor, while Dr. Yancopoulos is looking for
8 that, we'd like to move DTX 2730 into evidence.

9 THE COURT: Any objection?

10 MS. OBERWETTER: No objection, Your Honor.

11 THE COURT: Without objection, so admitted.

12 (DTX 2730 was admitted.)

13 BY MS. MAZZOCHI:

14 Q. Dr. Yancopoulos, to try to move things along, I'd
15 like to direct your attention to exhibit page 13 of DTX 2730,
16 specifically Column 1, the brief summary of the invention of
17 your '747 patent at lines 46 to 55.

18 Do you see that on the screen?

19 A. Yes.

20 Q. One of the things your invention in this patent was
21 about involved ameliorating an eye disorder, right?

22 A. Yes.

23 Q. And if we take a look here -- or starting around
24 line 50, one of the eye disorders you listed included
25 age-related macular degeneration? It's right there on the

GEORGE YANCOPOLOUS - CROSS

1 screen, sir.

2 A. Yes.

3 Q. And another embodiment you listed there was the eye
4 disorder to treat diabetic retinopathy?

5 A. Yes.

6 Q. Now let's go to the 15th page of this exhibit, which
7 is your '747 patent at Column 5, lines 3 to 26. And we've got
8 that up on the screen there for you.

9 Do you see that?

10 A. Yes.

11 Q. And do you see the text that is highlighted that
12 starts at line 25, over to line 26, that reads, sequence --
13 "SEQ ID" -- meaning sequence ID -- "and then VEGFR1R2-Fc delta
14 C1(a)."

15 Do you see that?

16 A. Yes.

17 Q. That's the sequence ID for aflibercept, right?

18 A. That, I'm not sure of.

19 Q. You're not sure?

20 A. I don't know.

21 Q. All right. Well, let's pull up PTX 3, which uses
22 your '572 patent we were looking at earlier. Let's go to -- I
23 think it's around exhibit page 11. Let's try 14. There we go.
24 Column 2, lines 51 to 56.

25 Isn't it true that you stated here that

GEORGE YANCOPOLOUS - CROSS

1 VEGFR1R2-Fc delta C1(a) was aflibercept?

2 A. It says here that that name refers to aflibercept,
3 yes.

4 Q. Okay. And --

5 A. I don't know that sequence corresponds to
6 aflibercept, but yes, the name here says it's otherwise known
7 as aflibercept.

8 Q. Okay. And that was a true statement you made in your
9 '572 patent asserted here, right?

10 A. I believe so.

11 Q. All right. Let's go back then to DTX 2730, which is
12 your '747 patent, exhibit page 16.

13 A. Which patent is this?

14 Q. This is your '747 patent, which is DTX 2730. And
15 we'll go to exhibit page 16, and I'd like to direct your
16 attention to Column 7, lines 5 through 28.

17 Do you see there there's a heading that's titled
18 "Methods of Administration and Compositions"?

19 A. Yes.

20 Q. And does it also say, starting at line 13, that
21 compositions -- strike that.

22 I'm sorry. I wanted to direct your attention to the
23 last part of this. It says -- starting at line 26, it says,
24 "Aqueous compositions of the invention have ophthalmically
25 compatible pH and osmolality." Do you see that?

GEORGE YANCOPOLOUS - CROSS

1 A. I see that.

2 Q. Can we agree that your '747 patent taught to put VEGF
3 inhibitor compounds, like aflibercept, into pharmaceutical
4 formulations that had ophthalmically compatible pH and
5 osmolality?

6 A. I don't know -- you're using certain legal terms, and
7 I'm not the guy who writes the patents. I don't know what you
8 mean by "taught." So I can't -- I can't comment on that. It
9 sounds like that means something that I don't understand.

10 Q. Okay. We'll phrase it this way for you.

11 Can we agree that on exhibit page 16 of DTX 2730,
12 your 2007, '747 patent at Column 7, lines 26 to 28, you wrote
13 that "Aqueous compositions of the invention have ophthalmically
14 compatible pH and osmolality"?

15 A. Yeah. And let me also clarify. I didn't write this
16 patent, but -- we have patent attorneys who write these
17 patents. But it says in here, "Aqueous compositions of the
18 invention have ophthalmically compatible pH and osmolality."
19 Yes, that's what it says.

20 Q. Do you have an understanding that an aqueous
21 composition with an ophthalmically compatible pH and
22 osmolality, as you use that phrase in your '747 patent, will be
23 isotonic?

24 A. Ophthalmologically compatible could or could not
25 include isotonic.

GEORGE YANCOPOLOUS - CROSS

1 Q. But if it's ophthalmically compatible osmolality,
2 because that's the particular metric, right? pH plus
3 osmolality will determine whether it's isotonic?

4 A. Compatible means compatible. It doesn't mean the
5 same. Isotonic means, by definition, the same. Compatible
6 means something that would be compatible, which does not have
7 to be the same.

8 Q. Let me ask you this: When you used the term
9 "isotonic" in your '572 patent, did you intend for it to just
10 mean the same as what we get in the eye?

11 A. Well, isotonic, by definition, means the same
12 tonicity. So, yes, I intended it to mean the same tonicity.

13 Q. Do you know whether there's any range that is
14 permitted for that tonicity within the eye?

15 A. For compatibility? For what purpose? For
16 compatibility?

17 Q. Any purpose.

18 A. Well, yes, there can be -- compatibility has to be
19 tested, and presumably a range of tonicities have been used and
20 can be used that would be compatible with research in the eye.
21 It doesn't mean they have the same tonicity. That's a chemical
22 term, "same tonicity." "Iso" means same tonicity.

23 Q. And if it is iso-osmolar, will it also be isotonic
24 based on your understanding of how you use the term isotonic
25 and osmolality in your patents?

GEORGE YANCOPOLOUS - CROSS

1 A. Now we're going back to chemistry 101. I believe
2 that iso-osmolar would be the same as isotonic, but this is not
3 something that I'm an expert on.

4 Q. If we can compare what you said in your '747 patent
5 about some of these formulations with what you have in your
6 '572 patent, do you believe that your '747 patent's description
7 of pharmaceutical formulations in the context of isotonic added
8 anything different beyond what we saw in your '747 patent about
9 requirements for the isotonic solution?

10 A. I think you said '747 twice; so I'm a little
11 confused.

12 Q. I'm sorry '747 patent versus '572 patent. Let me
13 start over because I don't want you to be confused.

14 Did you add anything conceptually that you considered
15 to be new in terms of describing an aqueous composition of the
16 invention that has an ophthalmically compatible pH and
17 osmolality that we saw in the '747 patent as compared to what
18 you talked about for pharmaceutical formulations that were
19 isotonic in your '572 patent when we were looking at Column 6,
20 starting around lines 18 to 34?

21 A. Ophthalmically compatible pH and osmolality would
22 include, as we said, a range that could, for example, be
23 hypertonic, hypotonic, or isotonic. We specifically
24 highlighted the isotonic solution in the '572 patent.

25 Q. Now, the description of isotonic solution that you

GEORGE YANCOPOLOUS - CROSS

1 provide here in your '572 patent, that's not something that you
2 actually came up with, right?

3 A. No, I did not.

4 Q. And you did not actually come up with this idea of a
5 formulation that has the isotonic solution containing glucose
6 that may be used in combination with an appropriate solublizing
7 agent, such as an alcohol, right?

8 A. As I said before, I relied on our formulation experts
9 to develop and recommend and show me data as to which was the
10 best formulation that they had recommended.

11 Q. And just to be clear, when we're looking at this
12 isotonic solution in your '572 patent, you did not actually
13 come up with the idea of a formulation that was isotonic and
14 also had a solublizing agent, right?

15 A. I did not come up with the formulation. As I said, I
16 relied on my experts and chose between the choices that they
17 gave me and the recommendations at the time.

18 Q. Sure. I'm talking more specifically about what you
19 actually wrote here in -- or what is written here in your
20 patent.

21 Do you believe you came up with an idea of an
22 isotonic solution that may be used in combination with an
23 appropriate solublizing agent?

24 A. No, I did not come up with that idea.

25 Q. All right. Did you come up with the idea of an

GEORGE YANCOPOLOUS - CROSS

1 isotonic solution that might also be combined with a nonionic
2 surfactant?

3 A. No, I did not come up with that idea.

4 Q. Let's go ahead and jump ahead to exhibit -- let's go
5 ahead and pull up DTX 5073.0001. So, Dr. Yancopoulos, let's go
6 through a little bit with the Court about what the Eylea
7 formulation was that was used in your clinical trials.

8 Dr. Yancopoulos, do you dispute that the ingredients
9 of the 2-milligram Eylea formulation that the FDA approved in
10 November 2011 were also the same ingredient list for the
11 2-milligram formulation that was actually given to the doctors
12 performing the VIEW 1-VIEW 2 clinical trials with aflibercept?

13 A. Do I dispute?

14 Q. Right.

15 A. Can you ask that again?

16 Q. Sure. Maybe I'll -- since you don't like the word
17 "dispute," I'll rephrase it this way.

18 Do you agree that the Eylea formulation that the
19 FDA -- the ingredient list for the Eylea formulation that the
20 FDA approved in November of 2011 was the same formulation
21 ingredient list for the 2-milligram formulation that was
22 actually given to the doctors performing the VIEW 1 and VIEW 2
23 clinical studies?

24 A. I believe it was.

25 Q. Okay. And if we can take a look at the first page of

GEORGE YANCOPOLOUS - CROSS

1 DTX 5073, can you see that this is titled 2.7.1, "Summary of
2 Biopharmaceutic Studies and Associated Analytical Methods"?

3 A. Yes.

4 Q. And do you have an understanding that these are the
5 types of things that are submitted by Regeneron in connection
6 with its BLA with the FDA?

7 A. Yes.

8 Q. Is this work that you, as president and chief
9 scientific officer, ultimately were responsible for overseeing?

10 A. These functionalities reported up to me. I did not
11 directly oversee them.

12 Q. That's fine.

13 MS. MAZZOCHI: Your Honor, we move DTX 5073 into
14 evidence.

15 THE COURT: Any objection?

16 MS. OBERWETTER: No objection.

17 THE COURT: Without objection, so admitted.

18 (DTX 5073 was admitted.)

19 BY MS. MAZZOCHI:

20 Q. And let's go ahead and move along to -- let's have
21 you take a look at DTX 5082, and we'll start again with exhibit
22 page number 1. This is a part of the Regeneron BLA that is
23 titled "2.3.P Drug Product."

24 Do you see that?

25 A. Yes.

GEORGE YANCOPOLOUS - CROSS

1 Q. And is this also work that you, as president and
2 chief scientific officer, were ultimately responsible for
3 overseeing?

4 A. When you said formulation development, that did
5 report up to me. If we're talking about some of the aspects
6 that are under here -- you know, the manufacturing, the drug
7 process, and so forth -- that reports up to our head of
8 manufacturing.

9 Q. And does your head of manufacturing report to you, or
10 do they just report to your CEO?

11 A. They report to our CEO.

12 Q. Let's go ahead, and we'll move along.

13 Now, ultimately, though, Dr. Yancopoulos, you would
14 agree that pharmaceutical formulations is not an area of
15 expertise for you, right?

16 A. Yes, I would agree.

17 Q. Dr. Yancopoulos, we did look earlier -- I think it
18 was PTX 311. Let's go ahead and call that up.

19 This was your 2012 article titled "Intravitreal
20 Aflibercept VEGF Trap-Eye in Wet Age-Related Macular
21 Degeneration."

22 Do you have that?

23 A. Yes.

24 Q. Let's take a look as well at the exhibit that you had
25 pulled up. I believe it was PDX 3-0311-B. See if we can pull

GEORGE YANCOPOLOUS - CROSS

1 that up on the screen. I think it was the one that had what
2 you called the integrated data on it.

3 MS. MAZZOCHI: Pardon me, Your Honor, with a lot of
4 these exhibits going on.

5 BY MS. MAZZOCHI:

6 Q. All right. There we go. Dr. Yancopoulos, is this
7 the slide -- can you confirm that up on the screen you have
8 PDX 3-0311-B?

9 A. Yes.

10 Q. And this is one of the slides you testified about in
11 your direct examination?

12 A. Yes.

13 Q. Can you confirm that, if we take a look at the
14 integrative data, the dose that performed the best in terms of
15 letter ranking was the 2q4 regimen in yellow, yellow-orange?

16 A. Numerically, it had a higher number at the end;
17 statistically, these were all no different from each other.

18 Q. Right. And my questions are just going to be at the
19 end of the dosing regimen. So can we agree, then, that the 9.3
20 2q4 aflibercept monthly dosing regimen was the best numerically
21 in terms of number of letters gained?

22 A. Well, in VIEW 1 it was numerically better; in VIEW 2
23 it was actually numerically worse. They were reversed to the
24 point that I made before, and then they were within less than a
25 letter difference at the end of the trial.

GEORGE YANCOPOLOUS - CROSS

1 Q. That's why I asked you about the integrated data. So
2 can you confirm that at Week 52 the integrated data curve from
3 the VIEW 1-VIEW 2 study put the monthly aflibercept dosing
4 regimen numerically at the top with 9.3 letters gained?

5 A. There was not statistically significant difference of
6 0.9 letters, in which the 2q4 was 0.9 letters numerically
7 different from the 2q8, but not statistically different.

8 THE COURT: Yes or no, Doctor.

9 BY MS. MAZZOCHI:

10 Q. Do you need me to repeat the question?

11 A. Yes.

12 Q. Can you confirm that in the integrated data set for
13 the VIEW 1-VIEW 2 clinical studies, the aflibercept 2q4 dosing
14 regimen numerically performed the best with 9.3 letters?

15 A. It was numerically higher.

16 Q. Right. And then the next numerically higher number,
17 at 8.7 letters, was ranibizumab dosed monthly, right, with 8.7
18 letters gained?

19 A. I think this was a misrepresentation of the data. I
20 can't -- I can't in good conscience say yes to things that are
21 misrepresentations. You're making -- trying to make a point
22 about .3-letter differences that are statistically
23 insignificant, that didn't repeat in the two studies.

24 Q. All I'm asking you, Dr. Yancopoulos -- this is your
25 slide --

GEORGE YANCOPOLOUS - CROSS

1 A. Right.

2 Q. -- can you confirm that the integrated data set you
3 presented here had ranibizumab monthly, R q4, at 8.7 letters?

4 A. It had it at 8.7.

5 Q. All right. And, likewise, right below that, at 8.4
6 letters, was your aflibercept 2q8 regimen, which was three
7 monthly loading doses followed by every-eight-week dosing?

8 A. At 8.4 for 2q8.

9 Q. And your -- that at 8.3 letters was your
10 0.5-milligram dose given monthly, right?

11 A. Those are the numbers.

12 Q. And if we look at your VIEW 1-VIEW 2ETDRS letters in
13 A and B, even -- can we agree that the letter range variation
14 for the monthly Eylea dosing was from 7.6 to 10.9?

15 A. Yes.

16 Q. And can we agree that for the ranibizumab, the
17 ultimate letter range in VIEW 1 and VIEW 2 ranged from 8.1 to
18 9.4?

19 A. Yes.

20 Q. And can we agree that for the 2q8 dosing -- so the
21 three loading doses followed by eight-week dosing with
22 aflibercept -- that dosing range was from 7.9 to, I believe,
23 8.9?

24 A. Yes.

25 Q. And for the 0.5 dose of aflibercept given monthly,

GEORGE YANCOPOLOUS - CROSS

1 your letter variation range was from 6.9 to 9.7 across those
2 trials?

3 A. Yes.

4 Q. Now, when it comes to this Heier -- oh, I'm sorry.
5 When it comes to the Heier publication that you're a coauthor
6 on, PTX 311.001, you did at some point submit a version of this
7 publication to the *New England Journal of Medicine*, right?

8 A. Yes.

9 Q. And the *New England Journal of Medicine* rejected your
10 manuscript?

11 A. Yes.

12 Q. All right. Let me put before you DTX 915. It's also
13 in your binder, and I'd like to go to the first page of the
14 exhibit.

15 Can you confirm that DTX 915, the first page includes
16 an email from you to Bala Dass and others dated Thursday,
17 January 19, 2012?

18 A. Yes.

19 Q. And did you write the commentary in this email? "I
20 would agree with Peter and Dave and do whatever is necessary to
21 get the first paper out in NEJN," meaning *New England Journal*
22 *of Medicine*.

23 A. Whatever is necessary refers to the line below that
24 says "withdraw a related paper from consideration in another
25 journal."

GEORGE YANCOPOLOUS - CROSS

1 Q. By the way, that was -- you did write commentary in
2 this email, right?

3 A. Right.

4 MS. MAZZOCHI: Your Honor, we move DTX 915 into
5 evidence.

6 THE COURT: Any objection?

7 MS. OBERWETTER: No objection.

8 THE COURT: Without objection, so admitted.

9 (DTX 915 was admitted.)

10 MS. MAZZOCHI: Thank you, Your Honor.

11 BY MS. MAZZOCHI:

12 Q. If we go to the second page of this exhibit within
13 the email string, did you receive various reviewer comments
14 about your manuscript from the *New England Journal of Medicine*?

15 A. Yes.

16 Q. All right. Let's take a look at a few of them.

17 If we can go to exhibit page 6 in DTX 915.

18 I'd like to go through a couple of the comments from
19 Reviewer Number 1, particularly Item 18, which was commenting
20 on your manuscript page number 11. Let's pull that up for you
21 on the screen.

22 Do you have it?

23 A. Yes.

24 Q. And did they -- if we go to the -- three, four, five,
25 six -- seventh line down in terms of talking about the CATT

GEORGE YANCOPOLOUS - CROSS

1 study, did the reviewers tell you that the -- I'm sorry -- in
2 talking about your study, that the average number of injections
3 in your VTE, meaning VEGF Trap-Eye, 2q8 group was 7.6 and the
4 average number of injections -- average number for the
5 ranibizumab prn group equivalent in efficacy to ranibizumab
6 monthly was 6.9.

7 Is that what the reviewer wrote to you?

8 A. I see that. I'm not sure it's correct, though.

9 Oh, this is the ranibizumab prn group. I'm sorry.
10 This is not in our study. This is comparing cross-study
11 comparisons. Sorry. I didn't understand comparing our study
12 from the study from CATT, yes.

13 Q. Yup. And then the reviewer took that data and said,
14 "While the argument of decreased burden for the patient by
15 eliminating five monthly monitoring visits in the first year is
16 solid, the argument for increased patient safety is overstated,
17 particularly relative to ranibizumab prn."

18 Is that one of the comments you received?

19 A. Yeah. This is comparing our regimen to a regimen
20 that is now obsolete because it's considered not as effective,
21 yes.

22 Q. Sir, I just wanted confirmation that these are the
23 comments you received. Because you're not an expert, I'm
24 actually trying to not invite commentary. I'm just trying to
25 confirm the commentary you received.

GEORGE YANCOPOLOUS - CROSS

1 A. I'm just putting it into context.

2 Q. Let's take a look at exhibit pages 6 and 7, the text
3 that goes from the bottom of page 6 in DTX 915 and over to the
4 top of page 7, which are some of the comments from Reviewer
5 Number 2.

6 If we look at the top paragraph of the text on
7 DTX 915, exhibit page 7, Reviewer 2 gave you the feedback that
8 "The primary finding that may differentiate VEGF Trap as
9 compared to the many prior reports is an apparently noninferior
10 semimonthly dosing schedule as opposed to monthly dosing.
11 Although clearly of burden -- benefit to patients and
12 physicians, this is not a major conceptual advance."

13 That was the feedback you got from Reviewer Number 2,
14 right?

15 A. That was.

16 Q. Okay. Now let's go a little bit more than halfway
17 down, exhibit page 7 in DTX 915. We now have comments for the
18 author from Reviewer Number 3 that I'd like to pull up on the
19 screen.

20 And let's take a look at Reviewer Number 3's first
21 full paragraph of text and the second-to-last sentence.

22 Reviewer Number 3 said of your manuscript, "The paper
23 also lacks balance and is much too heavy-handed in its
24 treatment of every-two-month dosing, so much so that it comes
25 off as the beginning of a marketing campaign."

GEORGE YANCOPOLOUS - CROSS

1 Was that feedback that you received from Reviewer
2 Number 3?

3 A. That is what he wrote.

4 Q. Let's go to exhibit page 11 in DTX 915 and look at
5 some more feedback you received from Reviewer Number 3. And
6 this time I'll ask that the top paragraph be put up on the
7 screen. So we're in exhibit page 11. Let's pull up the top
8 paragraph. It's pretty lengthy. We'll scroll on through it.

9 Let's begin around the fifth line down on DTX 915,
10 page 11. It says -- actually, to be fair, let me do the whole
11 sentence.

12 So do you see starting in the third line down there's
13 a reference to the CATT and HARBOR clinical trials?

14 A. Yes.

15 Q. And in the CATT clinical study, ranibizumab,
16 Lucentis, was tested head to head against Avastin, bevacizumab,
17 in connection with wet AMD, right?

18 A. Yes.

19 Q. And they found that there was really no clinical
20 difference in that class -- in that CATT study between the two
21 drugs, right?

22 A. No. That's incorrect.

23 So as I said, at this time, prn was very much in
24 favor. And particularly with the early results from CATT and
25 HARBOR, some people were failing to see the problems with prn.

GEORGE YANCOPOLOUS - CROSS

1 Once the field evolved, probably a year or two after
2 this, especially when they had the subsequent year's data, it
3 became very clear that these prn regimens were just not
4 delivering the visual acuity outcomes. And the evidence for
5 this is they rapidly dropped out of favor and were no longer
6 being utilized to this day. So these experts are among the
7 experts at the time that had it wrong in terms of favoring at
8 that time based on early data prn regimens.

9 So I don't want to be -- I had publicly at that time
10 pointed out the difficulties with prn dosing which have since
11 been validated, though, as I said, people at the time were
12 still stuck in that regimen. But history has proven these
13 ineffectual and obsolete now.

14 MS. MAZZOCHI: Your Honor, I'd like to move to strike
15 because my question --

16 THE COURT: Denied. That motion is denied. We're
17 reviewing random comments from reviewers for a medical journal.
18 I'm about to ask the question what is the relevance of this
19 line of questioning anyway, Counsel?

20 MS. MAZZOCHI: Your Honor, the relevance of this line
21 of questioning is that many of the arguments that we're going
22 to hear from Regeneron's witnesses in connection with
23 unexpected results are making exactly the type of arguments
24 that were made in that Heier paper that the -- that Regeneron's
25 going to rely on.

GEORGE YANCOPOLOUS - CROSS

1 And they're trying to treat those comments that are
2 in the Heier paper as if they are gospel and uncontested. And
3 our point is that no, in fact, there were people who disagreed
4 with some of the premises that you put into that paper;
5 therefore, it shouldn't be accepted as truth in this case.

6 THE COURT: This is getting to one of the many
7 reasons the Court denied all the motions for summary judgment.
8 I think there's a genuine dispute that the doctor just
9 articulated on that. So the motion to strike is denied. You
10 may ask your next question.

11 BY MS. MAZZOCHI:

12 Q. The question with regard to CATT is did they discover
13 any differences between the number of letters gained between
14 bevacizumab versus -- versus ranibizumab for comparable dosing
15 regimens?

16 A. I think it's hard for me to remember all the details
17 now, but the ultimate conclusion after looking at the follow-up
18 data of CATT was that prn regimens were not as effective. And
19 that largely explains why they are no longer being followed.
20 Also, that Avastin was not as effective and, even under prn
21 regimens, had to be dosed more frequently than Lucentis.

22 Q. In a way that was statistically significant, to your
23 recollection?

24 A. I don't remember all the details, but clearly the
25 field had -- has come to the conclusion that prn dosing is

GEORGE YANCOPOLOUS - CROSS

1 suboptimal and that Avastin is suboptimal to Lucentis when
2 given the same way.

3 Q. If we carry on with the reviewer comments, one of the
4 reviewer comments back to your manuscript was that you state
5 that CATT and HARBOR still required mandatory monthly visits.
6 In the next line you refer to the CATT prn treatments as
7 difficult treatment decisions. "I would not characterize these
8 as difficult since they are what clinicians do every day in
9 their practice."

10 Was that also feedback that you received?

11 MS. OBERWETTER: Your Honor, I am going to object at
12 this point to the continuation of this line as to the series of
13 unidentified reviewers as to the relevance and probative value.

14 THE COURT: Overruled for the reasons counsel
15 previously articulated.

16 BY MS. MAZZOCHI:

17 A. So we can talk about subjective judgments. I don't
18 think anybody would disagree that bringing an elderly patient
19 in once a month or once every two months is not more difficult
20 and much more burdensome on the patient, no matter what
21 characterizations your treatment is on. I think everybody
22 would agree, if you've ever had an elderly parent, bring him to
23 the doctor once a month or once every two months is twice as
24 burdensome.

25 Q. But in your clinical trials, the VIEW 1-VIEW 2

GEORGE YANCOPOLOUS - CROSS

1 clinical trials, even in the every-eight-week dosing regimen
2 you still required the patients to show up every month, right?

3 A. The FDA deemed that that was what was conducted in
4 the trial, but the data clearly showed that there was no need
5 to be bringing them in. So the label did not require any of
6 those monitoring issues. So the FDA, which is the ultimate
7 arbiter, said that there is no need for these burdensome
8 monitoring visits.

9 They were required for the protocol to make sure that
10 there would be no need. And the studies showed to the FDA's
11 satisfaction that there was no need for monthly monitoring
12 visiting, thus cutting the number of burdensome visits by half
13 and also taking all need to do these various testings, whether
14 you think they're difficult or not -- I mean, physicians may
15 like to do them because they are compensated for doing these
16 assessments, but what the FDA agreed was there was no need for
17 the patients to come in, and there was no need for the doctors
18 to do these assessments if you used their approved regimen.

19 Q. Didn't the FDA require you in the Eylea label to
20 include language that said patients should be assessed
21 regularly?

22 A. And regularly would be consistent with coming in
23 every two months for their dose.

24 Q. Let's go to the last eight lines on exhibit page 11
25 in DTX 915, first paragraph. I'd like to direct your attention

GEORGE YANCOPOLOUS - CROSS

1 to some additional text that says, "Lastly, you say that
2 aflibercept will decrease treatment burden."

3 Did *New England Journal of Medicine* Reviewer Number 3
4 give you feedback that said, "Lastly, you say that aflibercept
5 will decrease treatment burden. So does prn dosing, which is
6 the primary way Lucentis and Avastin are used, and maybe to a
7 greater degree in the first year and maybe with an equivalent
8 result"?

9 Do you see that?

10 A. Once again, the field at the time, which we've
11 already acknowledged, believed that prn dosing was the way to
12 dose. It has been almost completely abandoned now because it
13 was realized that it was not a way to get the best visual
14 outcomes. So they're comparing us.

15 So the whole point of prn was to decrease treatment
16 burden. Everybody says treatment burden was so important. Prn
17 was devised to try to decrease treatment burden. It's now been
18 abandoned because it did not lead to equivalent visual
19 outcomes. We delivered a way to avoid all that, to decrease
20 the treatment burden by half and deliver the same visual
21 outcomes as the FDA agreed.

22 So you're trying to say that yes, of course, I could
23 not treat the patients at all and there would be no treatment
24 burden, but of course they would lose their vision. So you're
25 comparing us to a regimen that's no longer being utilized. I'm

GEORGE YANCOPOLOUS - CROSS

1 sorry, but the reviewers at the time were trapped in their old
2 paradigm. No matter how expert they were, no matter how
3 utilized they were by the *New England Journal of Medicine*,
4 they've now been proven wrong by history.

5 Q. In what year do you believe history decided to prove
6 the prn regimens wrong in your understanding?

7 A. From that period of time, which was --

8 Q. This was in 2011.

9 A. -- 2011, over the ensuing five years, prn gradually
10 completely fell out of favor.

11 Q. Dr. Yancopoulos, let's go back, then, to PTX 3, your
12 '572 patent. And I'd like to start at exhibit pages 21 to 22,
13 which has your Example 7. And we'll pull that up for you on
14 the screen.

15 Dr. Yancopoulos, let's take a look at the first
16 regimen you put in your Example 7 titled "Dosing Regimen."

17 It says, "Specific nonlimiting examples of dosing
18 regimens within the scope of the present invention are as
19 follows." And then it says, "VEGF T 2 milligrams, 0.05
20 milliliters, administered by intravitreal injection once every
21 four weeks, monthly."

22 Do you consider your '572 patent -- strike that. Let
23 me start over.

24 Do you believe that you invented a monthly dosing
25 regimen for aflibercept?

GEORGE YANCOPOLOUS - CROSS

1 A. I don't know what the legal definition of invention
2 is. We were the first to actually utilize this regimen and
3 demonstrate its efficacy in clinical trials.

4 Q. Now, you've spent a lot of time today saying how much
5 you hate the prn dosing regimen, that you thought it was just
6 the dumbest thing that you could be doing. Well, let's move
7 over in your patent to exhibit page 22 and take a look at the
8 part of your Example 7 dosing regimens that appears in
9 Column 17 of your '572 patent at lines 33 to 37.

10 Now, this dosing regimen is basically a first
11 injection followed by nothing but a prn dosing regimen, right?

12 A. Could you direct me again to where we're talking.

13 Q. It's right here on the screen, but it's at Column 17,
14 lines 33 to 37, exhibit page 2.

15 A. Yes. It's one of the examples of regimens that could
16 be used.

17 Q. Okay. So you claimed as your invention a dosing
18 regimen that you called earlier today the dumbest dosing
19 regimen ever?

20 A. I think the point is that they're within the scope of
21 the present invention. Nowhere am I saying that this is the
22 preferred. This would work and provide some benefit to
23 patients, just not a -- it would not provide the best visual
24 outcomes, as we now know.

25 Q. Dr. Yancopoulos, you put a whole series of prn dosing

GEORGE YANCOPOLOUS - CROSS

1 regimens in Example 7 as supposedly within the scope of your
2 present invention, right?

3 A. Well, once again, I did not write the patent; but
4 yes, these are listed as regimens that are within the scope of
5 the invention, not necessarily highlighting which would be the
6 regimen that resulted in the best visual outcomes for patients.
7 That was what would be determined by our clinical programs and
8 our FDA-validated Phase III clinical program.

9 Q. Would it be fair to say, then, that in Example 7 you
10 were trying encompass all the ways in which aflibercept was
11 utilized and shown to have some efficacy?

12 A. Not being an expert in these patents, but I think all
13 these list dosing regimens that would be within the scope of
14 the present invention. And I don't think that we would be
15 saying which would be the best one that would produce the best
16 visual outcomes.

17 Q. Let's stay in PTX 3, exhibit page 22, and look at the
18 text that's at the end of Example 7, which I believe is near
19 the bottom of Column 17, starting at lines 45 to 53, which then
20 goes over onto the next column, 18, through line 3.

21 Do you have that on the screen?

22 A. Yes.

23 Q. All right. Now, if we look at this list of diseases
24 there which are described -- now, one of them is described as
25 wet AMD, right?

GEORGE YANCOPOLOUS - CROSS

1 A. Yes.

2 Q. You have FDA approval for that with aflibercept?

3 A. Yes.

4 Q. Do you have FDA approval for an indication that is
5 specifically called exudative AMD?

6 A. That's another way of saying the same thing.

7 Q. Now, you do have -- do you have an FDA approval
8 for --

9 I'm sorry. Can you keep that up, please.

10 Do you have FDA approval for choroidal
11 neovascularization?

12 A. Choroidal neovascularization is something that marks
13 a variety of different diseases, including AMD. So if we look
14 at the list, we have an approval, age-related macular
15 degeneration, wet AMD. That's the first one. Retinal vein
16 occlusion, RVO, yes.

17 (Reporter clarification.)

18 THE WITNESS: I'm reading the list in order.

19 So the first one is AMD and particularly wet AMD.
20 Yes, obviously, we have the approval.

21 Retinal vein occlusions, yes, we have the approval.

22 Central ventral vein occlusion, yes, which is example
23 macular edema following -- yes.

24 Branch retinal vein occlusion, BRVO, yes.

25 Diabetic macular edema, DME, yes.

GEORGE YANCOPOLOUS - CROSS

1 Choroidal neovascularization, that marks a variety of
2 different diseases, including AMD and DME; so it's not a
3 specific disease.

4 Iris -- so we did not do Phase III trials in iris
5 neovascularization. So we've knocked off the first whatever it
6 is on the list. We haven't necessarily done all of those
7 things subsequently on the list. It is pretty remarkable that,
8 of the first five or six things that we've tried, there's
9 extraordinary clinical benefit and they're all approved.

10 BY MS. MAZZOCHI:

11 Q. Can we agree that one of the things that is not here
12 on the list is diabetic retinopathy?

13 A. Well, vascular retinopathy, I see is on the list.
14 It's the last thing actually on the list.

15 Q. I'm talking about specifically diabetic retinopathy.

16 A. Like I said, vascular retinopathy is the same
17 category. It's just that it occurs in diabetes.

18 Q. Does this language contain any statement of
19 preference to use a particular dosing regimen from Example 7
20 for diabetic macular edema?

21 A. Not in this paragraph.

22 Q. All right. Let's stay in PTX 3 but go to exhibit
23 page 15, which --

24 THE COURT: Counsel, before we do that, can I ask you
25 how much longer you anticipate cross taking?

GEORGE YANCOPOLOUS - CROSS

1 MS. MAZZOCHI: I apologize, Your Honor. I've
2 probably got, I would guess, another maybe 30 minutes. I'll
3 try to move it along. I'd hoped we'd be able to go faster.

4 BY MS. MAZZOCHI:

5 Q. Let's stay in PTX 3 but go to exhibit page 15, which
6 is Column 4 of your '572 patent, lines 22 to 31. And this is
7 the paragraph that starts off "The methods of the invention may
8 comprise administering to the patient any number of secondary
9 and/or tertiary doses of a VEGF antagonist."

10 Are you there on the screen?

11 A. Yes.

12 Q. All right. And now let's highlight the next sentence
13 that reads, "For example, in certain embodiments only a single
14 secondary dose is administered to the patient. In other
15 embodiments, two or more -- e.g., two, three, four, five, six,
16 seven, eight, or more -- secondary doses are administered to
17 the patient."

18 Do you see that?

19 A. Yes.

20 Q. You did not put any upper limit on "or more" for the
21 secondary doses, right?

22 A. That is correct.

23 Q. And likewise if we take a look at the tertiary dosing
24 description administered to the patient, you did not put any
25 upper limit on the number of tertiary doses, right?

GEORGE YANCOPOLOUS - CROSS

1 A. Correct. These are intended to be treatments for
2 life for these elderly patients.

3 Q. Can we agree that, of the options you've listed here,
4 we're going to have at least ten or more options for secondary
5 doses and certainly more than ten different options for
6 tertiary doses in terms of the number given?

7 A. There is a number of embodiments.

8 Q. Right. But in terms of the actual number of options
9 that are contemplated here, can we agree there's going to be at
10 least ten or more for the secondary doses and at least ten or
11 more options for the tertiary doses?

12 A. Yes.

13 Q. And if we -- and if a patient is going to be taking
14 tertiary doses for a lifetime, that could be as many as 100 or
15 200 doses, right?

16 A. It's possible. These are elderly patients, however.

17 Q. If these doses can be given either on a fixed-dose
18 regimen, a prn-dosing regimen, or a treat-and-extend basis,
19 that's three additional options to impose on the dosing
20 intervals, right?

21 A. Now I'm totally confused. What do you mean by that?

22 Q. Sure. Well, you don't specify here that the
23 secondary dose is going to -- I'm sorry. Let me strike that
24 and take a step back.

25 You don't specify that the tertiary doses are going

GEORGE YANCOPOLOUS - CROSS

1 to be administered either on a fixed monthly basis, a prn
2 basis, or a treat-and-extend basis, right?

3 A. I'd have to go over this, but I thought that the
4 secondary doses would be given monthly. Okay? So let me just
5 read what it says here.

6 "In one exemplary embodiment of the present
7 invention, a single initial dose is administered to a patient
8 on the first day followed by two secondary doses, each
9 administered four weeks after the immediately preceding dose,
10 i.e., at week four and eight, followed by at least tertiary
11 doses each administered eight weeks after the immediately
12 preceding dose, i.e., weeks 16, 24, 32, 40, and 48. The
13 tertiary doses may continue at intervals of eight weeks
14 indefinitely during the course of the treatment regimen. This
15 exemplary administration is depicted graphically in Figure 1."

16 So I think the embodiments, yes, they cover a variety
17 of ways to do it. But we specifically give exemplary examples
18 that the secondary doses, for example, are intended to be given
19 monthly. So the whole notion -- the whole idea was a short
20 period of intense dosing monthly and then switching to an
21 every-eight-week regimen, which is obviously eventually what we
22 studied in the clinic. But that's, for example, what is in
23 Figure 1, a single exemplary embodiment. But I agree, the
24 embodiments, you could try to do some math and say that there's
25 a lot of them.

GEORGE YANCOPOLOUS - CROSS

1 Q. Okay. Well, let's stay on this exhibit page and look
2 at your '572 patent at the text that appears at Column 3,
3 starting at line 66, and which then runs over to Column 4,
4 line 1. Now, I understand you said that you gave an example of
5 monthly dosing, but your specification says here that the
6 secondary dose can be administered on an interval of two, two
7 and a half, three, three and a half, or four weeks, right?

8 A. Right. Once again, my expertise is not in writing
9 these patents. My understanding is that they give embodiments
10 that will cover a lot of possibilities. But in the key
11 exemplary embodiments, we highlight what ends up being relevant
12 to the particular examples and -- including the ones that
13 ultimately were the ones that we tested in Phase III and got
14 approved by the FDA.

15 Q. Sir, did you give the possibilities of two, two and a
16 half, three, three and a half, or four weeks for your secondary
17 dose interval?

18 A. Right. There are a listing of many numbers that you
19 just listed, yes.

20 Q. Right. And, likewise, for the dosing range on the
21 tertiary dose, did you also give an interval option of 8, 8 and
22 a half, 9, 9 and a half, 10, 10 and a half, 11, 11 and a half,
23 12, 12 and a half, 13, 13 and a half, 14, 14 and a half, or
24 more weeks after the immediately preceding dose?

25 A. Yeah, that's what's written in the patent.

GEORGE YANCOPOLOUS - CROSS

1 Q. All right. And that's an additional -- that's at
2 least 13 different tertiary interval options, right?

3 A. Yes. I mean, if you multiply these, you can get all
4 sorts of possibilities. But like I highlighted, the ones that
5 we put into a figure and ended up utilizing are just specific
6 ones. You couldn't possibly test all of these.

7 Q. Now let's jump over to page 15 of Exhibit PTX 3 to
8 Column 7 of your '572 patent, top of the column, from lines 1
9 down to 28.

10 Do you have that on your screen?

11 A. Yes.

12 Q. This is where you're listing all the possible doses
13 to include in your dosing regimens, right?

14 A. Yes.

15 Q. And because the hour is late and our court reporter
16 is heroic, I'm just going to ask if you'll accept my
17 representation that there are at least 60 different dosing
18 possibilities listed there.

19 A. Yes.

20 Q. Thank you.

21 And, likewise, you do not require -- or your regimens
22 did not require using the same dose for the secondary and
23 tertiary doses; you contemplated also having one dose for the
24 secondary doses and a different dose for the tertiary doses,
25 right?

GEORGE YANCOPOLOUS - CROSS

1 A. Yes.

2 Q. All right. Now, let's go to -- let's pull up, if we
3 can, PTX 3333. I believe on one of these pages you said that
4 there was some data that you relied on. Let's see if I can get
5 the exact exhibit page number.

6 A. Are you looking for Slide 47, the one that we were
7 talking about during the prior --

8 Q. Well, unfortunately, the versions that we got from
9 plaintiff's counsel didn't have an exhibit number on them.
10 It's the one that ends in page 3752. So it looks like it's
11 about ten pages from the end of the exhibit.

12 Let's go four more pages forward, please. 372 are
13 the last four Bates numbers -- I'm sorry -- the last three
14 Bates numbers. There we go.

15 The data, particularly this idea of the three month,
16 three month, three month, and the arrows that you put on here
17 that you said represented your great insight as to what needed
18 to happen with these dosing regimens, did you put any of that
19 data in your '572 or '601 patent?

20 A. Did we put the data from the PIER study into the
21 patent?

22 Q. Right.

23 A. I would have to read the patent to know, but you can
24 tell me, I'm sure.

25 Q. I didn't see it. Did you put your insight that you

GEORGE YANCOPOLOUS - CROSS

1 needed to make sure that you weren't getting any vision loss
2 before you did your next dose interval anywhere in your patent?

3 A. Say that again.

4 Q. Whatever you called your great insight as to why
5 Lucentis failed, did you put that guidance anywhere in your
6 patent specifications?

7 A. The thought processes about when Lucentis would fail,
8 okay, I think, as we summarized in this slide and the very next
9 slide, was the basis of deciding for us what design to do in
10 our Phase III program. I do not think that we put in when
11 Lucentis failed in our patent.

12 Q. And you didn't put in your reasoning as to why you
13 believed Lucentis, as you put it, failed in your patent, right?

14 A. Yeah. I didn't say that this was any great insight,
15 by the way. I think it's obvious that, after the first three
16 injections, you lose vision. I just pointed it out. I didn't
17 say it was a great insight. But it's right there. It was in
18 the Genentech FDA label. We probably cited the Genentech label
19 as a reference in our patent. We should look at that.

20 Q. You also talk --

21 A. Can you check to see -- I mean -- so before I say we
22 didn't, we probably had the Lucentis label as a reference in
23 our patent. So this data was in there then.

24 Q. Did you provide your reasoning or explanation? That
25 was the point, sir. Your reasoning, your explanation, your

GEORGE YANCOPOLOUS - CROSS

1 insight.

2 A. I'd have to read the patent in detail, but I don't
3 know.

4 Q. It's not there.

5 All right. You also talked about how you needed to
6 have some meaningful Phase III data. Can we agree that, in
7 your '572 and '601 patents, there is no Phase III data for DME?

8 A. That is probably the case. We did not have Phase III
9 data at that time.

10 Q. And, likewise, there was no clinical diabetic
11 retinopathy data from any phase, Phase I, II, or III, in your
12 '601 or '572 patent, right?

13 A. It's hard to remember all the timelines, but I think
14 in general we create these patents and you try to cover the
15 embodiments that you will try in the future as in your
16 Phase III trials.

17 Q. Dr. Yancopoulos, you're not a board-certified
18 ophthalmologist, right?

19 A. No, I'm not.

20 Q. And at some point do you recall the situation where
21 patients were being denied Eylea monthly treatments when they
22 needed them and prescribers were being denied payments for
23 monthly administration of Eylea?

24 A. Yes.

25 Q. And in response, Regeneron prepared a labeling

GEORGE YANCOPOLOUS - CROSS

1 submission to the FDA to allow for a change in the label,
2 right?

3 A. Yes.

4 MS. MAZZOCHI: Your Honor, we'd like to call up
5 DTX 902.

6 BY MS. MAZZOCHI:

7 Q. Dr. Yancopoulos, can you confirm this is an email on
8 which you were copied on this issue?

9 A. Yes.

10 Q. And one of the reasons Regeneron was willing to make
11 these changes for the label for AMD and make a similar change
12 for DME was to allow for patients who were being denied their
13 physician-recommended treatment to actually get insurance
14 coverage for the monthly dosing treatments they were being
15 denied, right?

16 A. Yes.

17 Q. Dr. Yancopoulos, you would agree that, while clinical
18 trial results may show results for the overall population or an
19 average patient, we all know that individual results for almost
20 any drug for any disease are going to vary for each individual,
21 right?

22 A. That is quite possible, yes.

23 Q. And, Dr. Yancopoulos, you also know that the FDA and
24 current practice allows physicians the individual freedom to
25 treat individuals differently for various reasons, right?

GEORGE YANCOPOLOUS - CROSS

1 A. Yes.

2 Q. And while a doctor may have to defend their decision
3 if they prescribe off-label, you know that they do have the
4 freedom to prescribe Eylea, or aflibercept, off-label, right?

5 A. Yes.

6 Q. And while you talked about your current Eylea product
7 here today, Regeneron is planning on launching a new version of
8 its aflibercept intravitreal product, right?

9 A. Yes.

10 Q. You're trying to get FDA approval for an extended
11 dosing interval that is as long as 16 weeks, right?

12 A. Right, with a different, more concentrated
13 formulation of aflibercept.

14 Q. Because from your perspective, there remains a need
15 to alleviate treatment burdens with intravitreal VEGF
16 inhibitors, right?

17 A. Yes. We would agree that, even treating patients
18 every eight weeks, and as you said some people might require
19 more frequent treatment, alleviating treatment burden further
20 would have more advantages, yes.

21 Q. Let's pull up DTX 228.0002 that counsel asked you
22 about.

23 A. Which book am I in?

24 Q. This is in the ones that your attorneys used with
25 you. And let's look particularly at the -- what was described

GEORGE YANCOPOLOUS - CROSS

1 as Lucentis control VT 0.5 q4w, VT 0.2 4qw, and then VT 2.0
2 q8w, dose somewhat still undecided.

3 Do you see that?

4 A. Yes.

5 Q. You testified that this reference to VT 2.0 q8w
6 actually referred to not just an eight-week dosing regimen but
7 one with three loading doses.

8 Do you have any documents that you're aware of that
9 corroborate that statement.

10 A. It's hard to remember any documents from 15 years
11 ago.

12 Q. Okay. But somehow you're remembering that that
13 actually meant three loading doses even though three loading
14 doses aren't written there?

15 A. Yes. I distinctly remember that because that was
16 exactly what we were planning on designing.

17 Q. Let's take a look at PTX 3216. This is the key
18 opinion leader discussion.

19 You said that some unnamed key opinion leader told
20 you that there were safety concerns with DME dosing. Who was
21 that key opinion leader?

22 I believe it was in the slide presentation.

23 A. Can you say again? What is it that you're referring
24 to that an expert said?

25 Q. Yeah. If we take a look at -- it's the page of the

GEORGE YANCOPOLOUS - CROSS

1 exhibit that ends in 5555; so second-to-last page of the
2 exhibit.

3 You said that there were key opinion leaders who told
4 you that there were possible safety concerns with the diabetic
5 population.

6 Who do you contend told you that?

7 A. Well, I think there were already in the label, the
8 original label for Lucentis, there was a possible association
9 with what they called ATPC events or events related to heart
10 attacks and strokes and so forth. And I think the concern was
11 that the diabetic population might be more prone to the same
12 safety concerns that were seen with AMD because, as we all
13 know, if you have diabetes, it increases your risk of heart
14 attacks and strokes.

15 So there was already the concern with the class, and
16 that was in the Lucentis label, that it might be associated
17 with an increased risk of heart attacks and strokes for AMD,
18 and the possible safety concern in the diabetic population was
19 that perhaps anti-VEGFs would have even more of a risk, which
20 caused us to be concerned about going to even higher doses.

21 Q. Doctor, I'm not asking you what the basis was. I'm
22 asking you who offered that opinion at your key opinion leader
23 meeting.

24 A. I would not remember an individual, but I think that
25 a lot of individuals were concerned about that, both internally

GEORGE YANCOPOLOUS - CROSS

1 and externally.

2 Q. Can you give me the name of any one of your key
3 opinion leaders who attended that meeting who you believe
4 expressed that concern?

5 A. I'm sorry, but at this point I can't give you the
6 name of any key opinion leader who even attended the meeting.

7 Q. Okay. This brick of an exhibit, PTX 1170 -- it's
8 about 4 inches thick -- did any of this data, to your
9 knowledge, make its way into your '572 or '601 patent?

10 A. I have no recollection.

11 Q. Do you recall whether you even put any DME monthly
12 visual -- I'm sorry.

13 Do you recall whether you put any monthly visual
14 acuity data results for DME anywhere in your patent
15 specification?

16 A. We could review the patent. I don't remember off --

17 Q. Well, the only place where you have any actual DME
18 data is in Example 5. So let's go ahead and pull that one back
19 up, PTX 3. I believe it's exhibit page 22.

20 I'm sorry. Let's go to Example 5. It's one or two
21 pages earlier. And let's go down to Table 2.

22 Did you provide any monthly data showing mean change
23 in visual acuity?

24 A. Apparently, yes.

25 Q. Sorry. Did you say yes?

GEORGE YANCOPOLOUS - CROSS

1 A. Apparently, yes, in this table.

2 Q. On a month-by-month basis?

3 A. It says here "VEGF Trap .5 milligram
4 monthly, .2-milligram monthly."

5 Q. Then my question was too confusing. I apologize. I
6 don't mean did you have a monthly dosing? I mean did you
7 provide the letter results each and every month?

8 So you had that graph that you were pointing us to
9 earlier where you showed the drop-off for the Phase II DME
10 data.

11 A. Right. You're saying the -- is this the Da Vinci
12 study that we're talking about?

13 Q. Yes. It's Example 5.

14 A. So you're saying that we previously saw the graphs
15 over time, and here we have the table of the results at
16 Week 24.

17 Q. Right.

18 A. So we did not show the data between months zero and
19 24, yes.

20 Q. But it was the data that you saw in those -- at each
21 of those intervening months that caused you to realize you
22 wanted to have more loading doses, right?

23 A. Well, I think, as I said before, there was a lot of
24 data, from here to the data that you're referring to to much
25 other data that I used to come up with that decision to use

GEORGE YANCOPOLOUS - CROSS

1 five loading doses, yes. So there's a lot more data that was
2 utilized than is in this patent.

3 Q. Just so the record is clear, let's pull up
4 PTX 1028-C.0011.

5 A. Which book is that in?

6 Q. That's your plaintiff's counsel's book, I believe.

7 A. PTX --

8 Q. 1028-C.0011, the Da Vinci mean change in visual
9 acuity data that was set forth on the month -- I'm sorry -- the
10 every-four-week basis.

11 Can you confirm you did not put that data into your
12 patent?

13 A. Yes. As we just reviewed, this graph does not appear
14 in the patent.

15 Q. But can you also confirm that, if we take a look at
16 the 16-week mark, that is where the three loading doses
17 followed by every-eight-week dosing dropped off, right?

18 A. Yeah. I don't think -- as I said before, we consider
19 a lot of these changes in these very small number of patients
20 noise. So if -- let me just use my laser pointer.

21 If you're trying to make the point that this line
22 here meant anything different than this line here or this line
23 here, it did not. So, no, I don't think you can make any
24 conclusions because I think we all agree the change here looks
25 just like the change here looks just like the change here. So

GEORGE YANCOPOLOUS - CROSS

1 you could draw no conclusions from these small numbers of
2 patients and the extreme variability seen in these small
3 numbers.

4 Q. Let's take a look at PTX 1028-C.0016, the mean change
5 in retinal thickness. Can we agree that, numerically,
6 according to this graph, your 2q8 dosing regimen, which was
7 three loading doses followed by every-eight-week dosing,
8 numerically had performed the worst by Week 16 for mean change
9 in retinal thickness?

10 A. Yes.

11 Q. And that was the fifth dose day, right? The fifth
12 dose given within the context of that regimen?

13 A. I'm not sure that's correct.

14 Q. Well, there was a dose given at baseline at week
15 zero, right?

16 A. Yeah. It was not the fifth dose.

17 Q. For the 2q8 regimen, was the first dose given at time
18 equals zero?

19 A. Yes.

20 Q. The second dose was given at time equals 4?

21 A. Yes.

22 Q. And the next one was given at time equals 8?

23 A. Yes.

24 Q. Then skip the dose on week -- on Week 12?

25 A. Yes.

GEORGE YANCOPOLOUS - CROSS

1 Q. All right. And then a dose was given at Week 16?

2 A. Yes. That would be the fourth dose.

3 Q. Now, for the prn dose at Week 16, those patients
4 performed better numerically, right?

5 A. Yeah. The prn, I think at that point, was monthly
6 dosing at that point.

7 Q. All right. Your understanding is that the prn was
8 still doing monthly dosing in the Da Vinci study at the 16-week
9 mark?

10 A. Let's go to it.

11 Q. That's fine. I'll withdraw it. Let's move along.

12 A. Yes.

13 THE COURT: How much longer do we have, Counsel?

14 MS. MAZZOCHI: Sorry?

15 THE COURT: How much longer do we have?

16 MS. MAZZOCHI: Your Honor, let me just wrap this up
17 here, and I'll warn my colleagues that, if there's anything
18 further they think I need to do, then they can start
19 gesticulating frantically.

20 THE COURT: They're your sticky notes.

21 Go ahead, Counsel.

22 BY MS. MAZZOCHI:

23 Q. Dr. Yancopoulos, is it true that your net worth has
24 been pegged at over \$1 billion because of the value of
25 Regeneron's stock that you own?

GEORGE YANCOPOLOUS - CROSS

1 A. I honestly have no idea what my net worth is. I
2 don't follow those sorts of things.

3 Q. We can at least agree, Dr. Yancopoulos, that your
4 current stake in Regeneron is worth over \$100 million, right?

5 A. Probably for sure, yes.

6 Q. All right. And, finally, you have not actually been
7 treating patients for the many conditions that we've discussed
8 today any time in the last 10 to 15 years; is that fair?

9 A. No, I have not been a practicing physician.

10 MS. MAZZOCHI: Thank you, Your Honor. We'll pass the
11 witness.

12 THE COURT: We're going to take up recross tomorrow,
13 assuming it's longer than five minutes.

14 MS. OBERWETTER: This will be very short, Your Honor.

15 Would you like a break? Your Honor, as long as we're
16 coming back to finish this, then I'm happy to have a break.

17 THE COURT: I was going to come back tomorrow morning
18 to finish it. What's your definition of very short, Counsel?
19 Let me ask that.

20 MS. OBERWETTER: Five minutes, plus moving in the
21 exhibits that I identified earlier.

22 THE COURT: I've fallen for that trick before.

23 MS. OBERWETTER: I'm pretty sure it's not a trick,
24 Your Honor.

25 THE COURT: I didn't mean -- that was nothing

GEORGE YANCOPOLOUS - REDIRECT

1 personal.

2 REDIRECT EXAMINATION

3 BY MS. OBERWETTER:

4 Q. Dr. Yancopoulos, just a few more questions for you
5 today.

6 First of all, Ms. Mazzochi had some questions for you
7 about DTX 4070, which was an article by Dr. Nguyen, if we could
8 pull that up briefly.

9 And, Dr. Yancopoulos, do you recall the questions
10 about this exhibit generally?

11 A. Yes.

12 Q. Okay. If we could actually take a look at the last
13 page of text of this document, which appears at the top of
14 DTX 40700009, and if we could actually hone in on just the top
15 five lines there.

16 Dr. Yancopoulos, this is an article that you included
17 in that Bayer 2007 PowerPoint that we looked at earlier today,
18 correct?

19 A. Correct.

20 Q. How did Dr. Nguyen conclude his article?

21 A. In terms of you want me to read this or --

22 Q. Yes. Yes. What were the questions that he was
23 posing after the data he presented?

24 A. Whether the different patterns of response to the
25 Lucentis in different patients was because of different levels

GEORGE YANCOPOLOUS - REDIRECT

1 of VEGF production in these patients and what was the optimal
2 timing for injections.

3 Q. Okay. And that is where he ended in terms of
4 identifying regimens, correct?

5 A. Yes.

6 Q. We can take that document down.

7 If we could put back up PDX 3-0311-B, which was that
8 colorized excerpt from the Heier 2012 reference.

9 And you recall Ms. Mazzochi had some questions for
10 you about the numeric differences in Table C on this page, the
11 integrated data. Do you recall that?

12 A. Yes.

13 Q. Could you please explain, briefly, the difference
14 between the numeric data and looking at things from the
15 standpoint of statistic significance?

16 A. Right, which is how the FDA looks at it.

17 When you're doing any study, even if two things are
18 identical, you use the same exact regimen twice, there's always
19 going to be numeric differences that can be very misleading and
20 meaningless. So the FDA is focused on whether statistically
21 significant differences, which they were not between these, as
22 the FDA concluded.

23 So these were meaningless differences that one could
24 not make any points about, which is why trying to say there's a
25 difference between 8.7 and 8.4 is just scientifically invalid

GEORGE YANCOPOLOUS - REDIRECT

1 and misleading.

2 Q. And, Dr. Yancopoulos, if we go back to the first page
3 of this document, which is PTX 311, the Heier 2012 reference,
4 what journal was this published in?

5 A. *American Association of Ophthalmology*, known in the
6 field as *Ophthalmology*.

7 Q. Is that a peer-reviewed journal?

8 A. It's a peer-reviewed journal.

9 Q. Ms. Mazzochi asked you some questions about
10 individual reviewer opinions from the *New England Journal of*
11 *Medicine*.

12 Are all important innovations published in the *New*
13 *England Journal of Medicine*?

14 A. No, they are not.

15 Q. And apart from the reaction of the *New England*
16 *Journal of Medicine* reviewers that Ms. Mazzochi asked you
17 about, what was the reaction of clinicians at large when Eylea
18 came onto the market with the approved regimen?

19 MS. MAZZOCHI: Objection, Your Honor. He's not
20 competent to testify to physicians at large. He can talk about
21 his own experience.

22 MS. OBERWETTER: Your Honor, it's my last question,
23 and she marched us through eight anonymous reviewers. So I
24 think he's allowed to --

25 THE COURT: Overruled. Ask the question again. I'm

GEORGE YANCOPOLOUS - REDIRECT

1 sorry.

2 BY MS. OBERWETTER:

3 Q. Yes. Dr. Yancopoulos, apart from the reaction of
4 those *New England Journal of Medicine* reviewers, what was the
5 reaction of clinicians at large when Eylea came onto the market
6 with the approved regimen?

7 A. I think the physicians spoke with their actions, just
8 like almost immediately when Lucentis came out, physicians
9 almost completely started switching over to Lucentis from
10 Macugen in the same way, very rapidly with Eylea, Eylea became
11 the preferred drug of choice for the majority of
12 ophthalmologists.

13 MS. OBERWETTER: Thank you.

14 At this point I would like to move into evidence the
15 exhibits that we have used with Dr. Yancopoulos, which I am
16 prepared to list if that's the easiest way to do this. I can
17 also reconcile it with your clerk after we go off the record.

18 THE COURT: In Madam Court Reporter's survival
19 interests, we're going to reconcile those afterwards. But were
20 there any that there's any objections to?

21 MS. MAZZOCHI: Your Honor, as long as -- let me put
22 it this way: We accept that a lot of these are business
23 records and that sort of thing. I will say, though, again, I
24 just want to ensure that it's not with any prejudice to us to
25 continue to raise this issue that some of these documents

GEORGE YANCOPOLOUS - RECROSS

1 probably shouldn't even be admissible or, at the very least,
2 relied on because they were not part of -- to the extent I
3 think I know where counsel's going to use them for, they were
4 not disclosed, timely disclosed either in the expert report or
5 the discovery responses; so...

6 THE COURT: That's an issue we'll take up in the
7 posttrial briefing and the rest. Thanks.

8 It's a bench trial. This Court will receive evidence
9 for the parties' opportunity to create a relatively appropriate
10 record, and then we'll place the appropriate weight, if any,
11 upon the evidence as it comes in and its findings of fact and
12 conclusions of law.

13 But the transcript will be clear as to what exhibits
14 were referenced. If there are specific objections, we can take
15 those up at another time.

16 Is there any recross at this point, Counsel?

17 MS. MAZZOCHI: Two things, Your Honor.

18 RECROSS-EXAMINATION

19 BY MS. MAZZOCHI:

20 Q. First, Dr. Yancopoulos, I'd like to go back to
21 DTX 4070, exhibit page 009. Since your counsel only showed you
22 a portion of the results about optimal timing for injections,
23 let's put the whole thing up.

24 Did the whole thing -- did the whole set of sentences
25 say, "What is the optimal timing for injections? There

GEORGE YANCOPOLOUS - RECROSS

1 appeared to be a plateau in the amount of reduction of foveal
2 thickening during the first three months of the study when
3 monthly injections of ranibizumab were given" -- then let's add
4 this in -- "with additional benefit achieved by switching to
5 injections every other month."

6 Is that what the article said?

7 A. That's what it said.

8 Q. Let's call up DTX 916.

9 Can you confirm that this is an email that you were
10 cc'd on dated January -- Saturday, June 9, 2012? And after you
11 got rejected, did you then use your connections to get your
12 manuscript published in *Ophthalmology*?

13 A. I did not use any connections since I didn't have
14 them with *Ophthalmology*.

15 Q. But you'd agree that this is at least an email that
16 you were cc'd on in around Saturday, June 9, 2012?

17 A. Well, it says here, "In full agreement with you, I
18 want to write back and suggest we" --

19 THE COURT: Slow down, please, Doctor.

20 THE WITNESS: Well, I'm reading it. I haven't seen
21 this --

22 THE COURT: Doctor, here's the issue with your
23 reading. Madam Court Reporter can't listen --

24 THE WITNESS: Sorry.

25 THE COURT: Doctor, one second, please. Thank you.

GEORGE YANCOPOLOUS - RECROSS

1 Madam Court Reporter can't read it while you're
2 speed-reading it as well. So if you're going to read, that's
3 perfectly fine. I understand it's your answer to the question.
4 I just need you to slow down while you do that to ensure we
5 have an accurate record. Thank you.

6 BY MS. MAZZOCHI:

7 Q. Dr. Yancopoulos, I just want to confirm that this is
8 an email you were cc'd on.

9 A. Right. I'm just saying I'm reading this email, and
10 it says, "I am in full agreement with you. I saw this email
11 this morning and wanted to write back and suggest that we
12 submit to *Ophthalmology*. It is a very fine journal."

13 MS. MAZZOCHI: Your Honor, we request that DTX 916 be
14 moved into evidence.

15 THE COURT: Any objection?

16 MS. OBERWETTER: No objection, Your Honor.

17 MS. MAZZOCHI: We're done. We're done, Your Honor.
18 Thank you.

19 THE COURT: Without objection.

20 Rerredirect.

21 MS. OBERWETTER: None, Your Honor.

22 THE COURT: Doctor, you may descend the stand, sir.
23 Thank you very much.

24 I'll leave it to counsel to tidy up the exhibits
25 there.

1 Is the doctor subject to recall, or is he free to go?

2 MS. MAZZOCHI: As far as we're concerned, he's done.

3 THE COURT: All right. We'll proceed then at 9:30 in
4 the morning, subject to counsel squaring up the list of
5 exhibits that were used during the witness's testimony, and
6 we'll see everyone then. Thank you very much.

7 You can leave whatever you'd like in the courtroom.
8 Nobody will be in here in the interim. But to give everybody
9 advance warning, we do have another criminal matter we need to
10 take up at noon tomorrow or whenever we take a lunch break,
11 just as a planning FYI.

12 Have a pleasant evening. We'll see you tomorrow.

13 (Proceedings concluded at 5:46 p.m.)

14

15

16

17

18

19

20

21

22

23

24

25

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