

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 Volume 8

8 Biocon Biologics,

9 Defendants.

10 - - -

11 Proceedings had in the bench trial of the above-styled
12 action on June 22, 2023, before Honorable Thomas S. Kleeh
District Judge, at Clarksburg, West Virginia.

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1 Thursday morning session,
2 June 22, 2023, 9:00 a.m.

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4 THE COURT: This Thursday we convene for day eight of
5 trial. Counsel is present. The Court did see the joint
6 stipulation the parties filed. The Court's digital signature
7 is being affixed to that as we speak and will be entered
8 forthwith.

9 Anything else we need to take up before we hear from
10 Mylan's next witness, then?

11 MS. OBERWETTER: No, Your Honor. We're ready to call
12 our next witness.

13 THE COURT: Okay.

14 From the defense standpoint, anything else?

15 MS. MAZZOCHI: No, not right now, Your Honor.

16 THE COURT: All right. Regeneron may call its next
17 witness, then.

18 MS. OBERWETTER: Yes, Your Honor. Regeneron calls
19 its next witness, Dr. Karl Csaky.

20 THE COURT: Hello, again, Dr. Csaky.

21 If you wouldn't mind repeating the drill. Come all
22 the way to the front. We'll have you sworn in and ask you to
23 take the witness stand. Thank you, sir.

24 **KARL CSAKY, MD, PHD, PLAINTIFF'S WITNESS, SWORN**

25 MS. OBERWETTER: Before we start, Your Honor, I

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1 believe everyone should have their advance copies of the binder
2 and slides.

3 THE COURT: I believe I do. Thank you all very much.

4 Good morning again, Doctor. If you wouldn't mind
5 adjusting that mic. Stay close to that for us.

6 Counsel, you may proceed.

7 DIRECT EXAMINATION

8 BY MS. OBERWETTER:

9 Q. Good morning, Dr. Csaky. Can you please reintroduce
10 yourself to the Court.

11 A. Yes. My name is Karl Csaky. I'm a retina specialist
12 from Dallas, Texas.

13 Q. And we're going to cover -- since you were here with
14 us last week, we're going to cover some material today that
15 relates some other of your opinions besides those bearing on
16 infringement. I'd like to start first with your definition of
17 the POSA.

18 If we can please pull that up onto the screen.

19 For the record, that's PDX 8.002.

20 Can you please read for us your definition of the
21 POSA.

22 A. Yes. So this is the definition that I used during my
23 opinions.

24 A person of ordinary skill in the art relevant to the
25 claims is an ophthalmologist with experience in treating

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1 angiogenic eye disorders, including through the use of VEGF
2 antagonists, and would have access to individuals with
3 experience with intravitreal injection formulations.

4 Q. Okay. And if we take that slide down, how would you
5 characterize the POSA's goals in the pre-2011 time period in
6 coming up with a potential treatment regimen for treating an
7 angiogenic eye disorder such as wet AMD or DME or diabetic
8 retinopathy?

9 A. Right. So our goals back then were very similar to
10 what our goals are today, right? First is to maximize
11 patient's vision. That's our number one obligation.

12 Second would have been -- as we've seen through
13 multiple testimonies, injections are not a good thing. And so
14 we would have tried to reduce the number of injections that we
15 were giving to patients to achieve that maximum vision that we
16 could offer them.

17 And then of course we also wanted to reduce the
18 burden on having them come to the office. That was another big
19 burden that this new type of therapy was kind of challenging
20 us. And, of course, last but not least was of course the
21 safety, right? And we'll talk about that these were these new
22 class of drugs that we weren't really that familiar with. And
23 so we wanted to ensure that we were doing these in a safe way
24 and not exposing patients to undue risks.

25 THE COURT: Ms. Oberwetter, I'm sorry. My machine

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1 just booted up, and my digital sticky note just reminded me.

2 For those charged with lunch arrangements and whatnot
3 today, we're going to take a lunch break starting at 11:00. So
4 if anyone needs to alert Panera, Subway, or whomever, my
5 apologies. The vagaries of one of the Klee children's camp
6 schedules and softball tournament schedules require us to move
7 our lunch break up a little bit.

8 We'll break from 11:00 to 12:30 because we have a
9 criminal matter we have to take up at 12:15. So for those
10 charged with the all-important lunch arrangements, you're
11 hereby on notice.

12 And, with that, I'm sorry, Ms. Oberwetter. You may
13 resume.

14 MS. OBERWETTER: Thank you, Your Honor. That seems
15 like information that should be spread far and wide.

16 THE COURT: Yes. I see the flurry of digital
17 communications ensuing. And my apologies. Like I said, my
18 digital reminder just prompted me.

19 But go right ahead.

20 MS. OBERWETTER: Thank you, Your Honor.

21 BY MS. OBERWETTER:

22 Q. Dr. Csaky, I'd like to address at a high level some
23 of the treatment strategies for administering anti-VEGF
24 treatments that existed before 2011. What were the strategies
25 that were regularly in use?

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1 A. Right. So as we'll talk about, there really were the
2 monthly injection strategy, right? And I think -- as we'll
3 talk about through my opinions this morning, one thing that I
4 think I really want to remind everyone in the court in
5 particular that the advent of these anti-VEGF agents in
6 ranibizumab, not only was it a novel therapy for patients, but
7 the key was also the amazing success that we got.

8 I happened to be practicing in the era before
9 anti-VEGF. And patients went blind, right? So, first of all,
10 we wanted to achieve that maximal benefit to patients. And so
11 monthly we knew could achieve that. So that was a -- still in
12 use.

13 But, again, because of the burden of monthly
14 injections, we had started to pivot to these individualized prn
15 approaches. And eventually that kind of morphed into treat and
16 extend. So those were really the ones that were practically in
17 use for most of this period.

18 Q. Beyond those strategies that you just described, were
19 there clinical trials that had attempted other approaches?

20 A. Right. We'll talk about that briefly. One of the
21 easiest approaches that we first thought of in terms of the
22 treatment burden was simply to extend the intervals. And one
23 of those approaches of that was simply to say let's go out --
24 rather than every month, let's go out to every three months.
25 And so those were multiple attempts to do that right really

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1 from the very beginning of approval of ranibizumab in
2 particular.

3 Q. Okay. And prior to 2011, how were those efforts
4 going?

5 A. Well, as we'll talk about, those were less than
6 successful, right? And, again, I think what's critical to
7 understand is that we were able to offer patients this ability
8 to really dramatically improve their vision, right? It wasn't
9 just that they were having some activity; we needed to make
10 sure that these patients were getting -- you know, over a third
11 of patients would get three or more lines of vision gained.
12 That was unheard of before anti-VEGF therapies. So it was very
13 important for us to continue those. And so these kinds of
14 approaches were not achieving that.

15 Q. What was the predominant method of attempting to do
16 extended dosing prior to 2011?

17 A. So again, you know, as we said, we were pivoting to
18 these personalized approaches, right, these personalized prn,
19 as we've heard, and treat and extend. And those were really
20 kind of the major efforts that were ongoing.

21 Q. Can you remind us what prn stands for?

22 A. So pro re nata. It's basically a way -- you know,
23 it's as needed. And as we'll talk about, we'll kind of
24 indicate how that was used in the real world.

25 Q. Why was it that prn was the prevailing strategy?

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1 A. Well, part of it really was the development -- and so
2 this is an interesting fact, that at the same time that we were
3 doing these injections, there was technology that was becoming
4 available called optical coherence tomography. And this was
5 a --

6 THE COURT: Will you say that again, Doctor. I'm
7 sorry?

8 THE WITNESS: Optical coherence tomography. We'll
9 call it OCT for short. Okay?

10 THE COURT: Thank you.

11 THE WITNESS: And what this does is it's a
12 noninvasive way. We shine a little bit of laser into the eye.
13 It reflects back, and it gives us detailed structure of the
14 retina, right?

15 And so suddenly now we were able in real time to look
16 at patients and determine what degree of activity -- we would
17 call it angiogenic activity -- we would be able to see because
18 this OCT could show us changes in the retina that might reflect
19 activity of disease.

20 BY MS. OBERWETTER:

21 Q. Why don't we take a look at just what an OCT scan
22 looks like.

23 If we can pull up slide PDX 8.004, which is images
24 taken from DTX 3131. Can you explain what we're looking at
25 here?

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1 A. Yes. If I could just one second ask for a laser
2 pointer that I forgot to bring up.

3 THE COURT: Yes, sir, you may approach.

4 THE WITNESS: I apologize. I should have brought
5 that. Thank you.

6 So the key thing here -- and I think this is really a
7 critical aspect of understanding where we were in this period
8 of time. So here we have -- and this is from an article that I
9 cited in my report.

10 Essentially these are images from an OCT device. And
11 what you see here on Month 24 is what we would call normal
12 morphology, right? So you could actually in real time start to
13 see cross sections of the retina. And in this case there's
14 retinal structures here. Underlying it there's some normal
15 retinal structures. And you've heard on several testimonies
16 this idea of a dry macula.

17 This is what we would call a dry macula. There's no
18 swelling. I think this is a good example of -- if you go over
19 here to -- on the left-hand side, you can see the difference,
20 right? This area represents a change in OCT. Black just
21 means, in some case, fluid.

22 And so all of a sudden now in real time I'm able to
23 look at a patient and say, you know something? There's
24 activity here because this doesn't look like that. And this
25 has now fluid and activity. And in the concept of anti-VEGFs,

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1 right, we would actually call this approach a VEGF meter,
2 meaning you would assume that, when there was activity, the
3 VEGF levels were going up, causing fluid to reaccumulate. And
4 when there was no fluid, we would assume that the VEGF levels
5 were then normal, right?

6 THE COURT: Is this the same eye?

7 THE WITNESS: This is the same eye.

8 So this would be -- this is actually in this prn
9 article. And this is what the attempt was. The patient would
10 come in. If this was the appearance, you would inject, try to
11 achieve this. The patient comes in now to the clinic looking
12 like this. I go "don't need to treat" because I don't see any
13 swelling.

14 So this was a critical technology that was integral
15 to this development of prn, personalized, because it turned out
16 that the rate of this fluid reaccumulation after treatment was
17 all very individualized. Each person had their own rate, and
18 we could now measure that rate with this OCT device.

19 BY MS. OBERWETTER:

20 Q. Dr. Csaky, the images that you took here were from an
21 article about the PrONTO trial; is that correct?

22 A. Correct.

23 Q. What was the PrONTO trial?

24 A. So the PrONTO trial was really one of the first
25 trials to try to understand if using this approach, right,

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1 would accomplish again these similar outcomes that we saw with
2 monthly.

3 Again, this monthly was, you know, this very high bar
4 that we were trying to achieve. And so in this case we were
5 trying to see could I use this approach to tailor my
6 treatments -- not treat here, only treat here -- and see in
7 this way -- hold back injections, and in this way decide if
8 this approach would get me some better outcomes than I did when
9 I was trying to just simply -- extending my dosing every three
10 months.

11 Q. And what did the PrONTO trial show?

12 A. So while the PrONTO trial was still a relatively
13 small trial, it was very encouraging. There was -- the data
14 suggested that the outcomes of this approach -- which, again,
15 was very different than fixed -- that using this type of
16 approach in a small study, we could start to achieve some of
17 these really good outcome in patients.

18 And so you can well imagine how dramatic this was. I
19 didn't have to treat this patient. I could have this patient
20 come back next month. If the patient looked like this, I
21 didn't have to treat. Next month, no treatment. Next month,
22 reaccumulation, then treat.

23 So I could see -- you can understand this is very
24 personalized, right? And each person would have their own
25 individual time for when the fluid may or may not come back.

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1 Q. Dr. Csaky, is prn still a predominant methodology for
2 treating patients?

3 A. It kind of fell -- it kind of evolved into treat and
4 extend. And the reason why is prn required frequent visits,
5 right? So the idea was I would see the patient back almost
6 every month. And every month I would do this. And poor
7 Mrs. Smith would say, "Well, Dr. Csaky, I wasted a trip. You
8 told me nothing's going on. Yay."

9 But I'd have to see her back the next month and the
10 next month. And then when she got fluid, I would treat. And
11 so we eventually kind of figured out that these intervals that
12 patients would demonstrate for recurrence could be not quite
13 like the stock market, but we could be predicted to some
14 degree. And so we would play around with these intervals,
15 eventually getting to the point where we were trying to prevent
16 this from happening just before it would happen.

17 So that was kind of the treat and extend. We would
18 start to extend these intervals. When there was fluid, we
19 would then back off and continue to treat on that interval.

20 Q. Okay.

21 We can take that slide down.

22 Dr. Csaky, is a fixed extended-dosing interval the
23 same as a personalized approach?

24 A. No. It's completely different. As I said, with
25 fixed we simply are having patients come back in on a very

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1 regimented kind of schedule, and we just continue to inject.
2 That was what -- ANCHOR and MARINA was the first trial to do
3 that. And so this was a -- these -- the injections on prn and
4 OCT, we would call conditional. You had to show some activity,
5 change in vision plus fluid, in order to treat; whereas fixed,
6 I go ahead and treat every time.

7 Q. I'd like to take a look at a slide from Dr. Albin's
8 presentation that he referred to as extended regimens.

9 If we can put up PDX 8.0005, Slide 5.

10 You were here for Dr. Albin's testimony?

11 A. Yes, I was.

12 Q. And what was your reaction to the way he grouped this
13 set of references as a category under extended regimens?

14 A. Well, what he outlined here were all these -- either
15 based off various publications and surveys or articles was
16 really either some type of prn or treat and extend. All right?
17 So when I looked at the heading, I felt as if it was somewhat
18 of an incomplete heading because, while this does allow you to
19 have extended regimens, the key point, as I just pointed out,
20 is these are all personalized based, right? So these are all
21 based off individual response, individual recurrence of fluid.
22 When do I treat on these varying intervals?

23 So I would have kind of added, to be a little bit
24 more accurate, the adjective that these are personalized
25 extended regimens.

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1 Q. All right.

2 And we can take that slide down.

3 I want to change topics a little bit and talk at a
4 high level about clinical trials. If we can talk briefly about
5 the phases of clinical trials. And you were here for Ms. Chu's
6 testimony also, correct?

7 A. Correct.

8 Q. Before we get into clinical trials, can you remind us
9 briefly of your experience with clinical trials in treating
10 angiogenic eye disorders.

11 A. Yes. So I've had a fair amount of experience. When
12 I worked at the NIH as a government employee, I worked closely
13 with the FDA on end points in clinical trial designs. I've
14 been involved with being a study chair, which I overran
15 studies. And I've been involved in Phase I, Phase II, and
16 Phase III trials.

17 Q. And very briefly, what are Phase I, Phase II, and
18 Phase III trials?

19 A. Right. Well, as you heard briefly, so Phase I at
20 least -- and this is from the POSA's perspective -- we kind
21 of -- you know, when I'm doing a Phase I, what we're really
22 looking for is to make sure that nothing horrible happens to
23 the eye. So when you inject these new drugs into the eye, what
24 you're really trying to make sure is that nothing terrible
25 happens to the eye. And that's really the intent.

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1 And many times there's a dose escalation. So if a
2 little bit of it doesn't do anything bad, you slowly, with a
3 small number of patients, increase the dose and just ensure
4 that there's nothing terrible happening with these early --
5 with the drug.

6 Q. And then Phase II?

7 A. In Phase II -- so once you have kind of a sense that
8 there's -- at least the eyes are not going -- something
9 terrible is not going to happen, then you start to think about,
10 okay, how can we start to decipher a dose and some type of
11 regimen that may or may not give us some ideas of activity.

12 Phase IIs typically are also underpowered to be sure
13 of efficacy, to make sure there's a benefit, but it starts to
14 give you some signals as to where you might want to go with
15 your Phase III trials.

16 Q. And then just very briefly, Phase III?

17 A. Phase IIIs are the -- you know, they're the big ones.
18 They're the hundreds and hundreds, if not thousands, of
19 patients, very -- with very clear guidelines with a goal
20 ultimately of -- with these large number of patients, being
21 able to demonstrate safety and efficacy for the FDA's
22 requirements and then submission to the FDA for approval.

23 Q. Do most drugs make it through the development process
24 all the way through Phase III?

25 A. No. No. I mean, that's -- there's so many steps

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1 along the way. And, you know, having been in this for a while,
2 we see lots of examples that animal work doesn't translate to
3 humans. There's various issues that come up along the way.
4 Safety is one of them, for example, that can be unpredicted.
5 So there's lots of reasons why, again, we don't reach that bar
6 of true efficacy and safety.

7 Q. I'd like to pause for a moment to talk about what
8 have some of the failures been over time in the category of
9 treating angiogenic eye disorders.

10 A. Right. Even back in that period of time, because of,
11 you know, MARINA and ANCHOR and the fact that there was this
12 tremendous enthusiasm, lots of companies were looking at
13 different technologies. There was siRNA technologies, the
14 company I worked with, trying to inhibit the production of VEGF
15 at the RNA level, for example. That failed.

16 And then of course going through the history, there
17 were other failures where -- you know, for example, trying to
18 augment the activity of anti-VEGF. Those also failed. And of
19 course we've had more recent failures. And many times there's
20 even failures at the very end because of safety.

21 Q. Can you speak briefly about a drug called Beovu.

22 A. Yeah, Beovu, brolucizumab, was a -- somewhat unusual.
23 And it too actually was derived -- it's an interesting
24 history -- from antibodies found in camels. Camels have very
25 small antibodies. And so the thinking was that these smaller

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1 antibodies might be -- you can get them more concentrated. And
2 so that was a -- brolucizumab. So the idea was that would also
3 be an anti-VEGF agent. You could give more.

4 Turned out that, because it was this kind of --
5 again, I hate to use the word "weirdo," but it was another
6 weirdo kind of molecule. While there was some efficacy, what
7 eventually happened was that, in a group of patients, there was
8 this devastating -- what we call occlusive vasculitis. That
9 means the vessels in the retina shut off, and these patients
10 would go blind. And so essentially it became something that
11 many of us eventually just -- even though it was approved, most
12 of us don't use.

13 Q. Okay. And I'd like to talk a little about how the
14 POSA actually makes use of data derived from various of these
15 categories of clinical trials. Can there be difficulties in
16 drawing comparisons across different clinical trials?

17 A. Yeah. That's something that we were always taught
18 not to do, right? Each trial has its own set of patients that
19 come into the trial. There's various categories. We're all
20 different, right?

21 So if I take a group of patients in one trial, I
22 can't really fully compare it to a group of patients in another
23 trial. There's regional differences. There's ethnic
24 differences.

25 And so we typically are very much aware of the fact

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1 that, while there may be a little bit of teachings going on, we
2 rarely try to put a lot of emphasis on cross-trial comparisons.

3 Q. And are there limitations in making visual acuity
4 comparisons across trials that use different numbers of loading
5 doses?

6 A. Yes. So, again, this is where we have to be very
7 careful because there's so much variabilities in these kinds of
8 aspects. So you would be -- it would be very challenging, and
9 you would not want to place a lot of confidence on trying to
10 figure out manipulating -- if I had done that in this trial
11 versus that trial, in drawing some conclusions. There's just
12 so much variability in human disease and how we respond.
13 That's something we don't do.

14 Q. I'd like to talk a little bit about the development
15 status of some of the various anti-VEGF agents prior to 2011.
16 Where was Eylea relative to Lucentis in clinical development
17 prior to 2011?

18 A. Yeah. So it was behind, right? I mean, ANCHOR and
19 MARINA, 2005/'6, was approved. We were using it full-on in the
20 clinic. And so it was behind in its development.

21 Q. Okay. And how did the molecular structure of
22 aflibercept compare to the structure of other anti-VEGF agents
23 in use?

24 MR. McLAUGHLIN: Objection, Your Honor. This is
25 beyond the scope of his expert report. I don't recall seeing

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1 anything in his expert report about comparing the structure of
2 ranibizumab to aflibercept.

3 MS. OBERWETTER: It is in his report, Your Honor, if
4 we take a look at first paragraph 74.

5 THE COURT: Can I bum a copy from someone?

6 MS. OBERWETTER: Or if we can put it up on the page.
7 Either way.

8 THE COURT: Oh, yeah. If we've got that available up
9 on the screen, that will work for me.

10 MS. OBERWETTER: So this would be page 31,
11 paragraph 74. If it's easier, we're happy to provide a hard
12 copy, Your Honor.

13 THE COURT: Sure.

14 MS. OBERWETTER: Approach?

15 THE COURT: What page and paragraph again,
16 Ms. Oberwetter?

17 MS. OBERWETTER: There's going to be two things we
18 look at. The first will be in paragraph 74, where Dr. Csaky
19 references his 2009 publication with Dr. Do as it relates to --
20 I don't want to -- we have the witness on the stand, but
21 paragraph 74 starting at "In a 2009 publication."

22 THE COURT: Is this in his opening?

23 MS. OBERWETTER: This is in his response.

24 THE COURT: Response? Okay. Paragraph 74?

25 MS. OBERWETTER: Yes.

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1 THE COURT: All right. And where else?

2 MS. OBERWETTER: And then also at paragraph 114. If
3 we scroll forward at the bottom of paragraph 114 on page 53,
4 "Aflibercept was a different molecule than ranibizumab and,
5 unlike ranibizumab, was a genetically engineered fusion
6 protein."

7 THE COURT: Understood.

8 Objection overruled.

9 You may proceed.

10 BY MS. OBERWETTER:

11 Q. Dr. Csaky, how did the molecular structure of
12 aflibercept compare to the structure of other anti-VEGF agents
13 in use?

14 A. Right. So, you know, ranibizumab was a FAB fragment.
15 It's an antibody fragment. It's something that we kind of were
16 familiar with. We had studied immunology. We knew what
17 antibodies were. So we knew what kind of an FAB fragment was
18 from Lucentis. Avastin was the same as Lucentis; it just had
19 the larger IgG tail. So those were two molecules that we were
20 using. And we knew what they were. They were antibodies. We
21 felt comfortable with it.

22 Along comes aflibercept. And to be quite honest, the
23 colloquial term we used was it was a "weirdo protein" because
24 it was this fusion -- a completely genetically engineered
25 protein. And that was not something that -- the POSA, we were

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1 very comfortable with in terms of what the heck is that thing.

2 Q. I'd like to take a look at -- well, first of all,
3 would those differences have affected the POSA's thinking as to
4 how aflibercept might perform?

5 A. Yes. I mean, again, we had this experience with
6 antibodies, right? There was this kind of intuitive sense of
7 the body has antibodies. We kind of know that -- there were
8 other agents in treatment that were using antibodies. And so
9 kind of we were comfortable with that concept. But this idea
10 of this fusion protein that was completely genetically
11 engineered was something we were unsure about.

12 Q. If we take a look at an article on this subject.

13 If we can please pull up PTX 1027.

14 And, Dr. Csaky, what is PTX 1027 that we've pulled up
15 on the screen?

16 A. So this is an article that Dr. Diana Do and I
17 authored back in 2009. And we talked about the various issues
18 right in the middle of all this stuff that was happening and
19 these additional considerations that we needed to think about
20 as we were going down this path of more and more anti-VEGF
21 therapies.

22 Q. I'd like to take a look, if we scroll forward through
23 the article, at page -- what we've marked as 1027.0006. And
24 there's some paragraphs over on the right-hand side.

25 If we can focus in on that first paragraph for a

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1 moment.

2 If I can direct your attention to this paragraph,
3 what were you and Dr. Do trying to convey here?

4 A. Yeah. So, again, I think what we were trying to
5 convey or at least communicate was, again, that this VEGF Trap,
6 which, again, was just kind of coming into our world -- at the
7 beginning we were hearing about it and it was in trials -- to
8 kind of understand that, again, it was not just this simple
9 antibody, another antibody, as I say. It's a soluble fusion
10 protein, and it had, you know, sequences for VEGF receptors.
11 That was something that we didn't fully appreciate. What does
12 that mean?

13 And so that was, I think, one of the first things
14 that we highlighted is the idea that it was -- it was different
15 and that it had, again, alternative affinities which, again, we
16 weren't sure what that meant.

17 As I say, there's a lot of -- it may be something
18 that's going to be a good thing, but I think the other thing
19 that we wanted to highlight and -- during this period of time,
20 and as you saw the article's name, was there were safety
21 concerns. There was systemic safety concerns that were
22 foremost in our minds.

23 And so that also, then, raised this issue of whether
24 or not -- you know, the fact that this is this kind of unusual
25 protein, potentially higher affinity, longer lasting in the

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1 eye, longer lasting in the systemic circulation, we just wanted
2 to be really aware of the potential for, as we say in the very
3 last phrase, greater systemic safety risks.

4 Q. I want to take a look down at the next couple of
5 paragraphs of this article, if we highlight the next two. And
6 in particular, if I can direct your attention down to the last
7 several lines of this segment, talking about the VIEW 1 and
8 VIEW 2 trials.

9 Do you see that part?

10 A. Yes.

11 Q. What were you trying to convey there?

12 A. Yes. So, again, this was during the time of the
13 ongoing VIEW 1-VIEW 2 trials, and we just wanted to highlight
14 the importance of these Phase III trials in helping the
15 community kind of dissect what exactly VEGF Trap was going to
16 do, both from a efficacy perspective but also from a safety
17 perspective.

18 Q. We can take that down.

19 You recall Dr. Albini testifying in his -- testifying
20 last week about whether the POSA would have thought there were
21 safety issues with aflibercept?

22 A. Yes.

23 Q. And why don't we pull up some of his testimony on
24 that point, if we take a look at PDX 8.007.

25 We've put up an excerpt of Dr. Albini's testimony

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1 from page 793 of the trial transcript.

2 What was your reaction when Dr. Albini provided this
3 testimony?

4 A. I was a little, I want to say, incredulous because he
5 refers to the safety that was seen in the preliminary study by
6 Do and that that somehow would communicate to the POSA that
7 this was a safe molecule.

8 And I can tell you, living through that period, there
9 was a lot of sweating going on because this idea that these
10 drugs could be involved with strokes and heart attacks -- VEGF
11 is something that was -- something that was foremost in our
12 minds for a long period of time. And so I really thought it
13 underrepresented the enormous issue that this was in
14 everybody's mind at the time we were in this period.

15 Q. All right. And we can take that down.

16 I want to turn next, Dr. Csaky, to talking about the
17 diabetic macular edema and diabetic retinopathy claims in the
18 case. And we're going to start first with diabetic macular
19 edema, and let's start even preliminarily with the claims
20 themselves.

21 If we can pull up PDX-- I believe it's number 8 that
22 has Claim 11 of the '601 patent and Claim 25 of the '572
23 patent.

24 So we're on Slide 9. You've obviously had a chance
25 to review these claims?

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1 A. Yes.

2 Q. Okay. And you're aware that Dr. Albini has offered
3 opinions in this case that those claims would have been obvious
4 over various references, correct?

5 A. Yes.

6 Q. How does your opinion at a high level differ from
7 Dr. Albini's?

8 A. Yeah. I mean, I differ in that there was really
9 nothing in the literature that would have led the POSA to this
10 type of approach.

11 Q. Okay. And do some of your opinions in that regard
12 also relate to some of the safety concerns we were just
13 addressing?

14 A. Yes. Yes. Absolutely. So there was, again, this
15 issue, especially as we see here in these diabetic patients in
16 particular -- again, we'll talk about what happens when you
17 inhibit systemic VEGF, the risk of stroke and heart attacks
18 that was known; and of course in diabetics in particular, that
19 was something that we were very concerned about.

20 Q. I'd like to talk a little bit -- we can take those
21 down.

22 I'd like to talk a little bit about what was going on
23 with diabetic macular edema in particular during the pre-2011
24 time period. And let's start with Dr. Albini's timeline slide,
25 if we can pull that up. And so this is PDX 8.010 which

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1 references Dr. Albin's Slide 6.40.

2 Dr. Csaky, there's a lot going on here. Did you
3 commission a version of this slide that focuses just on the
4 references that relate to DME?

5 A. Yes. I thought for clarity it would be helpful to
6 separate out the DME world in this period from the AMD world.

7 Q. Okay. And let's advance to that next slide, which is
8 Slide 11.

9 Why did you want to look at DME separately?

10 A. Well, again, you know, for several reasons. You
11 know, first of all, it's a separate disease completely, right,
12 so we have to understand what was the POSA thinking, what was
13 available to the POSA for diabetic macular edema as opposed to
14 a completely different disease, which is macular degeneration.
15 So I think it's important, just for accuracy, to separate out
16 those two.

17 And then, of course, what I was trying to highlight
18 then was specifically his references in that regard.

19 Q. What are the four things that are left here on this
20 slide? If you can just walk through them briefly.

21 A. Right. So what we see here is essentially a
22 reference to the '747 patent. We see a reference to Diana Do's
23 Phase I trial. We see a reference to Dr. Lalwani's review
24 article. And then we see a reference to the press release in
25 September 14th of 2009.

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1 Q. Okay. And that's the Regeneron press release that is
2 at issue?

3 A. Correct, that's the Regeneron press release.

4 Q. And to be clear, is this collection representative of
5 the prior art prior to 2011?

6 A. No. And, again, so when I looked at this, I wanted
7 to make sure that we could represent more fully kind of all of
8 the available references and all of the available work that was
9 being done during this period of time.

10 Q. Did any of the references, either on this slide or
11 from Dr. Albini's testimony, report on five loading doses as a
12 strategy?

13 A. No. On this -- on Dr. Albini's timeline there was
14 nothing that called out five loading doses.

15 Q. All right. And we can take that slide down.

16 I'd like to turn to some of what Dr. Albini cited on
17 efficacy issues related to diabetic macular edema. And let's
18 pull up for starters what was Dr. Albini's slide in that
19 regard, which we have called in our slide deck PDX 8.012 which
20 references his Slide 152.

21 Were you here for Dr. Albini's testimony about this
22 slide?

23 A. Yes, I was.

24 Q. And why don't we first take a look at what Dr. Albini
25 said about this chart, if we can scroll forward to our

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1 Slide 13.

2 What did you understand Dr. Albini to be saying about
3 this chart?

4 A. So, again, I think he's indicating that -- he says
5 this details the clinical trial results that would have been
6 available to the POSA prior to the filing of the patents.

7 Q. Okay. And just so the record is clear on this point,
8 in your opinion is Dr. Albini's summary slide of these efficacy
9 results a comprehensive list of information from the prior art
10 for either AMD or DME?

11 A. No. No. And that's, again, what I tried to do was
12 ensure that we saw the entire landscape of what was happening
13 both for AMD and for DME.

14 Q. So let's take a look -- let's pull out two things,
15 the two things on this list that relate to DME, if we can
16 advance forward.

17 What kind of trials are these two trials that were on
18 Dr. Albini's chart, the one that says there READ 1 and Phase I
19 DME which referenced DTX 2733 and DTX 3102?

20 A. Yes. Again, these are relatively small, early-phase
21 studies, right, that are just at the very beginning of our
22 understanding of either the effects of ranibizumab and, again,
23 in the case of aflibercept, a very early Phase I study of
24 aflibercept in DME.

25 Q. If we go forward one slide to Slide 8.015, how many

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1 patients were in those two trials that we just looked at?

2 A. So you see, again, these are very small trials,
3 right? So the READ 1 had ten subjects; the Phase I aflibercept
4 study had five subjects. So, again, this fits into kind of
5 these early category studies where we're trying to get some
6 degree of, you know, is there some safety or something about
7 these drugs that would raise some concern.

8 Q. Prior to 2011 would the POSA have viewed either of
9 these Phase I trials as a valid basis for projecting the
10 magnitude of visual acuity gains you could get using
11 aflibercept?

12 A. Yeah. So, again, especially with aflibercept, I mean
13 it's very difficult to take five subjects, inject once your
14 drug, and then make some projection into the future about all
15 the aspects that are around drug development, not only the
16 efficacy when you start changing regimens, but also the safety.

17 So I think it would have been very difficult for us
18 to, you know, make any conclusions other than interesting,
19 hopeful, but nothing conclusive, nothing even that would point
20 anything to how -- what's eventually going to happen to
21 aflibercept.

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

23 One of the two references we were just looking at on
24 that slide was DTX 3102. If we can pull that one up.

25 And Dr. Csaky, what is this reference that is up on

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1 the screen?

2 A. Right. So this is a Dr. Do reference, this kind of
3 Phase I study where, essentially, five patients were injected
4 once with aflibercept.

5 Q. Okay. And would the POSA have understood Do 2009 to
6 provide a reasonable expectation of success with respect to the
7 use of aflibercept in DME patients?

8 A. No. Again, as I said, you know, if I present any
9 kind of series of five patients where I inject once the drug,
10 and if I ever stood up and said this is fantastic news, I think
11 I would lose all my credibility to the audience. So that's not
12 something that the POSA would look at.

13 Again, we were intrigued about the molecule, but this
14 isn't teaching us anything about where it will end up in our
15 armamentaria.

16 Q. Would the POSA have understood Do 2009 to provide any
17 reason for using a five loading dose 2q8 regimen for treating
18 DME or DR?

19 A. No. There's nothing in here. There are no details
20 about other regimens.

21 Q. Does Do 2009 teach anything about five loading doses?

22 A. No.

23 Q. Did it use any loading doses at all?

24 A. No. It does -- it used one -- simply one injection
25 and the idea was to assess safety.

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1 Q. I want to turn -- and we can take that reference
2 down.

3 I want to turn to talking about loading doses as a
4 strategy in DME. And first of all, I just want to be really
5 clear. Was five loading doses a strategy that had been
6 employed in any clinical trials that you have been able to find
7 prior to 2011?

8 A. Right. There was really nothing in the literature
9 that had any trial that was based off of a design of five
10 loading doses.

11 Q. And what about six loading doses?

12 A. There was nothing in the literature that referenced
13 six loading doses.

14 Q. And is that true just for DME, or is that a broader
15 proposition?

16 A. That's a broader proposition. There was nothing in
17 the literature on any of the ongoing trials for either AMD,
18 DME, and even some of the other trials for looking at five or
19 six loading doses.

20 Q. Okay. I want to take a look at Dr. Albini's slide
21 about loading doses. If we can pull up PDX 8.016, which refers
22 and turn to Dr. Albini's Slide 91.

23 Do you see that slide?

24 A. Yes.

25 Q. And do you recall Dr. Albini offered some testimony

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1 about this slide?

2 A. Yes.

3 Q. And let's pull up Slide 17.

4 What did you understand Dr. Albini to be saying about
5 the loading dose slide that he presented?

6 A. Again, I think what he was doing is taking these
7 various examples and indicating this range. As he says, I
8 think this slide nicely encompasses that range. And he was
9 trying to indicate that these all represented loading doses.

10 Q. And just for the sake of a clear record, Slide 17
11 refers to Dr. Albini's testimony at page 804 of the trial
12 transcript.

13 So, Dr. Csaky, do you agree with Dr. Albini's
14 characterization of this issue on his slide?

15 A. No.

16 Q. Have you assisted in preparing a demonstrative to
17 illustrate some of your issues with Dr. Albini's slide?

18 A. Yes.

19 Q. So let's scroll forward. And why don't we just walk
20 through -- and we'll deploy some light animation. But why
21 don't we just walk through some of your issues with
22 Dr. Albini's slide.

23 A. Again, I think -- so we were focused on a discussion
24 about loading doses in DME, right? And so I think the first
25 thing you have to do is remove references to AMD, or macular

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1 degeneration. As I said, it's completely different disease.
2 The POSA's not going to sit there and equate those two
3 diseases. So that's the first thing I did.

4 Q. Okay. And then I want to focus your attention on the
5 Number 6 in the bottom left hand of the exhibit. What is -- do
6 you have an issue with the Number 6?

7 A. Yes. So this is, again, in relationship to the
8 COPERNICUS trial, which was a trial to central retinal vein
9 occlusion.

10 Central retinal vein occlusion, again, completely
11 different disease from diabetic macular edema, for one, has a
12 completely different etiology. And what's interesting about
13 the trial designs for vein occlusion is that the end points are
14 six months.

15 So the FDA requires only six months of treatment to
16 get approval. And so when you look at the Number 6 in this
17 regard, it really represents a six fixed monthly loading -- not
18 loading -- six fixed approach to treatment, and that's really
19 what the intent of treatment is for a vein occlusion. You give
20 six treatments every month. It's almost always if you were
21 doing an ANCHOR or MARINA. So it's six fixed monthly regimen
22 through six months because that's the approvable end point for
23 the FDA.

24 Q. On Dr. Albini's presentation, the Number 6, the
25 citation is the September 2009 press release, correct?

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1 A. That's correct.

2 Q. Why don't we pull up the press release, which is
3 DTX 3198. And if we go to the second page of the press release
4 and take a look at the very top paragraph on that page.

5 Dr. Csaky, is this the portion of the press release
6 that talks about the COPERNICUS trial?

7 A. Yes.

8 Q. Would the POSA -- if we take a look in particular at
9 the section that says "patients in both studies" and just
10 highlight those few lines there.

11 Would the POSA have understood this reference in the
12 September 2009 press release to be a reference to six loading
13 doses?

14 A. No. I think, again, it clearly states -- and it was
15 known to some degree that vein occlusions only needed six month
16 of treatment, and this press release highlights essentially the
17 regimens of six monthly injections. There's no reference to
18 loading doses in this press release. And the POSA would know
19 that that's the way this regimen was to be administered. It's
20 a fixed six-month regimen.

21 Q. Okay. Is there any chance that the POSA would have
22 understood this paragraph to be -- and the reference to six
23 doses to be the same as the concept of loading doses?

24 A. No. No. This is, again, the idea -- and even our
25 approach was based off of FDA approval -- was simply to get to

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1 six months and to do a fixed -- every-month six-month schedule.
2 And that's, again, conceptually different than when we think of
3 loading doses.

4 Q. Have you created a slide to set forth a more
5 representative look at the loading dose regimens that were in
6 use for DME?

7 A. Yes.

8 Q. And why don't we pull up Slide 19.

9 And what does this slide show?

10 A. So, again, what I tried to do was paint again a
11 little more comprehensive picture of the landscape, right? I
12 think it's important to recognize what was happening during
13 this period of time. And these are -- include other studies
14 that were being done for DME during this period of time.

15 Q. And in light of -- and the ones that you have listed
16 there toward the bottom are READ 1, DRCR Protocol 1, and
17 RESOLVE, correct?

18 A. Correct.

19 Q. And would this landscape have rendered it obvious to
20 go to five loading doses followed by a fixed dosing interval?

21 A. No.

22 Q. Why not?

23 A. Well, again, I think you can see. I mean, there's --
24 the monthly loading dose range is three to four, and again, the
25 maintenance dosing for the majority of these trials was then

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1 based off of a prn strategy.

2 Q. I want to take down this slide, and let's talk a
3 little bit more about the September 2009 press release as
4 relates to DME.

5 So if we pull up DTX 3198. I want to look again at
6 the second page of this document and this time at the second
7 paragraph at the top of this document, if we can pull that out.

8 Dr. Csaky, you understand this paragraph to refer not
9 by name but to the DA VINCI trial?

10 A. Yes.

11 Q. Okay. And does this portion of the September 2009
12 press release describe five loading doses?

13 A. No.

14 Q. Would the POSA have understood these five lines of
15 this press release to be a teaching to go to five loading
16 doses?

17 A. No.

18 Q. And why not?

19 A. So, again, I think, first of all, there was five
20 regimens. One regimen was laser, and the other four, if you
21 look, was fixed monthly either at .5 or 2 milligrams. And then
22 the other two regimens, as you can see, were included either
23 three -- well, both of them included three monthly loading
24 doses or three monthly loading doses followed by prn.

25 So in both cases this was teaching us that, if you

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1 were going to use a loading regimen, that you'd really want to
2 stick with a three-monthly-loading-dose regimen.

3 Q. Okay. And you're familiar with Dr. Albin's opinions
4 that the POSA just would have added an additional loading dose
5 between loading dose three and the first eight-week extended
6 interval date.

7 Do you recall that generally?

8 A. Yes, I understood that.

9 Q. Do you agree with that position?

10 A. No.

11 Q. And why not?

12 A. So, again, I think it's important conceptually to
13 understand the concept of a loading dose, right? For the POSA,
14 a loading dose was meant to indicate that these are the
15 treatments that you give one after another, every month, again,
16 fixed, meaning I don't look at OCTs, I don't do -- these are
17 not conditional injections. And so the loading dose has a very
18 specific context.

19 And so to simply start putting in an extra injection
20 here or there and then somehow transfer that into a concept of
21 loading dose would be -- would not represent the mindset of the
22 POSA. The POSA was really -- again, a loading dose regimen had
23 a very specific goal in mind. And so if you were going to
24 change any of these regimens, you would want to then have two
25 additional, specifically called-out monthly loading doses.

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1 Q. Thank you, Dr. Csaky.

2 We can take that slide down.

3 I want to turn back to the topic of safety for a
4 moment in DME patients. I'd like to take a look at one of the
5 references from your report, which is PDX-- I'm sorry -- DTX--
6 we have a slide containing DTX 3186.

7 If we can pull up Slide 20, please.

8 Dr. Csaky, this is a reference that you cited in your
9 report?

10 A. Yes, I cited this report.

11 Q. Okay. And can you please just tell us briefly what
12 this article is and what the authors of this article were
13 relaying on the right-hand side of Slide 20.

14 A. So, again -- you know, this again, 2008, we're right
15 in the heyday of all of these anti-VEGF therapies. And there's
16 a concern, right? I won't go into the details because it's not
17 in my report, but there was lots of issues about the safety
18 that was on the minds of everyone.

19 And this report simply further accentuates those
20 concerns, especially as it relates to diabetics, right?
21 Diabetics, they are -- VEGF at low levels does good things. We
22 talked about it in the eye. Systemically, you need some VEGF.

23 You start dropping VEGF systemically, bad things
24 happen, especially for the POSA. All we care about are
25 eyeballs. Somebody has a stroke, I freak because that's not

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1 something that I'm used to dealing with.

2 And so here he's outlining this concern that in
3 diabetics, in particular, until we start getting some long-term
4 safety data, long-term trial data, we need to be cognizant of
5 the possibility that there could, in some patients, be a
6 concern with injecting these anti-VEGF agents into the eye.

7 Q. Thank you.

8 We can take that slide down.

9 Can you provide -- in addition to the safety concerns
10 about diabetics in particular, can you provide other reasons
11 that the POSA would not have wanted to go up to five loading
12 doses without a really good reason?

13 A. Yeah. So, again, I mean, beyond -- so we have the
14 safety concern. We talked about injections. I don't think any
15 of us were just saying we should do more injections at that
16 time. So that was clearly something that we were concerned
17 about.

18 Again, we didn't see anything in the literature that
19 suggested that other trials were pushing towards five loading
20 doses. And even in diabetes, as you saw, this prn dosing, this
21 use of OCT, was really something that was driving our
22 decision-making. And so these -- the ideas that we would just
23 go to fixed five loading doses was really not something that we
24 were heading towards in terms of our approaches.

25 Q. And a couple up other questions on a similar topic.

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1 Is DME typically a slow progressing disease or a rapidly
2 progressing disease?

3 A. It's a slow progressing disease.

4 Q. And how would that fact affect what the POSA would or
5 would not want to do?

6 A. Yeah. Again, there too we have a little bit of some
7 flexibility, right? I can give -- and I think it's
8 representative in these trials -- the thinking, I give three,
9 maybe, and then I do some prn'ing. I know that I have a little
10 bit of time to figure out what then is the right strategy after
11 that with my OCT imaging and stuff.

12 So, again, this idea that I would then mandate five
13 loading doses right up front was again not -- the disease was
14 not driving us towards that.

15 Q. Okay. I want to talk about another reference that
16 Dr. Albini included in his testimony, which is what has been
17 colloquially called Lalwani 2009B but also has the evidentiary
18 title of DTX 2733.

19 If we pull that up.

20 And, Dr. Csaky, is this a reference that you reviewed
21 in forming your opinions in this case?

22 A. Yes, I did.

23 Q. What kind of article is this by Dr. Lalwani?

24 A. This is a review article, you know, that she's
25 attempting to kind of summarize some of the various aspects at

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1 that time.

2 Q. Did Dr. Lalwani mention anything in her conclusions
3 in this article about increasing the number of loading doses as
4 a strategy for treating DME?

5 A. No. There's no place in her review article that she
6 mentioned that has a potential strategy.

7 Q. And, instead, what was the approach tested in some of
8 the studies that she mentioned in her review article?

9 A. Right. So I think, you know, the only thing we
10 understood was that the VEGF levels in diabetics was a little
11 bit higher at baseline. And so if you think about it, okay,
12 I'm going to take my anti-VEGF agent, a reasonable alternative
13 is just to give more drug at the beginning. And so that was --
14 she summarized two studies in this article that explored that
15 option of just more drug at the beginning.

16 Q. After she summarized those two trials, if we can go
17 to page 2 of this document, she has a section in the right-hand
18 column that says "both these higher-dose trials."

19 Do you see that?

20 A. Yes.

21 Q. What was her conclusion after describing some of the
22 things that were being tried?

23 A. Yes. So, again, I think it kind of showed us a
24 little bit of the uncertainty in diabetes and diabetic macular
25 edema. Again, lots of heterogeneity. We were still kind of

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1 struggling to figure out what was the best way to do this. And
2 I think she summarizes it nicely, right, that additional trials
3 will be necessary to determine the most effective dosing and
4 treatment interval strategies.

5 Q. Right below this section --

6 If we can take that down.

7 -- there's a section called "VEGF Trap." Do you see
8 that?

9 A. Yes.

10 Q. Did Dr. Lalwani -- so -- and she refers to the
11 ongoing Phase II trial here?

12 A. Yes.

13 Q. Did she say anything to suggest that the ongoing
14 DA VINCI trial pointed to a solution for a DME dosing regimen?

15 A. No.

16 Q. Okay.

17 We can take that document down.

18 I'd like to talk about another reference that
19 Dr. Albini focused on, which is the Do 2012 reference.

20 And first of all, why don't we start with PDX 22.

21 And we're going to talk more about priority date
22 issues in a little while, but you understand there's an issue
23 in the case about whether the priority date for Claim 11 of the
24 '601 and Claim 21 of the '572 should be January 2011 or July
25 2013, correct?

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1 A. Yes. Yes, I've been told about this discussion.

2 Q. Okay. And you understand that the reference cited
3 between those two dates by Dr. Albini is this August 2012 Do
4 2012 reference, correct?

5 A. Correct.

6 Q. So let's take a look at Do 2012, which is DTX 3105.
7 What is this article that we are looking at? What is
8 Do 2012?

9 A. So these are the one-year results of this DA VINCI
10 trial, some of which we just discussed. And so she's reporting
11 the one-year outcomes.

12 Q. And what type of information is presented in this
13 document?

14 A. So, you know, this is the type of information that,
15 you know, is available to the POSA kind of as a nice summary of
16 various aspects of the trial design, you know, what was
17 actually happening. It could give us information, for example,
18 about the various dosing regimens that were under investigation
19 in the trial. It will give us information about patient
20 selection, for example, also, inclusion/exclusion criteria.

21 One of the interesting things about here is already
22 now we're starting to see, as part of the exclusion criteria,
23 excluding patients -- these diabetic patients who had more
24 systemic problems, again suggesting that we were concerned
25 about enrolling patients that might be at higher risk for a

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1 stroke. So, again, it's starting to tell us that we need to be
2 aware of some of these safety issues. And then of course it
3 then gives us the outcomes.

4 So there's a -- you know, it gives us kind of now a
5 little bit of a beginning overview of where we might be going
6 with this technology.

7 Q. In your review of this reference, is there any
8 language that suggests that an increase in loading doses should
9 occur in future trials?

10 A. No.

11 Q. In your opinion, would Do 2012 have made obvious the
12 use of a five-loading-dose 2q8 regimen for using Eylea with
13 DME?

14 A. No.

15 Q. Or for DR?

16 A. No.

17 Q. And why not?

18 A. So, again, as I summarized in the press report, it's
19 a very similar, you know, position, right? If I read this
20 carefully, I'm looking for, you know, are there, you know,
21 regimens of five loading doses? There aren't in any of
22 these -- any of the groups, right? So that's the first thing
23 I'm looking for.

24 And then I'm looking for potentially, you know,
25 something that the authors would offer to say, you know, this

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1 would be a reasonable approach going forward. And so those are
2 some of the kinds of information we would be looking for in
3 trying to figure out what is our future strategies.

4 Q. And if we take a look at page 7 of this document, one
5 of the conclusion paragraphs toward the bottom left of this
6 page, it starts "because there is considerable individual
7 variation."

8 Do you see that?

9 A. Yes.

10 Q. What was Dr. Do conveying in this paragraph?

11 A. So, again, I think, as we've talked about, this
12 personalized approach using OCT -- you know, we use OCT in DME
13 as well -- vision, and that perhaps because, again, these
14 diseases have so much variability, that she's suggesting that
15 some form of as-needed treatment may be the way to go and,
16 again, just speculating about other approaches. But, again,
17 all of us were waiting for the -- these critical Phase III
18 clinical studies to really understand the full safety and
19 efficacy of this agent in diabetic macular edema.

20 Q. Okay.

21 We can take that down.

22 I want to talk about the diabetic retinopathy claim,
23 if we transition to that for a moment, and pull up Slide 23,
24 which has Claim 19 of the '601 patent on it.

25 Do you see that?

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1 A. Yes.

2 Q. And you've obviously had an opportunity to review
3 this claim?

4 A. Yes.

5 Q. Are diabetic retinopathy and DME the same thing?

6 A. It's a form, but not the same.

7 Q. And can you have diabetic retinopathy without having
8 diabetic macular edema?

9 A. Yes.

10 Q. Over time, have there been different treatments
11 applied to DME as opposed to the category of diabetic
12 retinopathy patients?

13 MR. McLAUGHLIN: Objection, Your Honor. This is way
14 beyond the scope of his expert report. In his expert report he
15 talks about DME being a subset or complication of DR. He never
16 goes into the different variations of diabetic retinopathy.

17 MS. OBERWETTER: I would say, first of all, I believe
18 this is very similar to what Dr. Albini testified.

19 THE COURT: I got it. That's not the objection,
20 though.

21 MS. OBERWETTER: Let's see. If we take a look at
22 response report 220, which is at page 119, "This fundamental
23 distinction has important implications for how
24 ophthalmologists, including the POSA, would have thought about
25 these conditions and their approaches" --

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1 MR. McLAUGHLIN: I'm talking about the distinction
2 between DME --

3 THE COURT: Okay. One at a time.

4 MR. McLAUGHLIN: Sorry.

5 MS. OBERWETTER: -- "would have thought about these
6 conditions and their approaches to treatment of the same,"
7 which I believe is exactly what I just asked him.

8 MR. McLAUGHLIN: Again, this is talking about the
9 distinction between AMD and DME/DR. Right here, these groups,
10 DME and DR, as similar angiogenic eye disorders. And the
11 distinction is between those two and AMD.

12 MS. OBERWETTER: Yes, Your Honor. I believe --

13 MR. McLAUGHLIN: Look --

14 THE COURT: I'm going to say this one more time.
15 One at a time.

16 Ms. Oberwetter?

17 MS. OBERWETTER: I believe this is a disclosure that
18 he's talking about the difference in how the various disorders
19 are treated.

20 THE COURT: Counsel?

21 MR. McLAUGHLIN: This is an opinion we're hearing for
22 the very first time today. Look at the very next sentence. He
23 has DME/DR.

24 THE COURT: Sustained. Sustained.

25 BY MS. OBERWETTER:

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1 Q. Dr. Csaky, you obviously listened to Dr. Albin's
2 testimony in this case, correct?

3 A. Yes.

4 Q. Did you hear Dr. Albin identify any prior art that
5 would have rendered obvious a five-loading-dose 2q8 regimen as
6 to the overall disease state of diabetic retinopathy?

7 A. No, I did not.

8 Q. What was Regeneron's Phase III diabetic retinopathy
9 study called?

10 A. The PANORAMA study.

11 Q. And if we pull up PTX 1794.

12 What is PTX 1794?

13 A. So this was a study to look at specifically the
14 effects of aflibercept on patients who had essentially in this
15 case nonproliferative diabetic retinopathy and -- without
16 necessarily having diabetic macular edema, and trying to
17 understand what the efficacy of aflibercept would be in this
18 class of patients.

19 Q. Okay. And this article was published well after the
20 priority date?

21 A. That's correct.

22 Q. Okay. And in light of the Brown reference or
23 otherwise, would the POSA have found it obvious to use a
24 five-loading-dose 2q8 regimen to treat diabetic retinopathy?

25 A. No. There would have been nothing to lead the POSA

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1 to think that way.

2 Q. Okay.

3 We can take that document down.

4 I want to turn to talking briefly about some of Mylan
5 and Biocon's anticipation arguments and Dr. Albini's testimony
6 about those.

7 If we can pull up -- first of all, you're aware that
8 Dr. Albini testified that the '747 patent would have
9 anticipated the DME and DR claims, correct?

10 A. Yes. I heard him claim that.

11 Q. And you're aware that Dr. Albini provided some
12 testimony on Example 17 of the '747 patent in particular,
13 correct?

14 A. Yes, I did hear him say that.

15 Q. Okay.

16 And let's pull that up. Let's pull up PDX 8.025.

17 And you've had an opportunity to review the '747
18 patent in its entirety, correct?

19 A. Yes, I have.

20 Q. And if we focus on Example 17 for the moment, what do
21 you understand that example to be describing?

22 A. So I think it's important to recognize that this is
23 an example for the treatment of age-related macular
24 degeneration. That's point number one.

25 The other thing that is really interesting about this

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1 example is when you look at some of the descriptions that were
2 provided that are talking about periodic exams, they're talking
3 about continuously monitoring, performing periodic retinal
4 examinations. They're talking about additional VEGF Trap
5 protein may be required and may be given. So I focused and I
6 found that very interesting that there were these words and
7 sentences and descriptions in this example for macular
8 degeneration.

9 Q. Okay. And in your view, did this paragraph describe
10 loading doses and fixed extended intervals?

11 A. No. No, not at all.

12 Q. And why is that?

13 A. So, again, when I look at these kind of periodic
14 examinations may be required, you know, I think -- you know, I
15 look at this, and it sounds very much like prn or a
16 personalized treatment regimen.

17 Q. Does the '747 patent provide any criteria to instruct
18 the POSA to determine whether or not an injection should be
19 administered on any particular schedule?

20 A. No. No, there's nothing here that gives me any
21 guidance in that regard.

22 Q. So in your opinion, does the '747 patent disclose a
23 method of treating patients with DME or DR using five monthly
24 injections followed by an injection eight weeks thereafter?

25 A. No, it doesn't.

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1 Q. Does it disclose an approach of loading doses
2 followed by fixed intervals?

3 A. No, it doesn't.

4 Q. In your opinion, does the '747 patent anticipate the
5 asserted DME-DR claims?

6 A. No, it doesn't.

7 Q. In your opinion, does the '747 patent do anything to
8 make obvious the asserted DME and DR claims we've been talking
9 about?

10 A. No. I see nothing in here that would have led me to
11 that.

12 Q. I want to turn now to the September 2009 press
13 release again.

14 If we can pull up -- actually, we don't need to pull
15 up the press release itself.

16 But you understand that Dr. Albini offered some
17 testimony in this case that the September 2009 press release
18 would anticipate the DME claims, correct?

19 A. Correct.

20 Q. Okay.

21 Let's put up his slide on this issue for a moment,
22 which we have numbered as PDX Slide 26 and cites to
23 Dr. Albini's Slide 75.

24 Can you -- as you understand it, what was
25 Dr. Albini's argument in this regard?

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1 A. So, again, I think he -- as we've talked about, he
2 was taking one of the regimens of three loading doses and then
3 subsequent prn and trying to indicate that, in fact, this
4 somehow could be equated with five loading doses.

5 Q. Okay. And what is your reaction to that position?

6 A. So, again, I think it's critical to understand -- and
7 I think as we've talked this morning in the discussion of the
8 critical difference between a loading dose and a prn applied
9 dose, right? A prn is a conditional treatment, right? I wait,
10 I see, I examine, take OCT, so -- whereas a loading dose is a
11 fixed regimen. It's five loading doses that I do regardless.

12 So it's really -- and somewhat not correct to equate
13 a prn strategy to a fixed-loading-dose strategy.

14 Q. Okay.

15 And let's take this slide down for a moment and go to
16 the actual press release, which is, again, DTX 3198. And if we
17 look again at the second page of this document and pull out
18 that second paragraph at the top that refers to the Phase II
19 development in DME, can we highlight the language there for a
20 moment that describes the prn regimen.

21 And, Dr. Csaky, in your opinion, would a patient
22 receiving that regimen necessarily receive the claimed regimen
23 of five loading doses in an extended fixed-dosing arm?

24 A. No. No. Again, as we talked about, again, it's
25 important to really understand from a POSA's perspective the

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1 fundamental difference between a loading dose and a prn
2 injection.

3 Q. And does this section of the press release describe
4 five loading doses followed by an every-eight-week regimen?

5 A. No.

6 Q. Does it tell you how often the prn examinations will
7 happen?

8 A. No. I think that's the other thing that's quite --
9 that's missing from here, right? One of the issues -- again,
10 we wouldn't even know from this press release when those prn
11 exams were being scheduled in this trial. So beyond just some
12 of the conceptional inconsistencies, this doesn't educate us as
13 to how often I would be needing to see a patient in the prn
14 dosing arm. Could it be once a month? once every two months?
15 It doesn't give us those details.

16 Q. Okay.

17 We can take that slide down.

18 I'm going to change topics a little bit, Dr. Csaky,
19 and we're going to turn now to talking about Claim 6 in the
20 angiogenic eye disorder claim.

21 So, first of all, let's just look at Claim 6 of the
22 '572 patent regarding angiogenic eye disorders.

23 If we can put that up. And that's Slide 29 from
24 PTX 0003.

25 I want to start with the words of an independent

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1 Claim 1, if we just start there. You understand those are part
2 of Claim 6, correct?

3 A. Yes. Correct.

4 Q. Okay. And you understand that Claim 6 depends, at
5 least in part, from Claim 1, correct?

6 A. Correct.

7 Q. And you understand that there's been an issue in the
8 case as to whether we should be looking at Claims 2 and 3. And
9 so we will be focusing today on the Claim 1 portion limitations
10 in Claim 6. Is that all right?

11 A. Correct.

12 Q. Okay. I'd like to discuss briefly a summary of some
13 of your opinions as relates to Claim 6.

14 If we can pull up PDX Slide 30.

15 Can you explain to us what you are summarizing here
16 as it relates to your opinions on anticipation and obviousness.

17 A. Right. So I think, you know, as -- from my
18 perspective -- and I was using the perspective of an
19 ophthalmologist reading Dixon -- I think the -- this idea of --
20 while it does not discuss isotonic solution, right -- and,
21 again, as an ophthalmologist, we would always defer to some
22 type of formulator to tell us what's going on from a
23 formulation perspective.

24 So for the POSA, the Dixon article doesn't call out
25 isotonic, and it really doesn't give the POSA much information

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1 as it relates to anticipation.

2 Q. And can you compare that, then, to the testimony
3 you're offering about obviousness as it relates to Claim 6.

4 A. Right. So the other -- so, again, the issue with
5 obviousness as it relates to Claim 6 is there is discussion of
6 an approach. The approach is very similar to VIEW 1 and
7 VIEW 2. But I think, you know, for obviousness, the POSA would
8 have had to have some idea that this regimen would be -- have
9 some reasonable expectation of success.

10 And, again, as we've talked about, as we'll talk
11 about in AMD in particular, there was very little guidance to
12 suggest that some of the regimens in VIEW 1 and VIEW 2 would be
13 expected to reproduce some of these incredible results. And
14 so, again, I think, from the POSA's perspective, they would
15 have had a limited reason to expect that to be successful.

16 Q. Okay. We'll talk about all of that in more detail.

17 We can take this slide down.

18 I want to start just with the isotonic solution
19 limitation of Claim 6. And I'm going to frame these around
20 some responses to Dr. Albini's testimony which you heard on
21 this topic, right?

22 A. Yes.

23 Q. Okay.

24 Why don't we first pull up PDX Slide 31. Sorry. I'm
25 actually looking for the Dixon excerpt. Let's just start with

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1 that, DTX 204.

2 And this is a reference -- this is Dixon 2009,
3 correct?

4 A. Yes.

5 Q. And this is a reference you've had a chance to review
6 in connection with this case, correct?

7 A. Yes.

8 Q. I'd like to take a look at -- if we scroll forward to
9 page 3 and take a look at that 2.3 section called "Chemistry."
10 Do you see that part?

11 A. Yes.

12 Q. First I just want to talk about your understanding of
13 what practicing ophthalmologists know about. Would this
14 paragraph of Dixon have informed an ophthalmologist that VEGF
15 Trap-Eye was formulated as a "isotonic solution"?

16 A. No.

17 Q. And why do you say that?

18 A. Well, you know, ophthalmologists, we treat patients,
19 right? We're not chemists. And so if you ask an
20 ophthalmologist what a buffer is, he wouldn't be -- or she
21 wouldn't be able to tell you, right?

22 And so the idea of what even an isotonic solution is,
23 the ophthalmologist wouldn't be able to really talk to you
24 about what an isotonic solution is. That's way beyond -- we
25 look at eyeballs all day. We don't think about isotonic

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1 solutions or even what an isotonic solution is.

2 Q. In your experience, do ophthalmologists consult drug
3 formulation books?

4 A. I mean, we can. It's not something that we do on a
5 frequent basis, but I guess, if push comes to shove, I would
6 try to find a formulator if I had to.

7 Q. If you wanted to know whether it would be obvious to
8 use a particular formulation, would you talk to a drug
9 formulator about that?

10 A. Oh, absolutely.

11 Q. As of January 2011, to the best of your knowledge,
12 would the POSA have known the formulation of Eylea?

13 A. No.

14 Q. Okay. I want to --

15 We can take that slide down.

16 I want to talk briefly about some of the obviousness
17 opinions that Dr. Albini offered as relates to the other
18 limitations of Claim 6 and those limitations that are contained
19 in independent Claim 1.

20 So why don't we go back first to Dr. Albini's
21 timeline which we have marked in our deck as Slide 32.

22 Do you see that, Dr. Csaky?

23 A. Yes, I do.

24 Q. And this is again referencing Dr. Albini's Slide 40.

25 Did you commission, again, a project to make this a

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1 little more readable?

2 A. Yes. Yes.

3 Q. Okay. And if we now look at the next version of this
4 slide, which I believe is -- we're going back to Slide 33.
5 Recognizing -- so, first of all, is this a complete recitation
6 of the art relating to either aflibercept or anti-VEGF agents
7 generally prior to January 2011?

8 A. No. But still, I mean, this is -- there's
9 incomplete -- there's still references that we could have
10 included.

11 Q. Okay. And recognizing that this page is still pretty
12 crowded, what are some of the things that are missing from this
13 slide?

14 A. Well, I think, you know, there are -- you know, the
15 references that call out the attempts that we were making to
16 alter this fixed-dosing regimen in particular to extend it --
17 you know, this three-month fixed-dosing schedule, those are
18 missing from this.

19 Q. We're going to talk about those in a little more
20 detail. First of all, are you familiar with a trial called
21 PIER?

22 A. Yes.

23 Q. What is the PIER trial?

24 And we can call up Slide 35, please.

25 A. Right. So, again, the PIER -- and I think, to put it

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1 in context, we have to remember, ANCHOR and MARINA come out.
2 And I think it's really critical to fully appreciate how
3 revolutionary it was. It was essentially penicillin in terms
4 of its ability to take patients and not just stabilize their
5 macular degeneration but actually allow them to see
6 improvements -- dramatic improvements in their vision. So that
7 was the bar, right?

8 However, it came at a high cost, right? Every month,
9 every visit. And so the first thing that we talked about was,
10 okay, well, let's just give injections -- rather than every
11 month, let's give three loading doses. In the loading doses,
12 try to quell the disease that we talked about, try to normalize
13 the tissue, and then extend that to every three months. And
14 that's what Carl Regillo did here in this trial.

15 Q. And this is -- up on the screen there are excerpts
16 from DTX 4099, the Regillo 2008 reference, correct?

17 A. Correct.

18 Q. Can you just explain briefly what Dr. Regillo and his
19 coauthors were saying on the left-hand side of the screen.

20 A. Yeah, I mean, he points out specifically the outcomes
21 were not as strong as those observed with monthly dosing. And
22 in a way what he's highlighting -- and I think it's important
23 to know how to interpret these kind of graphs. Here's the
24 vision over time, right? So these are the loading-dose phase,
25 and the visions go up.

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1 And then what you see is these are the number of
2 letters that change over time. And as these patients started
3 to receive every-three-month injections, rather than stable or
4 improving, their vision starts to go down. And so while it
5 stabilized, they didn't lose vision as opposed to natural
6 history, it did not get, again, these results that we knew we
7 could give patients, these dramatic results with monthly
8 injections. And so that's why he's indicating that they were
9 not as strong.

10 Q. And just for the sake of the record, you are
11 laser-pointing at the visual acuity chart?

12 A. Correct.

13 Q. Okay. And I want to take a look now back at one of
14 Dr. Albin's slides. If we go back to -- if we take a look at
15 PDX Slide 34. And this is a slide we started to look at a
16 little bit earlier. And it has several AMD trials listed on
17 this slide, correct?

18 A. Yes.

19 Q. Let's just take one moment. What was the ANCHOR
20 trial? if we can just do these very briefly.

21 A. Right. So, again, the ANCHOR trial is our first
22 trial. Monthly injections, tremendous vision improvements.
23 That's our -- coming out of the box, we are incredibly elated.

24 The PrONTO study, that's our attempts at now
25 converting to prn, as is the CLEAR-IT trial.

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1 Q. And CLEAR-IT was -- CLEAR-IT 2, that was the
2 aflibercept Phase II trial, correct?

3 A. Correct.

4 Q. And, again, are these three trials representative of
5 the efficacy information contained in the prior art before 2011
6 for AMD?

7 A. Right. So these are starting to give us a little bit
8 of information, but there's still a lot -- this was an exciting
9 time. We had lots of interest in trying to decipher what was
10 happening. And so there's a significant amount of information
11 that's being done and presented during this period of time.

12 Q. And some of what was being done were those efforts at
13 extended 12-week intervals, correct?

14 A. Correct. So beyond this -- as we said, the PIER
15 trial was one of those efforts. There were other efforts as
16 well in parallel to do that.

17 Q. Okay. And if we advance forward one slide, have you
18 added some material on Slide 36 to Dr. Albini's slide?

19 A. Yes.

20 Q. If we go forward one more?

21 A. Yes. Yes.

22 Q. What have you added here?

23 A. Yes. And so these are these trials, these first
24 attempts at trying to do a fixed extended dosing, right? These
25 all have similar regimen. You can see at some point they're

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1 every 12 weeks.

2 And you can see, again, that these results, when you
3 compare them to ANCHOR and MARINA -- ANCHOR and MARINA, 12
4 letters is an enormous gain in vision that you can offer
5 patients. And none of these fixed every-three-month trials
6 were able to come close at all to that outcome.

7 And so for the most part, this type of approach kind
8 of fell into disfavor.

9 Q. Okay. And am I correct, Dr. Csaky, you have not
10 attempted to compile every single trial that was being done
11 prior to 2011, correct?

12 A. No, no, no. There were a lot of them.

13 Q. And why don't we advance forward to -- so if we just
14 advance forward back to Dr. Albini's timeline, have you
15 proposed some fixes to his timeline in light of what we just
16 talked about.

17 A. Yes. Yes.

18 Q. And if we go forward, what have you attempted to
19 change?

20 A. Well, a few things. I just wanted to correct the AMD
21 reference to a slightly different time frame. And then as I
22 said, I started to add, again, to just give a much more
23 complete view of the landscape, the addition of these
24 every-three-month fixed-dosing trials.

25 Q. And if we -- even this is not comprehensive of what's

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1 going on in AMD, correct?

2 A. No, no. There was a lot of work.

3 Q. If we go forward to PTX -- to Slide 39, have you
4 reviewed a review article that we've referred to as PTX 1146
5 from the 2010 time period?

6 A. Yes.

7 Q. Why don't we advance forward through this, and you
8 can tell us what we're looking at.

9 A. Yes. So this was a review article that
10 Dr. Schmidt-Erfurth had put together in this time period, again
11 highlighting some of these portion of all the trials -- not all
12 the trials, but a portion of the trials for this review
13 article.

14 Q. Okay. And, again, just so we're being clear, the
15 CLEAR-IT 2 reference is on here because it was from
16 Dr. Albini's list, not because she talks about it, correct?

17 A. Correct.

18 Q. What was the pattern that emerges from the trials
19 that are summarized in Dr. Schmidt-Erfurth's review article?

20 A. Right. So I think if you look up here, what you see
21 is, of course, our friend, the monthly injection regimen, which
22 gave us the best results. They were an additional attempt to
23 do monthly as well.

24 You can see there is this -- the PIER, these
25 every-12-week. But I think what's really interesting is, when

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1 you look, you see the acronym "prn" quite frequently, right,
2 again, just indicating that, really, the field was moving
3 towards this, you know, prn personalized strategy, again, part
4 of because of the advent of OCT and other technologies that
5 allowed us to try to individualize treatment.

6 Q. I think we heard during Dr. Albin's testimony that
7 Dr. Schmidt-Erfurth is from Austria.

8 Do you remember that?

9 A. That is true.

10 Q. Is she just talking about European studies here?

11 A. No. No. So Ursula, she's a world-renowned retina
12 specialist. She lectures all over the world. And what she's
13 really -- she's highlighting here is a compilation of trials.
14 The majority of these, the vast majority, actually occurred in
15 the United States.

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

17 I want to turn to talking about another reference
18 that Dr. Albin mentioned in his testimony involving a
19 quotation from Dr. David Brown.

20 Do you recall him talking about that generally?

21 A. Yes.

22 Q. Okay. Do you know Dr. Brown?

23 A. Yes, I know Dr. Brown.

24 Q. Why don't we pull up what we have marked as -- or
25 what is marked as PDX 41, which is the slide cross-referencing

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1 Dr. Albini's Slide 37.

2 You remember Dr. Albini testifying about this excerpt
3 from Dr. Brown, correct?

4 A. Correct.

5 Q. What additional context, if we can move forward to
6 Slide 42, did Dr. Brown provide about his quote?

7 A. Yeah. So I think it's important to recognize, again,
8 we're in this 2007 period, right? We're really pushing these
9 personalized prn treat-and-extend strategies. And
10 Dr. Rosenfeld, who was kind of a big proponent of these, was
11 putting together experts to talk about this.

12 And you can see, again, we have this question, what
13 is your strategy for keeping the macula dry? We know what dry
14 macula means. And so the question is how do we achieve that in
15 the best way possible for our patients?

16 And what the response to his -- the question from
17 Dr. Rosenfeld to Dr. Brown is this, again, talking about
18 various strategies. And Dr. Brown, his response is very
19 indicative of what's happening. So he's talking about in this
20 case selective patients with good initial visual acuities or
21 dealing with primary eyes. And I think this is the key issue.
22 "I treat and extend from the start. I give three monthly
23 injections and see them in eight weeks if fluid is absent at
24 that visit."

25 So, again, it's this conditional decision-making at

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1 that time which then would dictate, he says, "and then I give
2 another injection," and you can see this is now the extension
3 phase, right? The patient's come in in eight weeks. He does
4 an active process, evaluating the patients. It's a conditional
5 state. And at that point he makes a decision as to about, you
6 know, if there's no fluid, then I start to extend to ten weeks.

7 So this is now the first iterations of treat and
8 extend.

9 THE COURT: Counsel.

10 MR. McLAUGHLIN: I just want to object based on this
11 being new testimony. This explanation was not provided in his
12 expert reports.

13 MS. OBERWETTER: Your Honor, they didn't identify
14 Dr. Brown's statement in Dr. Albini's opening report and
15 certainly didn't use it to argue that there was a fixed
16 extended dosing interval approach being used in prior art. So
17 this is a perfectly fair response to what they did in
18 Dr. Albini's testimony.

19 THE COURT: Overruled.

20 BY MS. OBERWETTER:

21 Q. Dr. Csaky, does this article describe a strategy of
22 three loading doses followed by an eight-week fixed extended
23 dosing interval?

24 A. Not a fixed eight-week dosing interval.

25 Q. We can take that slide down.

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1 I want to turn to talking a little bit now about the
2 aflibercept clinical trials. Why don't we start first by
3 talking about Regeneron's VIEW 1 and VIEW 2 trials.

4 If we can please pull that up.

5 So we've put up on the screen PDX Slide 43, and what
6 do you understand this to be, Dr. Csaky?

7 A. So these are the treatment regimens that were
8 interrogated in the VIEW 1 and VIEW 2 trials.

9 Q. And one of those -- if you look at the third one, one
10 of those is the three loading dose 2q8 regimen that ultimately
11 went into the label, correct?

12 A. That's correct.

13 Q. All right. Given the state of the prior art at the
14 time, would the POSA have had a reasonable expectation of
15 success as of January 2011 as to whether the VIEW 2q8 regimen
16 would allow the POSA to maximize vision gains?

17 A. So, again, the answer is no, right? Again, I think
18 very important to put this in context, right? So we had to
19 achieve these outstanding vision gains, right? That's -- we
20 have this term "don't leave vision on the table," right? Would
21 be a disservice to a patient to give them a regimen where they
22 would not have the best possible vision. And so the bar was
23 high. For any trial going forward, right?

24 And so that was the first issue that we were thinking
25 about in terms of this q8-week dosing interval, right?

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1 The second issue, of course, was the fact that that
2 had not been tried before. We did not have any evidence or
3 data that extending out to between eight weeks was going to be
4 as good. If anything, the fact that, when we went out to every
5 12 weeks, we got much worse, way below what we were wanting,
6 was really a concern.

7 And as we just talked about, the field was definitely
8 going full-on prn, treat and extend, right? That's where we
9 were heading in terms of treatment strategies. And in my
10 report I actually cite an interesting conversation. Dave Brown
11 and Jeff Heier, who are both in this trial, both kind of opined
12 that they were not very optimistic that this approach would
13 work, again, because of all the reasons we just talked about.
14 The bar was so high that to get to that bar was really hard.

15 Q. Is there anything about the design of the VIEW trial
16 that would have had significance to the POSA at the time about
17 the reasonable expectation of success as to this strategy?

18 A. Nothing.

19 Q. Okay. Let me ask a slightly different way. What
20 would the POSA have gleaned from the very design of the trial
21 about the expectation of success?

22 A. Yeah. So I think just looking at the trial design
23 itself, right, I think the POSA would have said -- remember,
24 MARINA and ANCHOR, major -- had a trial design, fixed monthly,
25 two doses. And so we would have looked at that and said that

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1 makes sense, right?

2 And then we would have kind of scratched our heads
3 and said, well, what's going on with this third regimen? I
4 think many of us -- we understood kind of what it might be able
5 to accomplish if it was successful, but we kind of thought it
6 was the -- hate to say the Hail Mary of trial designs, hoping
7 that it might work and be successful, but clearly the top two
8 were the ones that -- were the ones that were the traditional
9 trial designs that we knew had been shown in ANCHOR and MARINA.

10 Q. You've also had an opportunity to review the
11 publications about the CLEAR-IT 2 trial, correct?

12 A. Yes.

13 Q. And why don't we pull up Slide 45.

14 And the CLEAR-IT 2 regimens are on the left side of
15 this page, and the VIEW 1 and VIEW 2 trial designs are on the
16 right side; is that correct?

17 A. Correct.

18 Q. And what would the POSA have understood in terms of a
19 reasonable expectation of success, if any, that could be
20 gleaned from CLEAR-IT 2 in terms of predicting what would
21 happen in VIEW 1 and VIEW 2?

22 A. Yeah. So, again, I think it's really interesting in
23 retrospect. So for the most part, most of the times when we
24 look at Phase II, the CLEAR-IT 2, what's typically done is then
25 that's just replicated in Phase III, right? And, in fact,

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1 there's articles written about this.

2 So the first thing that we would have noticed is the
3 trial design of this 2q8 regimen wasn't in the CLEAR-IT 2. So
4 where's the support for that that it's going to work, right?

5 I think the other thing is that we saw, you know,
6 four loading doses if we're comparing it to the 2q8 rather than
7 the -- and then suddenly now in VIEW 1 and 2 there's three
8 loading doses, not four.

9 And then I think, again, the other critical feature
10 is this is idea that, after this first 12-week period, all of
11 the patients went to prn dosing, right? And so the
12 relationship, as we just talked about, between prn and
13 fixed-dosing, our experience with fixed-dosing every three
14 months was much worse; some of the early data with prn were
15 suggesting that that individualized approach was giving us some
16 benefit; and the fact that, you know, Regeneron had chosen to
17 essentially do a maintenance phase, if we would call it, of
18 this trial with prn suggested to us that that's what was going
19 to be the next step, right, that prn dosing would have been the
20 next obvious way to go.

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

22 I want to touch briefly on another document that
23 we've seen during this case. If we can pull up Slide 46.

24 And before I ask any questions about this document,
25 just to clarify one thing. To be clear, as of January 2011,

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1 would you think that Eylea would at least have activity in
2 terms of some effect on visual acuity?

3 A. I mean, I think, clearly, we were seeing from the
4 various trials, even CLEAR-IT 2, that there was clearly
5 activity. But, again, I really want to reiterate that it was
6 this bar, it was this enormous bar that we had to hit. And to
7 do that in a large trial, boy, that was tough. That was tough.

8 Q. And now we've got up on the screen our Slide 46,
9 which refers to DTX 212. You were here for Dr. Yancopoulos's
10 testimony back -- it feels like a while ago at this point?

11 A. I have -- I was here.

12 THE WITNESS: Thank you.

13 THE COURT: You're welcome.

14 BY MS. OBERWETTER:

15 Q. Dr. Csaky, you heard the testimony about DTX 212 and
16 Dr. Stahl's comments back in 2006 that we see up on the screen?

17 A. Yes, I do.

18 Q. The line in Dr. Stahl's email says, "Their thoughts
19 on their Phase II trial and end point, do they concur with our
20 perspective that it is impossible to get meaningful VA" --
21 visual acuity -- "data without doing a Phase III study?"

22 Do you see that?

23 A. Yes.

24 Q. Would the POSA have agreed with the perspective
25 reflected here in this email?

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1 A. Yes. I think I've overly expressed that opinion that
2 that is the opinion of the POSA.

3 THE COURT: Yes, Counsel.

4 MR. McLAUGHLIN: Objection. This is outside the
5 scope of his expert report, Your Honor. This document was
6 cited once, and that's in the context of a conception,
7 reduction to practice footnote with no analysis, no discussion
8 of this document. Doesn't appear anywhere else in his expert
9 report, at least that we've seen.

10 MS. OBERWETTER: I believe it is quoted, Your Honor,
11 in paragraph 106 of the report and on page 49, spilling onto
12 page 50.

13 MR. McLAUGHLIN: Which part?

14 MS. OBERWETTER: The responsive part.

15 THE COURT: Overruled.

16 BY MS. OBERWETTER:

17 Q. I believe I got an answer to the question; so I will
18 proceed, and we can move on past DTX 212.

19 I want to talk for a moment, Dr. Csaky, about the
20 reference called Dixon 2009 that we've heard quite a bit about
21 over the course of the trial.

22 And for the sake of the record, that's DTX 204. If
23 we could pull up our slide, PDX 47.

24 You've had an opportunity to review Dixon, correct?

25 A. Correct.

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1 Q. And I want to talk about a few excerpts of Dixon that
2 have not yet had discussion in the trial.

3 First of all, what kind of reference -- let's just
4 talk about Dixon for a moment. What kind of reference, what
5 kind of article is the Dixon article?

6 A. So, again, similarly, it's a review article trying to
7 summarize kind of the state of the art and where we are with
8 treatments and understanding of disease at this period of time.

9 Q. Okay. And a big-picture question: In your opinion,
10 did the Dixon reference tell the POSA that the Phase III VIEW
11 trials would secure either efficacy or interval improvements
12 for patients?

13 A. No. No.

14 Q. I want to -- let's just walk through some of the
15 language in Dixon that relates to your opinion on that point.

16 Can you just walk us through -- let's go quote by
17 quote. If you can start with the one at the top that's under
18 "2. Background."

19 A. Right. So, again, if we look in the background
20 section, there's a quotation that says, "These later studies
21 seem to indicate that quarterly dosing is associated with
22 poorer outcomes, but it may be possible to extend the time
23 between injections if the patient is frequently monitored."

24 So, again, a reference that we've been talking about,
25 prn, treat and extend.

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1 Q. And what would that portion of Dixon have told the
2 POSA?

3 A. It would have told the POSA that the future of
4 treatment is personalized treatment.

5 Q. Let's take a look at the line that's excerpted here
6 from the Dixon references' conclusion, if you can walk us
7 through that one.

8 A. Yes. So, again, it's still -- we were still unclear
9 of what the full kind of ability of any alternative dosing to
10 be effective, and they're just pointing out that there's still
11 a degree of uncertainty about where we are and what new
12 treatments may or may not be able to do as it relates to
13 ranibizumab.

14 Q. Okay. And if we take a look at the last one -- and
15 if you need to remind yourself of the further context around
16 that, you should feel free to look at DTX 204 in your binder.
17 But what does that last excerpt under "4. Excerpt Opinion,"
18 refer to where it says, "Its adoption into clinical practice
19 will depend on efficacy at 4- and 8-week intervals"?

20 A. Correct. So I think this, again, highlights this
21 idea that this enormous efficacy -- I keep saying that because,
22 truly, unless -- when we lived through it, it was something
23 that I'll never live through ever again in my life, that the
24 efficacy was so high. And so what he's pointing out is that
25 you've got to be able to reach that efficacy; and if you don't,

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1 any new approach, new treatment, new paradigm is not going to
2 be adopted into clinical practice.

3 Q. In your opinion, would the POSA have found Claim 6 of
4 the '572 patent to have been obvious in light of Dixon's
5 disclosures about the VIEW trial?

6 A. No. That's exactly -- this question about efficacy
7 was definitely on our minds.

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

9 I'm going to turn now to talking about some other
10 issues that have been raised in the case, and we're going to
11 pivot now to talking about some of Dr. Stewart's testimony and
12 the Section 112 issue.

13 You were here for that testimony as well, correct,
14 Dr. Csaky?

15 A. I was also here for that.

16 Q. I'm not sure I'll be able to be quite as speedy as
17 Dr. Stewart was on some of those issues, but why don't we start
18 with Claim 6 of the '572 patent, if we can pull up that slide
19 again. And if we don't have that handy, I will come back to
20 that just so we can refresh ourselves on the language.

21 Why don't I ask you this: First of all, were you
22 asked to review Dr. Stewart's enablement and written
23 description and indefiniteness opinions in this case?

24 A. Yes.

25 Q. Okay. And the first thing we're going to talk about

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1 is the language in Claim 6 relating to angiogenic eye
2 disorders.

3 You recall Dr. Stewart's testimony about that
4 language?

5 A. Yes, I did.

6 Q. Let's pull up the slide -- we're going to start with
7 enablement. Let's pull up the slide, Slide 49.

8 Have you been asked to assume a standard for
9 enablement in connection with rendering your opinions in this
10 case?

11 A. Yes. This was provided to me in terms of the
12 requirements to render an opinion on enablement and -- as well
13 as to include evaluating this question of experimentation.

14 Q. Okay. And in answering questions about both
15 enablement and written description, let's start first with the
16 discussion of angiogenic eye disorders that appears in the
17 specification. And for convenience, we're going to use the
18 specification of the '572 patent which is PTX 0003. Okay?

19 A. Yes.

20 Q. And feel free to use your binder, although I think
21 we're also going to have some snippets to put up on the screen.

22 With respect to the -- let's just start with what the
23 specification says about angiogenic eye disorders. Let's start
24 with Column 1, and let's look at lines 30 through 36.

25 And what does this language of the '572 patent

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1 discuss?

2 A. So this is the field of the invention and discusses
3 how the present invention relates to the field of therapeutic
4 treatments of disorders and then specifies that to the
5 invention as it's related to the administration of VEGF
6 antagonists to treat eye disorders caused by or associated with
7 angiogenesis.

8 Q. And let's take a look at the next portion of the
9 specification at Column 2, lines 43 through 46. What does this
10 section of the specification say about the methods of the
11 present invention?

12 A. So it further defines and it gives us some of these
13 angiogenic eye disorders, including age-related macular
14 degeneration, diabetic retinopathy, and diabetic macular edema.

15 Q. Okay. If we go forward several more pages to
16 Column 5, lines 30 through 48, there's a header on this page
17 called "Angiogenic Eye Disorders," if we go about halfway down
18 the page.

19 And what does this -- what do the inventors say about
20 angiogenic eye disorders as a group as listed in this section?

21 A. Right. So what the inventor is describing is the --
22 he's defining the angiogenic eye disorder as a disease of the
23 eye, which is caused by or associated with growth or
24 proliferation of blood vessels or by blood vessel leakage. So
25 he makes it very clear what -- how he's defining angiogenic eye

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1 disorders.

2 Q. Okay. And did he include any language here to
3 address commonalities between angiogenic eye disorders?

4 A. Yes. So, again, what he's talking about here is that
5 these common pathologic mechanisms by which these angiogenic
6 eye disorders would be associated with.

7 Q. Okay. Let's move forward to another excerpt, which
8 is at Columns 17 to 18. There we have it.

9 What else did Dr. Yancopoulos say about the use of
10 the administration regimens described in the patent?

11 A. Yeah. I mean, he points out that these regimens that
12 are being described may be used to treat these diseases, and --

13 Q. All right. So I want to talk -- we can take that
14 snippet down.

15 Having gone through those, I want to turn for a
16 moment to talking about some of Dr. Stewart's testimony about
17 angiogenic eye disorder opinions.

18 First of all, you heard him testify about several
19 conditions that he said he believed are not enabled by the
20 patent.

21 Do you recall that generally?

22 A. I do recall that.

23 Q. Okay. Do you recall him specifically talking about
24 pannus -- I hope I say this right -- pterygium, and one called
25 PVR?

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1 A. Correct.

2 Q. Do you recall him also mentioning corneal
3 neovascularization?

4 A. Correct.

5 Q. You recall -- this is just for orientation. He
6 mentioned a series of exhibits which are DTX 5429, DTX 5430,
7 and DTX 5431. I'm not going to put all of those up on the
8 screen, but do you have a copy of those there in your binder?

9 A. Yes, I do.

10 Q. Are you familiar with the disease -- are you familiar
11 with those diseases?

12 A. Yes, I am.

13 Q. And have you read all of those exhibits that
14 Dr. Stewart referred to in his testimony?

15 A. I did.

16 Q. Have you had a chance to respond to those references
17 yet?

18 A. Not officially.

19 THE COURT: One second, Doctor.

20 Yes, Counsel.

21 MR. McLAUGHLIN: Objection, Your Honor. This is,
22 again, beyond the scope of his expert reports. He didn't
23 address any of these references in his responsive expert
24 report.

25 MS. OBERWETTER: That's because they were raised in

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1 Dr. Stewart's reply.

2 THE COURT: Rebuttal evidence. Overruled.

3 BY MS. OBERWETTER:

4 Q. Why don't we take one example. So you've not had a
5 chance yet to provide a response to those, correct?

6 A. I have not had a chance to reply to a response,
7 that's correct.

8 Q. Let's take one of these exhibits that Dr. Stewart
9 referred to as an example, and that is the Shahraki reference,
10 which is DTX-- for the record, DTX 5431, and I believe we have
11 a copy of it up on the screen at this point.

12 First of all, just briefly, what is this article
13 about that Dr. Stewart mentioned?

14 A. So this is, again, a review article about an update
15 of the treatment of pterygium and some of its clinical features
16 and management.

17 Q. Okay. And did you hear Dr. Stewart testify about his
18 doubts that an anti-VEGF agent could treat pterygium?

19 A. Yes.

20 Q. Why don't we take a look at a portion of his paper
21 that I think wasn't discussed earlier this week. If we go
22 forward to page 11 of the document, and in particular there is
23 a section starting down toward the bottom left, Shenasi and
24 colleagues, if we could highlight that. That's the excerpt I
25 was looking for.

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1 I know there is some technical material that is
2 included in this discussion of the Shahraki reference, but what
3 do you understand this reference to be describing here?

4 A. So, again, what this reference is to a study of an
5 anti-VEGF agent, bevacizumab. And typically what happens is is
6 that these pterygium are removed and then the vessels can then
7 regrow on the sclera. And so the idea here was, if we add an
8 anti-VEGF agent, can there have some efficacy?

9 And I think what we see here is the recurrence --
10 that is the recurrence of blood vessels -- after this surgery
11 in the anti-VEGF group, the bevacizumab group, was 33 percent;
12 if you didn't add the bevacizumab, it was 90 percent.

13 Again, that would suggest and demonstrate that
14 anti-VEGF agent could be beneficial in the treatment of
15 pterygium.

16 Q. Did any of the references that Dr. Stewart cited do
17 anything in your mind to disprove that aflibercept in
18 particular may allow for the treatment of the conditions that
19 he mentioned?

20 A. No.

21 Q. And why not?

22 A. Because, again, I mean, there are, of course,
23 additional references. And when we look at the pathology of
24 pterygia, there's more and more evidence that anti-VEGF agents
25 could be used. And, obviously, bevacizumab is one of them.

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1 Aflibercept is an anti-VEGF agent; so it's reasonable to
2 presume that it would be equally as effective as bevacizumab in
3 the treatment of pterygium.

4 Q. Okay. Did you understand Dr. Stewart, in fact, to
5 agree, at least in part during his testimony, that these
6 disorders are mediated by VEGF?

7 A. Yes. Yes. I think he did say that.

8 Q. And do you recall him saying that there may be more
9 complex mechanisms associated with those diseases but that they
10 include VEGF?

11 A. Correct.

12 Q. And is that your opinion as well?

13 A. Yes. Yes.

14 Q. I'm cognizant we're about to be at our break, but one
15 more additional question.

16 In your opinion, would the POSA think that
17 aflibercept could be used to treat pannus, pterygium, corneal
18 neovascularization, and the PVR indication that we -- disorder
19 that we've been talking about?

20 A. Yes.

21 Q. And why?

22 A. Well, again, without going into too much technical
23 detail, there's more extensive literature, especially on these
24 conditions as it relates to anti-VEGF therapies, right? So
25 with the advent especially of bevacizumab, a lot of my

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1 colleagues -- corneal colleagues are using bevacizumab for
2 corneal neovascularization. They've shown some very nice
3 results.

4 There's a whole field of research on anti-VEGF
5 therapy in PVR. Andrius Kazlauskas at the University of
6 Chicago, Illinois, has been studying this extensively. And
7 there have been successful trials in PVR with anti-VEGF agents.
8 And so there's really a very complete -- if you look at the
9 entire landscape, there's support for all of these conditions
10 to some degree with an anti-VEGF agent.

11 THE COURT: Yes, Counsel?

12 MR. McLAUGHLIN: Objection. Again, this is not cited
13 anywhere in his expert report. These are brand-new opinions
14 that we're hearing for the first time today.

15 THE COURT: Counsel?

16 MS. OBERWETTER: I respectfully submit that the
17 references should have been provided before the reply report if
18 they did not want to hear a response for the first time here.

19 MR. McLAUGHLIN: He still could have provided these
20 opinions in his response report. Dr. Stewart's opinions were
21 set forth in his opening report. He had -- Dr. Csaky had every
22 opportunity to respond to those at that point in his response
23 report. These are new opinions. They shouldn't be coming in
24 for the first time today.

25 MS. OBERWETTER: Your Honor, they bear the burden of

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1 proof on these issues. And so I don't think Dr. Csaky had to
2 guess about which references and which disorders were going to
3 be the source of a responsive point.

4 THE COURT: But were those references disclosed in
5 the opening report?

6 MS. OBERWETTER: I do not believe so, Your Honor.
7 I'm happy to be corrected on that if they were in the opening
8 report.

9 MR. McLAUGHLIN: I don't recall if those specific
10 references were identified, but Dr. Stewart's opinions about
11 the inability to treat these disorders with aflibercept, that
12 was certainly in his opening expert report. It could have been
13 responded to at that point.

14 THE COURT: We're in a game of telephone. Coming
15 down the table to you, Counsel.

16 MS. MAZZOCHI: Your Honor, if I may.

17 Dr. Stewart specifically identified these diseases in
18 his opening report. Dr. Csaky, in his responsive report, then
19 complained, well, I don't see a literature reference. So then
20 Dr. Stewart in response said, well, here's literature
21 references. So he was initially basing it on his opinion,
22 experiences, et cetera.

23 THE COURT: So Dr. Csaky identified this as a
24 criticism of Dr. Stewart in his report?

25 MS. MAZZOCHI: Right.

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1 THE COURT: Objection overruled. Thank you.

2 We're going to take our break at this point.

3 Doctor, you've been here throughout; so these will be
4 familiar words to you. No one can communicate with you. They
5 are required to feed you, assuming the change in schedule's
6 been accommodated by our local eateries. But you're a man
7 without a country for the lunch break, sir. Thank you. You
8 may step down. Thank you very much.

9 Counsel, as I mentioned, we do have a criminal
10 proceeding that we need to take up that's scheduled for 12:15.
11 So if I could ask you to sort of just move everything back a
12 row, it would be much appreciated. Then we should be in good
13 shape to resume at 12:30 with Dr. Csaky's direct.

14 Thank you all very much.

15 (A recess was taken from 11:04 a.m. to
16 12:48 p.m.)

17 THE COURT: Good afternoon, Doctor.

18 Ms. Oberwetter, if you're ready to proceed, you may.

19 MS. OBERWETTER: Thank you, Your Honor.

20 Before we proceed with Dr. Csaky, I've been informed
21 I should clarify one exhibit reference in the record. There
22 was a reference to a Dr. Schmidt-Erfurth reference, and that
23 should be PTX 1145, not PTX 1146, as the source of the
24 underlying document.

25 BY MS. OBERWETTER:

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1 Q. Dr. Csaky, I'm now going to turn back to asking you
2 just a few more questions about the angiogenic eye disorder
3 topics that we were discussing prior to the break.

4 Dr. Stewart noted during his examination that
5 aflibercept has not become the standard of care for angiogenic
6 eye disorders since the patent issued. In your view, why is
7 that?

8 A. Well, I mean, the approval --

9 Q. Let me clarify my question. I'm talking about
10 pterygium, PVR. Apologies for the unclear question.

11 A. Sure.

12 So the main reason, of course, is the availability of
13 bevacizumab, right, which is obviously a very cheap anti-VEGF
14 agent that we can use off-label. And so in the majority of
15 these cases, we're going to be using something that's off label
16 and cheap. That's one of the advantages to bevacizumab. And
17 so the efforts that my colleagues have made in these angiogenic
18 disorders in which aflibercept has not been approved for is
19 with bevacizumab primarily.

20 Q. In your opinion, would the POSA have found that the
21 method of treating described in Claim 6 is enabled to treat a
22 full scope of angiogenic eye disorders?

23 A. Yes.

24 Q. Okay. And I want to focus for a moment on
25 Dr. Stewart's opinions suggesting that it would take undue

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1 experimentation to practice the invention. And if we pull up
2 for a moment again the enablement standard that you used. And
3 that's Slide 49.

4 What would the POSA need to do to practice Claim 6 as
5 to any of the angiogenic eye disorders that were listed in the
6 specification we looked at from the '572 patent?

7 A. Right. And so, you know, as I was instructed to do
8 when I made my opinion in regards to enablement, right, so I
9 read the standards, applied that to the specifications, went
10 through the various, you know, exercises and thinking about
11 what was in the specifications, what was available that a POSA
12 would already know going in. There's a lot of ground
13 evidence -- I mean, ground knowledge that a POSA would have.

14 And then I also, of course, went through some of
15 these factors for experimentation. And, again, when I kind of
16 checked the box and going through the list of my understanding
17 of the ophthalmologist POSA person, it really didn't require a
18 lot of experimentation. There's clear guidelines in the
19 specifications. You know, we're familiar with doing
20 intravitreal injections. It's something that we do all the
21 time.

22 We knew -- I mean, the wordings and the descriptions
23 are very clear to the POSA, right? We understood the state of
24 the prior art. We understood that, you know, this is what we
25 do for a living. We inject people's eyes. And we understood

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1 that we already had some evidence that using antiangiogenic
2 agents seemed to have some effect on these diseases. And,
3 again, the breadth of the claims were relatively modest and fit
4 into our wheelhouse of the POSA.

5 Q. Okay.

6 And we can take that slide down.

7 I'm going to change topics a little bit, Dr. Csaky,
8 to talk now about the diabetic macular edema and diabetic
9 retinopathy claims, so Claim 25 of the '601 patent and
10 Claims 11 and 19 -- I'm sorry; I have this backwards --
11 Claim 25 of the '572 and Claims 11 and 19 of the '601 patent.

12 You understand that Mylan and Biocon are arguing that
13 the DME and DR claims in the patents lack written description
14 and enablement. You understand that position?

15 A. Yes.

16 Q. And why don't we take those arguments one at a time.

17 Have you considered whether those claims have
18 adequate written description support in the specification?

19 A. Yes.

20 Q. And let's pull up again the slide with the standard
21 for written description. If we take a look at slide -- if we
22 take a look at Slide 50.

23 First of all, as we've been discussing throughout
24 this examination, you understand these claims to disclose a
25 regimen that includes 2 milligrams of aflibercept, five loading

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1 doses, and every-eight-week extended-dosing intervals, correct?

2 A. Correct.

3 Q. With respect to the portions of those claims reciting
4 a method of treating DME or DR, what indicated to you that the
5 inventor had possession of the invention if we again start
6 taking a tour through the specification?

7 And let's just start with Column 1 at lines 40 to 50.
8 And, again, we're looking at the '572 patent, which is PTX 003.

9 A. Right. So, again, I walked through the various words
10 in the claims and then went back into specifications and said,
11 okay, is there angiogenic eye disorders that are outlined and
12 the specific -- as it relates to diabetic macular edema? And
13 here in part of the specification, it clearly calls out a
14 diabetic macular edema as an angiogenic component as one of
15 these diseases as outlined in the claims.

16 Q. And does he single out DME in particular in this
17 paragraph?

18 A. Yes.

19 Q. Okay. Let's take a look -- if we move on to Column 2
20 of the patent, what else is in the patent specification
21 identifying diabetic retinopathy and DME?

22 A. Yeah, I mean, here's another section of the
23 specification where it clearly states that the present
24 invention can be used to treat. And these include diabetic
25 retinopathy and diabetic macular edema. So, again, from a

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1 POSA's perspective, it's pretty clear this patent, what it is
2 detailing for us.

3 Q. Let's go forward to Column 3 and see what else is in
4 the specification on these issues.

5 What -- are some of the diseases that we're talking
6 about in the particular claims called out in the angiogenic eye
7 disorders paragraph?

8 A. Yeah. Again, there are certain diseases that are
9 called out: the age-related macular degeneration; as you see
10 here, diabetic macular edema; and diabetic retinopathies.

11 Q. Those were all disclosed within the face of the
12 specification?

13 A. Absolutely. These are all in the specifications.

14 Q. I want to turn a little bit forward. I think we have
15 an excerpt that's numbered 22.6. And were there other places
16 in the specification that talk about diabetic macular edema and
17 diabetic retinopathy?

18 A. Right. So here too is now a further reference in the
19 specification towards these -- what the regimen can be used
20 for. And so it's clearly giving me the guidelines to say, you
21 know, Dr. POSA, if you want to use these regimens to treat
22 diabetic macular edema or vascular retinopathy -- which, in our
23 world, can include diabetic retinopathy -- yes, here are the
24 specifications for those.

25 Q. Okay. I want to focus --

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1 We can take that down.

2 I want to focus on portions of the specification that
3 identify loading doses and numbers of loading doses, if we can
4 take a look at some of that material for a moment.

5 Did you identify portions of the specification
6 directed to loading doses?

7 A. Yes.

8 Q. Okay. And let's take a look at Column 4. And what
9 does this portion of the specification describe?

10 A. Right. So this is, you know, some -- an outline of
11 the specifications where the inventor is communicating to the
12 POSA, saying, look, my invention comprises administering to a
13 patient any number of secondary and/or tertiary doses. And
14 then goes on and says, look, in certain embodiments, two or
15 more secondary doses will be administered. And, of course, in
16 that sequence there's the number 4, which would again -- you
17 know, it's something that we'd be quite familiar with in terms
18 of saying, oh, yes, I understand I have to give four secondary
19 doses.

20 Q. And four is part of a list of numbers that's
21 contained in this section, correct?

22 A. Correct.

23 Q. And what does the four secondary doses correspond to
24 as relates to the DME and DR claims that we've been talking
25 about?

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1 A. Right. So these would follow the initial dose. And
2 so it would be a total of five loading doses.

3 Q. And that is within the list conveyed by the patent?

4 A. That's within the list conveyed in the patent.

5 Q. I want to proceed further to a portion of the patent
6 under the header "Example 7." So if we go ahead to that
7 section of the patent.

8 You reviewed Example 7 that's in the specification?

9 A. Correct.

10 Q. What does Example 7 contain?

11 A. Yeah. So, I mean, if I'm looking here and
12 questioning whether the inventor is in possession of the
13 specification, in this case in line 35, this wording is almost
14 identical to what the claims are. It's an intravitreal
15 injection once every four weeks for the first 16 weeks -- that
16 would be the five loading doses -- followed by intravitreal
17 injections once every eight weeks.

18 Q. I'd like to turn to another component of the claim
19 limitations. And let's focus for a moment on the monthly
20 interval that occurs in connection with the loading doses.

21 Let's take a look at Column 3, the portion that
22 spills onto Column 4. What does this portion -- so we're
23 looking at Column 3 around line 66 spilling onto Column 4
24 toward the very top of Column 4. And, again, this is PTX 003.

25 What does this disclosure tell the POSA?

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1 A. Well, again, you know, we're looking at now
2 injections. And we're looking to see, okay, what are the
3 intervals that this invention may be communicating to us? And
4 I'm reading the specifications. And I see that there is this
5 delineation that each secondary dose be administered two to
6 four weeks after the immediately preceding dose in the initial
7 line.

8 So I now can see that, okay, there is this option to
9 do it four weeks after each dose. And, in effect, it goes on
10 to then, in a redundant fashion, say it again, that each
11 secondary dose may be administered to the patient four weeks
12 after the immediate preceding dose.

13 Q. Okay.

14 We can take that slide down.

15 With respect to -- sorry.

16 Now we're going to turn to another portion of the
17 claim limitations. If we -- with respect to the portion of the
18 claims that recite the use of an eight-week interval between
19 those fixed dosing periods after the secondary doses, what
20 indicated to you that the inventor had possession of that
21 aspect of the invention if we pull up, to start with, Column 3?

22 Again, I think we're looking at that same section,
23 just with some different language highlighted.

24 A. Correct. So this is now -- you know, I'm looking for
25 language that says, you know, is there something that tells me

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1 that he's in possession of thinking about tertiary dosing every
2 eight weeks? And in this section it clearly states -- in fact,
3 it's interesting that that's the first number that it tells
4 me -- each tertiary dose is administered at least eight weeks
5 after the immediate preceding dose. And then of course down at
6 the bottom, again in a repetitive fashion, it says the same
7 thing again.

8 Q. Okay. Let's advance forward again to Example 7.

9 And does Example 7 from the '572 patent -- in this
10 excerpt we're looking at around line 35 referring to four weeks
11 for the first 16 weeks, what does that example have to say
12 about the extended-dosing interval?

13 A. Yeah. So, again, it delineates quite clearly that
14 these tertiary doses -- in this case, once you finish the four
15 weeks -- every-four-week injections. So once you finish those
16 five loading doses, you now advance to injecting once every
17 eight weeks.

18 Q. In your opinion at the time of the January 2011
19 priority date, would the POSA have recognized that
20 Dr. Yancopoulos was in mental possession of the dosing regimens
21 set forth in Claim 25 of the '572 patent and Claims 11 and 19
22 of the '601 patent?

23 A. Yes. I mean, I think there's clear language that
24 would have directed a POSA to say yes. I mean, the aspects of
25 the claim are within the specifications.

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1 Q. I'm also going to ask you some questions related to
2 enablement about that same language that we were just looking
3 at.

4 And, again, if we can call up Slide 49, the standard
5 for enablement.

6 Have you considered the specification disclosures we
7 just went through relating to the increments associated with
8 the dosing regimen from the standpoint of enablement?

9 A. Yes. Yes.

10 Q. And have you reached a conclusion as to whether
11 Claims 25 -- Claim 25 of the '572 patent and Claims 11 and 19
12 of the '601 patent are sufficiently enabled?

13 A. Yes. You know -- and, again, injections in our world
14 are very common. This is what we do for a living. We dose
15 certain numbers. We have intervals. And in these
16 specifications we're being guided and told, look, here are some
17 number of doses, and we -- but we have specific intervals that
18 we have to follow. So I think these are not for us outside the
19 scope of what we're used to doing in our day-to-day practice.

20 Q. Would the POSA, with the benefit of the disclosures
21 we just looked at and the language of these claims, be able to
22 perform the method of administering aflibercept in the five
23 monthly loading doses every eight weeks -- every-eight-week
24 dosing to treat DME or DR?

25 A. Yeah, absolutely.

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1 Q. And would the POSA, with the benefit of the
2 disclosures we just looked at and the language of these claims,
3 understand that that method could be used to treat DME or DR
4 without undue experimentation?

5 A. Yes.

6 Q. Okay. I want to go back for a moment because I
7 believe there is a small unit that I forgot to cover when we
8 were addressing angiogenic eye disorders.

9 So if we take that slide down for a moment.

10 Dr. Csaky, we talked about angiogenic eye disorder
11 argument that Dr. Stewart advanced with respect to enablement,
12 but I have just a few questions about that with respect to the
13 written description standard as well.

14 You understand that Dr. Stewart advanced an argument
15 in connection with angiogenic eye disorders that the disclosure
16 of those disorders did not provide a sufficient written
17 description.

18 A. Yes.

19 Q. Okay. And what is your opinion in that regard with
20 reference to the section of the specification -- the sections
21 of the specification that we looked at in our angiogenic eye
22 disorder unit?

23 A. Yeah. I mean, as I said this morning, I mean, these
24 are descriptors and identification of diseases that are well
25 known and, in part of our world, involve vascular leakage,

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1 vascular growth, and so it falls well within our scope of
2 angiogenic eye disorder.

3 Q. Okay.

4 And if we pull up Slide 50 for a moment, please, just
5 so we have the written description standards available.

6 In your opinion, did Dr. Yancopoulos have possession
7 of Claim 6 of the '572 patent as of the January 2011 priority
8 date?

9 A. So this is the -- so as it relates to the treatment
10 of an angiogenic eye disorder, yes.

11 Q. Okay.

12 We can take that slide down.

13 I'd like to change topics just a little bit. First
14 of all, you understand that portions of the -- what issued as
15 the '572 patent and the '601 patent were added after January
16 2011, correct?

17 A. Correct.

18 Q. Okay. And you watched Dr. Stewart's testimony
19 earlier this week, correct?

20 A. I did.

21 Q. And did you see the two demonstratives that he used
22 for the '572 and '601 patents that were highlighted to indicate
23 in which years certain disclosures were made?

24 A. Yes.

25 Q. Do you have any disagreement with the way he

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1 highlighted that demonstrative?

2 A. Yes. I did not agree with his position.

3 Q. So let me just back up for a moment.

4 As to the actual highlighting, I'm not asking your
5 substantive opinion at the moment. Just as to the actual
6 highlighting in the document, did you agree with what he --

7 A. Yes. Yes. So he highlighted the difference -- I
8 apologize -- the highlighted differences where I agreed that
9 there were differences between the provisionals between those
10 two documents.

11 Q. Okay. And if we pull up for a moment -- we have a
12 snapshot of what is PTX 304, which is the cover of the '245
13 provisional application.

14 Do you see that?

15 A. Yes.

16 Q. Okay. And this is a document that you reviewed,
17 correct?

18 A. Yes.

19 Q. And you don't have any -- this document contains
20 certain language that ultimately appeared in the '572 and '601
21 patents, correct?

22 A. That's correct.

23 Q. And you are in agreement with Dr. Stewart on the
24 point that some language was added after that?

25 A. Yes. Yes. Yes. There's definitely language added

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1 that I agree with him on that.

2 Q. Okay. With the actual words that were added later
3 and the way he highlighted those on his patent demonstrative?

4 A. Yes.

5 Q. Does the absence of any of the language that was
6 added later from the '245 provisional alter your view as to
7 whether the DME and DR claims should be entitled to a January
8 2011 priority date?

9 A. No. So that's, I guess, what I was trying to answer
10 initially, is that when I reviewed that addition and if the
11 question is did that change my view of the specifications, the
12 answer is no.

13 Q. Okay. And we looked, for example, at Example 7 in
14 the patent, correct?

15 A. Right.

16 Q. And if you assume the patent specification without
17 Example 7, would your written description opinions in this case
18 remain the same?

19 A. Yes.

20 Q. Okay. And you heard Dr. Stewart testify that he
21 thought Example 7 also is not a disclosure that would support
22 the claimed regimens, correct?

23 A. Correct.

24 Q. Do you agree -- what is your response to that?

25 A. So, you know, the way I viewed Example 7 was it was

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1 a -- again, a detailed aspect of the specification. But in my
2 view, when I looked in previous sections of the specifications,
3 I saw that it's simply another kind of redundancy in terms of
4 detailing the approach. But the substance of these approaches
5 were also present in the previous sections of the
6 specifications.

7 Q. Okay. I'd like to turn to talking about a different
8 argument that Dr. Stewart made which relates to the concept of
9 indefiniteness.

10 Do you recall --

11 A. Yes.

12 Q. Okay.

13 And let's put up on the screen Slide 51 which has the
14 indefiniteness standard.

15 And, Dr. Csaky, is this a standard that you took into
16 account in connection with your opinions?

17 A. Yes.

18 Q. Okay. And, in particular, you recall that
19 Dr. Stewart offered testimony about the meaning of the word
20 "approximately."

21 Do you remember that?

22 A. Correct.

23 Q. And that is a word that exists in the claims in this
24 case?

25 A. That's correct.

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1 Q. Why might a patient not be able to receive an
2 aflibercept injection at, for example, exactly four weeks?

3 A. Well, there's lots of reasons. His physician may be
4 testifying in West Virginia for a while, and that would be an
5 approximate change in his or her schedule. So there's lots of
6 reasons why we use the word "approximate." It's a term we use
7 day to day in our lexicon in taking care of patients.

8 Q. As a POSA, do you have any confusion around the word
9 "approximately"?

10 A. No.

11 Q. Okay. And why not?

12 A. Again, you know, in medicine -- in real-world
13 medicine, we don't live in absolutes. And so we live in a
14 world where there's issues on scheduling, there's issues around
15 doctors' schedules. There's a bunch of issues. And so we're
16 very comfortable living in a world of approximate, about, those
17 kinds of term.

18 Q. Have you considered whether the POSA would have
19 reasonable certainty as to the scope of the claims at issue in
20 this case in light of the use of the word "approximately"?

21 A. I would have no concerns.

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

23 So I'd like to change topics again, and I'd like to
24 talk about something that relates to some of the obviousness
25 opinions discussed earlier in your testimony, and that's

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1 specifically with respect to objective indicia of
2 nonobviousness and some of those indicia that are outlined in
3 your report.

4 Dr. Csaky, have you offered an opinion in this case
5 as to whether objective indicia of nonobviousness support the
6 nonobviousness of the claims of the '601 and '572 patents that
7 are at issue in this case?

8 A. I have.

9 Q. Okay. And we're going to take some of these one at a
10 time, but why don't we start with the concept of long-felt
11 need.

12 In January of 2011 did there exist a reliable fixed
13 extended dosing regimen for the treatment of any angiogenic eye
14 disorders?

15 A. No. And, again, we talked about this, the fact that
16 what we had tried did not come close to equating to the very
17 strenuous monthly dosing regimen that we had.

18 Q. Why was it important to find a reliable fixed
19 extended dosing regimen for the treatment of angiogenic eye
20 disorders?

21 A. Well, you know, again, as we talked about, the field
22 was moving towards prn, and there was some advantages.
23 Obviously, prn was something that we were using OCTs. But the
24 challenge with prn or fixed dosing was that it did require,
25 lots of times, multiple visits. And so having this idea that

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1 you could have an extended fixed-dosing schedule is something
2 that would be in certain cases very attractive.

3 You know, as somebody who's practiced in small
4 clinics, you can well imagine that our OCTs sometimes don't
5 work, and getting a technician to come in and fix that machine
6 doesn't happen overnight, right? And so if I have a patient --

7 THE COURT: Doctor, could you tell me which machine
8 that is? As I made reference to a couple times during the last
9 couple weeks, I wear contacts; so I go for my annual and all
10 that. And my treater, they just have a room with all these
11 fancy machines in it, and they make me take my contacts out so
12 I'm blind, and they just steer me around.

13 Which of these machines are we talking about?

14 THE WITNESS: This is called the optical coherence
15 tomographer. It's not invasive. You put your chin up there,
16 and you'll see sometimes a little blue light or a light. And
17 what it does is it gives them a cross-section real-time view of
18 your retina. And it scans the retina, and so you can really
19 see if there's any pathologies, changes in the anatomy, that
20 you might have.

21 And so as we talked about, in prn dosing, treat and
22 extend, we use that extensively. It's almost a requirement.
23 And so if I'm using prn, I've got to have my OCT working. I
24 can tell you in these smaller clinics, sometimes it ain't
25 working. And if it ain't working, then I got to -- I have a

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1 new patient, want to be able to have a regimen that I can kind
2 of go to, and fixed extending dosing would be one that I would
3 have gone to because I wouldn't have needed always to have my
4 OCT to make those treatment decisions that we talked about.

5 BY MS. OBERWETTER:

6 Q. Thank you, Dr. Csaky.

7 I'd like to talk briefly also about the concept of
8 failure of others. And we've just talked about how prior to
9 January 2011 there was not a reliable extended dosing regimen
10 for the treatment of angiogenic eye disorders.

11 Had others besides Regeneron attempted to develop
12 such regimens?

13 A. Yeah. I mean, the only attempt for these 12-week or
14 three-month extended dosing, and as we've talked about
15 extensively, those just did not meet these criteria of really
16 very, very high bar. And so those had failed.

17 Q. Okay. I want to focus your attention for a moment on
18 a drug you talked about a few times, Macugen, if you can turn
19 your attention to that one.

20 Had there been efforts to develop extended dosing
21 regimens for Macugen?

22 A. Yes. So Macugen originally was a loading and a six
23 weeks' interval for Macugen. The Macugen data was really quite
24 poor. I mean, very few patients actually saw any degree of
25 vision gains whatsoever. And so that was quickly abandoned,

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1 even though when it was partnered with Pfizer, Pfizer then
2 tried to extend it and use it for diabetic retinopathy in a
3 12-week dosing schedule as well with Macugen. And all we know
4 is there was no data reported; so we have to assume that that
5 didn't work.

6 Q. Okay. I'd like to turn to a different topic, the
7 concept of industry praise. And if we can pull up Slide 53.

8 Dr. Csaky, does Slide 53, which cites to DTX 3112,
9 PTX 0841, and PTX 1155, does this contain some of the
10 discussion of industry praise that you included in your report?

11 A. Yes.

12 Q. And can you please just walk us through some of the
13 reaction after Eylea with its extended regimen was launched.

14 A. Yeah. I mean, I think we've got folks at the Food
15 and Drug Administration talking about how Eylea is an important
16 new treatment option for adults. I think they recognized that
17 their two-month dosing schedule was the same as monthly dosing
18 schedule, and so that was a big win.

19 And that was similar to some of the reports by my
20 colleagues who also then talked about, again, this idea that,
21 again, we could attain these visual gains. And, again, I think
22 really want to reiterate that the bar was high, and so
23 everybody was really impressed with the fact that, by reducing
24 the number of fixed dosing, you could still maintain that high
25 bar and then, of course, this idea that, because of that and to

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1 achieve that high bar, we might have an option for reducing the
2 number of injections.

3 Q. Okay. And one of those references identified up on
4 the screen is Ohr and Kaiser 2012. Do you see that one?

5 A. Yeah.

6 Q. And can you describe the concept that's discussed in
7 that quote.

8 A. Yeah. So the idea was they're discussing the
9 results. And these are both well-respected retina specialists.
10 And they're talking about the fact that you could not just
11 generate the visual gains, obviously, but maintain them with
12 this significantly smaller number of injections compared with
13 ranibizumab.

14 And, again, they're pointing out, which I think was
15 really this bar and how that was really impressive that we
16 could continue to maintain these high degree of visual gains in
17 these large studies over this period of time.

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

19 Dr. Csaky, there have been suggestions made in this
20 trial that the fixed extended regimens of the claims are not
21 actually beneficial to ophthalmologists or their patients.

22 Do you agree with that suggestion?

23 A. No.

24 Q. And can you explain why? And I know we've touched on
25 some of this.

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1 A. Again, we've talked about it in my prior deposition,
2 right? I mean, talked about how in certain settings for
3 patient scheduling and for their -- we use that and we -- I
4 referenced certain of my colleagues as well in other -- and I
5 do think that it's, like I said, important to recognize where
6 it kind of fit into our -- the landscape.

7 And, again, this idea, while treat and extend and prn
8 were clearly the dominating treatment regimens, the fact that
9 you could have this alternative approach in certain settings
10 with certain patients was an enormous advantage in our whole
11 armamentaria of treating patients during this period of time.

12 MS. OBERWETTER: Thank you, Dr. Csaky.

13 I pass the witness.

14 THE COURT: Understood.

15 Cross.

16 MR. McLAUGHLIN: Your Honor, Neil McLaughlin on
17 behalf of Mylan and Biocon. May not surprise you to hear that
18 we have a few binders for the Court.

19 THE COURT: That, in fact, does not surprise me.

20 MR. McLAUGHLIN: May we approach, Your Honor?

21 THE COURT: You may.

22 Whenever you're ready, Counsel.

23 MR. McLAUGHLIN: Thank you, Your Honor.

24 CROSS-EXAMINATION

25 BY MR. McLAUGHLIN:

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1 Q. Dr. Csaky, you stated to your peers that, looking at
2 overall practice patterns, there is not a significant
3 difference in terms of the use of ranibizumab versus
4 aflibercept based on the trial data from VIEW 1 and VIEW 2;
5 isn't that right?

6 A. I'm sorry. Repeat that question. I'm sorry. I
7 reported...

8 Q. Dr. Csaky, you have stated to your peers that,
9 looking at overall practice patterns, there is not a
10 significant difference in terms of use of ranibizumab versus
11 aflibercept based on the trial data from VIEW 1 and VIEW 2;
12 isn't that right?

13 A. If you can direct me to where I said that to my
14 peers. I don't recall. I'm sure I did. I'm sure you'll show
15 me where I did.

16 Q. Why don't we pull up DTX 9008.

17 This is from a publication called *Retina Today* from
18 the January-February 2012 issue. Do you see a statement
19 attributed to you at the top of page 14?

20 A. Yes. Exactly.

21 Q. And there you're quoted as saying, "Ultimately,
22 however, if you look at our overall practice patterns and how
23 frequently we are routinely injecting patients with
24 ranibizumab, which might add up to seven or eight times per
25 year, there is not a significant difference in terms of use of

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1 ranibizumab versus aflibercept based on the trial data from
2 VIEW 1 and VIEW 2."

3 Do you see that?

4 A. Yes.

5 Q. And you also stated that there's not any huge
6 difference, huge price difference, between ranibizumab and
7 aflibercept when it comes down to clinical use; isn't that
8 right?

9 A. I did say that, correct.

10 Q. And you go on to say, "We can agree" -- this is
11 further down -- "that because the two drugs are similar in a
12 safety and efficacy, whether a clinician chooses ranibizumab or
13 aflibercept may come down to personal preference."

14 Do you see that?

15 A. I do see that.

16 Q. We can take that down now.

17 Now, the Heier 2012 publication that we just heard
18 you rely upon, you said that that's persuasive and you've
19 relied upon it for your unexpected results opinions; is that
20 right?

21 A. I'm sorry. Could you refer me to the Heier -- which
22 Heier?

23 Q. Heier 2012.

24 A. Is that this?

25 Q. That's the publication that reported the VIEW 1 and

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1 VIEW 2 results.

2 A. Yes.

3 Q. You relied on that publication, correct?

4 A. I've relied -- can you direct me just so I can open
5 it up and refresh my memory of the details.

6 Q. Actually, let me ask you a couple follow-up questions
7 first.

8 You are aware that that publication was rejected from
9 the *New England Journal of Medicine* when it was originally
10 submitted, are you not?

11 A. I have been told that, correct.

12 Q. And you've previously referred to the *New England*
13 *Journal of Medicine* as the top medical journal in the country.

14 Do you remember that?

15 A. If I said it somewhere in my report or in my
16 deposition, then I'll trust that I've said that.

17 Q. Their opinions are widely read and respected.

18 Would you agree with that?

19 A. So the *New England Journal*, I think -- you know, the
20 critical aspect of the *New England Journal of Medicine* is it's
21 across all specialties, right? So it's not
22 ophthalmology-specific, right?

23 And so the reports that go in there, there has to be
24 decisions by the editors as it relates to the articles that
25 they accept, and that has to be across all specialties --

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1 pulmonary, cardiology, cancer, everything.

2 So it's a widely respected journal in general
3 medicine. That would be a true statement.

4 Q. Did you have occasion to review any of the documents
5 documenting the Regeneron email traffic that occurred after the
6 rejection of that manuscript?

7 A. I may have. I just don't recall exactly, but if you
8 can --

9 Q. Sure. Why don't we go to DTX 916. We'll go to
10 page 1.

11 A. If you'll bear with me just for a second, there's --

12 THE COURT: Is that Volume I or II, Counsel?

13 MR. McLAUGHLIN: Actually, that may not have made it
14 into the binders.

15 THE COURT: Doctor, that's just up on the screen.

16 MR. McLAUGHLIN: Okay. May I approach?

17 THE COURT: You may.

18 BY MR. McLAUGHLIN:

19 Q. And it's also displayed on the screen for you here,
20 Doctor. We're going to page 1. There's an email from Peter
21 Kaiser dated June 9th, 2012.

22 Do you see that?

23 A. Yes.

24 Q. In that email Peter says, "We cannot let the VIEW 2
25 team derail us from being published quickly. Get Andy to

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1 publish this in *Ophthalmology* and get this nightmare behind
2 us."

3 Is that what he said?

4 A. That's what Peter was telling this group.

5 Q. Do you know who Andy is?

6 A. Yes.

7 Q. Who is Andy?

8 A. Andy Schachat.

9 Q. Was he the editor in chief at *Ophthalmology* in 2012?

10 A. At that time he was.

11 Q. Is that typical for authors that articles have just
12 been rejected from the *New England Journal of Medicine* to call
13 up the editor of another journal and get a paper published?

14 A. You know, actually, it's not uncommon for us. It's
15 not so much to get it published, but for example, just recently
16 I submitted an article to *American Journal of Ophthalmology*,
17 and we wrote to the editor and asked the editor if he or she --
18 in this case it's a he, a Dr. Richard Parrish. We asked the
19 editor if this was appropriate for the journal and if he felt
20 that this was something that would be reasonable to be reviewed
21 by that journal.

22 So that's not an uncommon procedure that we sometimes
23 do in trying to figure out, you know where to publish certain
24 things. And so, yes, we -- it's not uncommon for us to have
25 conversations with the editor, again, just more about is this

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1 appropriate, what their initial thoughts are.

2 And then, of course, the way this works is the editor
3 doesn't have the decision-making. He can then -- he or she can
4 then take it in for consideration. It gets sent out to
5 multiple reviewers. The reviewers will then make their
6 recommendations. And based off those recommendations,
7 something may or may not get published.

8 But this type of conversation is not -- I know Peter.
9 He's a little -- should I say bombastic with his comments, but
10 the overall gist of what he's trying to say is something that
11 is not uncommon in any medical field in terms of trying to get
12 a discussion with the editor and seeing what their thoughts are
13 about is this worthy of review in their journal.

14 Q. We can take that down.

15 Let's move on to opinions you've provided about
16 industry praise.

17 Do you recall providing those opinions just a few
18 minutes ago, Dr. Csaky?

19 A. I did.

20 Q. You talked about industry praise for the VIEW 1 and
21 VIEW 2 clinical trial results?

22 A. I did.

23 Q. Now you report -- and your slides today didn't report
24 any praise, any industry praise for the DME or DR dosing ranges
25 relating to five monthly loading doses; isn't that right?

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1 A. I did not.

2 Q. And the industry praise evidence you provided didn't
3 say anything about the tonicity of the Eylea formulation; isn't
4 that correct?

5 A. No, no. As I said, I'm not a tonicity person; so I
6 wasn't looking for tonicity clips.

7 Q. Let's move on to the long-felt need. You also
8 provided opinions on reported long-felt need; is that right?

9 A. Yes, I did.

10 Q. You would agree, though, that Dixon reported in that
11 publication in 2009 the VIEW Phase III three loading dose,
12 every-eight-week dosing regimen, correct?

13 A. Yes. Can we just -- if we're going to talk about
14 Dixon, because I want to pull it up so I can just refresh my
15 memory. Would that be okay?

16 Q. Sure. That's DTX 204. We're going to page 4 of that
17 reference.

18 A. Found it. Okay. Yes, please. I'm sorry.

19 Q. It's also displayed on the screen here for you.

20 A. Yes. Thank you.

21 Q. You don't disagree that set forth here is the 2q8
22 dosing regimen that was being used in the VIEW 1 and VIEW 2
23 clinical trials, correct?

24 A. Oh, yes. So this is indicating the dosing regimens
25 that were going to be tested in the VIEW 1-VIEW 2 trials.

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1 Q. This was in 2009?

2 A. This was in 2009.

3 Q. That's well before the filing dates of the '601 and
4 '572 patents, correct?

5 A. That's my understanding.

6 Q. Now, at this point we pull up Claim 10 of the '601
7 patent, PTX 1, page 21.

8 Is it in front of you on your screen?

9 A. Could you just repeat that DTX number. I'm sorry.

10 Q. That is PTX 1.

11 A. PTX.

12 Q. It's also on the screen in front of you.

13 A. Okay. I'll look at the screen.

14 Q. Could we agree there's nothing in Claim 10 requiring
15 a Phase III efficacy result?

16 A. Correct. I mean, this is a claim and doesn't relate
17 anything to clinical trials.

18 Q. And, in fact, the word "efficacy" doesn't appear
19 anywhere in this claim, correct?

20 A. Correct. Again, my understanding is there were
21 subsequent claims that were dismissed that related to efficacy.
22 But in this alone, there are no efficacy details.

23 Q. While we're here on this claim, it doesn't say
24 "loading" anywhere in this claim, does it?

25 A. The word "loading" is not used. But, again, you

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1 know, when we talked about lexicon in our world, right -- so
2 this is a claim wording, but if I were to show this to an
3 ophthalmologist or a POSA and I asked him or her to say, "Okay.
4 What do you think this is telling you to do?" and it says you
5 will inject 2 milligrams approximately every four weeks for the
6 first five injections, that in our world would be five loading
7 doses.

8 Q. But the word "loading" doesn't appear anywhere in
9 this claim, correct?

10 A. The word -- absolute word "loading" is not available.

11 Q. I want to move on to another document here, DTX 4135.
12 I'd like to see what the Patent Trial and Appeal Board said
13 about whether these eight-week dosing regimen claims that are
14 silent on efficacy have any efficacy requirement.

15 Do you see that highlighted text up there?

16 MS. OBERWETTER: Objection, Your Honor. Foundation.

17 THE COURT: Fair. What's the --

18 MR. McLAUGHLIN: I'm sorry. I didn't hear the
19 objection.

20 THE COURT: Foundation. What are we looking at?
21 What are we talking about?

22 MR. McLAUGHLIN: You've heard a lot of discussion
23 from Dr. Csaky today about efficacy and meeting efficacy --

24 THE COURT: What document do we have up that we're
25 asking about?

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1 MR. McLAUGHLIN: This is an IPR. This is a decision
2 from the Patent Trial and Appeal Board that I think would have
3 been very informative to Dr. Csaky had he considered in
4 formulating his opinions on whether efficacy was something that
5 was read in these claims.

6 THE COURT: Let's start there and see whether he's
7 ever been provided this, reviewed it, or researched it at all.

8 MR. McLAUGHLIN: Sure.

9 BY MR. McLAUGHLIN:

10 Q. First of all, let me ask you this: Do you recall
11 relying on a declaration by Dr. Diana Do in the process of
12 formulating your opinions?

13 A. There were portions -- as I recall, portions of her
14 declarations that I relied on.

15 Q. And that declaration, you understand, came from these
16 IPR proceedings?

17 A. I would have to review exactly those declarations
18 that I reviewed in relationship to this document.

19 Q. Well, I'll represent to you that those did, in fact,
20 come from these prior IPR proceedings.

21 Have you seen this document before, Dr. Csaky?

22 A. I said in -- if I reviewed it, I was reviewing it in
23 the context of forming my opinion as it related to
24 infringement, for example, and gathering information that would
25 inform my opinion as it related to, in this case, infringement.

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1 So I -- if I did review it, it was specifically for
2 that purpose.

3 Q. Okay. And if I could go back to page 23 of that
4 document. I'm going to read this language to you briefly here.

5 "Based on the foregoing and our review of the record
6 as a whole, we find no persuasive support for considering the
7 preamble recitation of a method for treating a patient with an
8 angiogenic eye disorder as requiring such treating to achieve
9 any particular level of effectiveness, much less a high level
10 of efficacy."

11 Do you see that?

12 MS. OBERWETTER: Objection, Your Honor. I think
13 Mr. McLaughlin has established there's no foundation for him to
14 ask Dr. Csaky about this document with respect to these
15 opinions even if the preference would be to put PTAB decisions
16 in front of the Court.

17 THE COURT: Overruled.

18 MR. McLAUGHLIN: I'll also note this is also in his
19 Tab B of things that he's considered in the context of
20 formulating --

21 THE COURT: It's been overruled. Ask your question
22 again.

23 BY MR. McLAUGHLIN:

24 Q. Did you factor this language into your opinions as
25 you were developing your opinions in this case?

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1 A. I may have -- you know, I can't recall exactly the
2 specifics of this since I'm not that familiar with PTAB and
3 those proceedings; so I couldn't put that into context of my
4 world and what informed my opinion.

5 So these are the kinds of discussions and, again,
6 that I may have seen, but I don't know how much role it played.
7 I would have felt uncomfortable about allowing it to form my
8 opinion if I wasn't sure what the context, who was it, what are
9 the different requirements and things like that, as opposed to
10 a -- something that someone that I'm familiar with, another
11 POSA and what other folks commented on about their use of Eylea
12 in their clinical settings.

13 So I can only comment at this point about I may have
14 seen it, but again, because of my uncertainty about, again, all
15 the details and the impact and where it was being -- so I may
16 have seen it, but I don't think I would have used it to -- in a
17 big way because of my uncertainty about the context.

18 Q. Let me ask you this, Dr. Csaky: Even with the
19 Phase III data in hand from VIEW 1 and VIEW 2, we can agree
20 that, when it comes to treatment of angiogenic eye disorders,
21 there's still many patients with these disorders whose needs
22 are still not met. Isn't that correct?

23 A. That's true.

24 Q. And in fact, you're the moderator of an HCP live peer
25 exchange review titled "Unmet Needs for Patients with AMD."

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1 Isn't that right?

2 A. That's very true.

3 Q. If we put up DTX 9204.

4 Do you recall participating in this discussion?

5 A. Yes. And it's pretty recent, December 2021. So yes.

6 Q. The title is "Unmet Needs for Patients with AMD"; is
7 that right?

8 A. That's correct.

9 Q. If we go to page 1 of that document, is that you in
10 the upper left?

11 A. It's a resemblance of me. I hope that isn't the best
12 picture you have of me, but yes, it is.

13 THE COURT: You're an adverse expert, Doctor. They
14 picked that one on purpose. Just kidding. Just kidding.

15 MR. McLAUGHLIN: Promise that's not the case, Your
16 Honor.

17 THE COURT: I know.

18 BY MR. McLAUGHLIN:

19 Q. So I'd like to turn to this selection on page 1.
20 There's a quote attributed to you where you asked one of your
21 colleagues a question, "Jennifer, is the race over? Are we
22 going to be able to crack the durability nut? Is that the only
23 nut that we have left to crack?"

24 Do you recall asking that?

25 A. Yes. I asked it. I don't recall, but I asked it.

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1 Q. Dr. Jennifer Lim, her response is that "I believe the
2 durability question has been addressed to some point between
3 the PDS" -- port delivery system -- "and faricimab."

4 Do you see that?

5 A. Yes.

6 Q. Lim does not mention -- Dr. Lim does not mention
7 aflibercept, does she?

8 A. No.

9 Q. When this question was posed to another one of your
10 colleagues, Dr. Holekamp, she mentioned visual acuity. And she
11 says, "I must throw up my hands and say we don't control visual
12 acuity. There's no agent we've tested so far reliably, at
13 least in Phase III, that produces superior visual acuity
14 outcomes."

15 Do you see that?

16 A. Yes.

17 Q. We can take that down.

18 I want to move on and try and get a little bit of
19 clarity from you about where you stand on this question of the
20 value of fixed regimens versus office visits.

21 Now, we can agree that there is nothing in the
22 claims -- we just looked at Claim 10 of the '601 patent --
23 there's no language in the claims about excluding office
24 visits, correct?

25 A. Correct.

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1 Q. And now, even once clinicians had the VIEW 1-VIEW 2
2 data, you were still of the position that ultimately the issue
3 for retina specialists will be which of those patients you were
4 going to be able to inject and see back in three to four months
5 versus patients who received an injection and may need to come
6 back in every six to eight weeks. Until we can figure this
7 out, we will have to continue to see our patients on a
8 regularly frequent basis.

9 Was that a position you took in front of your peers?

10 A. Yes. I think it's always important to understand the
11 context. And I'm assuming -- can you give me the date of that
12 discussion?

13 Q. Sure.

14 Why don't we actually pull that up. That's DTX 9022.

15 And is that you that's third from the right there on
16 the cover of this magazine?

17 A. Yes. Yes, that's me.

18 Q. If we go to page 10.

19 I'm sorry. Let's stay here for a second.

20 Top right, do you see the date,
21 January-February 2012?

22 A. Correct.

23 Q. That refreshes your recollection about when this
24 occurred?

25 A. Yeah. Exactly.

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1 Q. If we go to page 10, the title of this selection in
2 this magazine is "Ophthalmic Formulations: Safety and Efficacy
3 of VEGF Neutralizing Drugs."

4 Do you see that?

5 A. Yes.

6 Q. So let's jump over to the page where you made that
7 statement. This is on page 13, bottom left corner.

8 Can you see this?

9 A. Yes.

10 Q. And it's true that you made this -- you made these
11 comments in the context of the VIEW trials; isn't that right?
12 If you look at the top of this paragraph.

13 A. Yes.

14 Q. And yet, again, even with that data in hand, you
15 still don't know which patients you're going to need to see in
16 three to four months and which you're going to need to see in
17 six to eight weeks; isn't that right?

18 A. That's correct.

19 So I think, again, it's important to understand the
20 context in which we were -- so this is very soon after Eylea
21 became available, right? And in many ways it's -- we're
22 learning, obviously, as I think I've said multiple times, that
23 prn and treat and extend were the directions that we were
24 going. Right?

25 It doesn't mean that this is -- that I exclusively --

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1 or anyone at that point exclusively used prn and treat and
2 extend. This was in the context of trying to figure out how
3 best to use Eylea. You know, we've learned a lot over the
4 years.

5 For example, it's a very interesting aspect that when
6 I -- even in this context I look back in 2012, and we
7 thought -- I'll give you a good example. We thought that
8 fluid -- I've showed you the prns. And we had to dry things
9 completely. Turns out that wasn't always necessary. So a lot
10 of this, you know, was a work in progress.

11 And it was clear that, while that was the direction
12 that we were heading as a group, it was nice and of course to
13 have this availability of fixed dosing if we needed it under
14 certain circumstances.

15 So I don't think this necessarily indicates that I
16 never used fixed dosing. I think it kind of reflects our
17 enthusiasm at the time of trying to see where we were with prn,
18 treat and extend. So it's kind of -- it's context- and
19 time-dependent. But at the same time, under certain
20 circumstances, as I've testified on numerous occasions and as
21 we've seen Dr. Do's testimony that I relied on and other forms,
22 that there was a role for a fixed every-other-month dosing in
23 certain patient populations in certain conditions.

24 So while this is -- and we've said this over. This
25 was the direction of the field. It didn't preclude the fact

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1 that we had this in our back pocket, fixed dosing.

2 Q. And turning now to those -- the fixed-dosing regimens
3 that you're talking about having in your back pocket back in
4 that time frame, you, in fact, called these fixed-interval
5 dosing regimens, including the eight-week regimen, burdensome;
6 isn't that right?

7 A. Well, again, if you were going to think about this
8 from a -- from every patient, it could have been construed at
9 that time as burdensome. But at the same time, I would have
10 hoped that I would have also said that prn dosing was
11 burdensome. And so there were different approaches that we
12 were trying to take.

13 And, again, I would have said that, for certain
14 patients -- again, this was not a treatment regimen that I
15 would have given to everybody, but it's something that I
16 definitely would have said -- given to certain patients under
17 certain circumstances. And, again, we're always trying to
18 balance -- when we say burdensome -- all of the context for
19 that patient and his or her family.

20 Q. Sure. And let's go ahead and take a look at what
21 you've said about prn treatments and treat and extend in
22 relation to fixed dosing.

23 A. Sure.

24 Q. Let's go to DTX 9013.

25 This is an article from just last year, is it not?

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1 A. Correct.

2 Q. From 2022?

3 A. Correct.

4 Q. This is titled "YOSEMITE and RHINE Phase III

5 Randomized Clinical Trials of Faricimab for Diabetic Macular
6 Edema: Study Design and Rationale."

7 So in this -- and you're a coauthor on this
8 publication, correct?

9 A. Yes, I am.

10 Q. Here in the bottom left of page 1, going from the

11 left-hand column to the right-hand column, you say,

12 "Personalized treatment regimens such as treat and extend and
13 pro re nata are often used to reduce treatment burden
14 associated with fixed interval, every-four-to-eight-week
15 intravitreal injections."

16 Is that what you said in 2022?

17 A. That was in the article, correct.

18 Q. And the reasons that a POSA like yourself would use
19 personalized regimens is because, unlike in a clinical trial
20 where you try to have a defined patient population, in the real
21 world, as you state here, these personalized approaches may
22 also address heterogeneity in individual anti-VEGF responses;
23 isn't that correct?

24 A. Yes.

25 Q. Let's turn to another document, DTX 9009, and page 7.

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1 I want to direct you to page 7. I want to direct you
2 to a quote from a Dr. Singh where he states near the bottom of
3 this paragraph, that "In CATT, ranibizumab and bevacizumab had
4 equivalent visual outcomes when injected on the same schedule.
5 But that's not how we treat patients in the real world. We use
6 treat and extend. We try to get them as dry as possible as
7 fast as possible. We need to extend them as quickly as we
8 can."

9 Do you see that?

10 A. Yes.

11 Q. Now, it doesn't sound like an endorsement for a
12 rigid, extended fixed-dosing regimen, does it?

13 A. So again, I think with -- I think, as you've seen and
14 as I think as I've presented to the Court, clearly this
15 treat-and-extend prn dosing was a strategy that we were all
16 pushing for, right? But the reality is that even in treat and
17 extend, it can be burdensome because in some cases you can have
18 patients that come in even more frequently than fixed every
19 other month.

20 So while this is a nice general statement, the
21 reality is that, as you pointed out, there's lots of
22 heterogeneity. And in some cases this idea of having a
23 fixed-schedule approach with a drug and a patient can obviate
24 multiple visits and trying to find in certain patients that
25 sweet spot.

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1 The other issue, of course, is, you know, treat and
2 extend is such an unusual concept for patients, right? As we
3 try to explain to certain patients how this is going to work,
4 there are -- again, as I mentioned in my initial deposition,
5 there are circumstances where, again, just explaining something
6 simple is -- it's a very easy way to communicate to a patient
7 to make sure that that patient understands what's happening.

8 So yes, this is the world -- this is relatively, you
9 know, recent after CATT and HARBOR. And so we are still in
10 this world of struggling what's the best way to treat. And as
11 I said, even some of this data is what I would call outdated.
12 So when Dr. Singh said dry as possible, there's now newer
13 publications that says a little bit of fluid, actually, you do
14 okay.

15 So this is the constant evolution. And I think in
16 many ways it allows us to think about, in some cases, looking
17 back at these fixed-dosing schedules and seeing that there was
18 some degree of certainty that you would have these great
19 outcomes that we saw in VIEW 1 and VIEW 2.

20 Q. Would it surprise you to learn that this was
21 published in 2021?

22 A. No, not at all.

23 Q. Further down after Dr. Singh made his comment, you
24 were quoted as saying, "Where I practice in Texas, it can take
25 some time to process the insurance paperwork. We start with

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1 bevacizumab, but usually the patient is approved for a branded
2 treatment in time for their second visit."

3 Do you see that?

4 A. Yes.

5 Q. Was that a true statement?

6 A. Yeah, there are some patients -- depending -- the
7 majority of patients who are on anti-VEGF are on -- usually
8 have CMS and copay. And then depending on the type of CMS and
9 copay, you may or may not have to have prior authorization and
10 other aspects that dictate what you can begin with and then
11 what you can follow up with.

12 So yes, it's -- this is not an uncommon situation.
13 It's also -- there's been many patients where I've started
14 right off the bat with Eylea without having to have
15 preauthorization.

16 Q. There are many patients that you've started off with
17 bevacizumab; is that right?

18 A. For some patients, I start off with bevacizumab.

19 Q. And that's an off-label use of bevacizumab; is that
20 right?

21 A. That's an off-label use of bevacizumab.

22 Q. So you're not discouraged from using bevacizumab in
23 the absence of an FDA-approved intravitreal injection label; is
24 that right?

25 A. Well, it's -- you know, it really depends on kind of

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1 the time frame of bevacizumab. So I do think we have to be
2 careful. It depends on the time period, right? So if we're
3 talking when Phil Rosenfeld first presented his early data with
4 using bevacizumab in 2005, that enthusiasm about bevacizumab is
5 dramatically different than what happened in 2012, 2013, '14,
6 and going forward.

7 So there was an evolution in bevacizumab. And having
8 been involved in a lot of those discussions and at the CATT
9 trial, there was a fair amount, as I think -- of concern about
10 using an off-label drug. I mean, you use an off-label drug,
11 guess who bears the liability burden? Thank you, attorneys.

12 And so there was a lot of concern, which is one of
13 the reasons that Dan Martin -- and I actually helped Dan Martin
14 with the CATT study because there were some people who either
15 wouldn't use it because it wasn't absolute evidence that it
16 worked. We actually in some cases had a separate consent form
17 to make sure that patients fully understood that it was
18 off-label back then.

19 So the evolution of bevacizumab is an interesting
20 and -- evolution -- you really need to tell me if this is now
21 in 2005 or '6 or is this in 2010, '11, or '12 when I made this
22 comment.

23 Q. I think we just established this is 2021, Doctor.

24 A. Oh. So even more so that now in 2021 we've got CATT
25 data, we have, obviously, millions of injections. And I think

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1 we now have a much higher comfort level with bevacizumab.

2 Q. And you've been using bevacizumab for years; isn't
3 that right?

4 A. Yes.

5 Q. Now, I'd like to direct your attention to page 10 of
6 this article. Specifically, I'd like to direct your attention
7 to this portion here that's highlighted on the screen where you
8 say -- this is attributed to you, Dr. Csaky, right?

9 A. Yes.

10 Q. It says, "Aflibercept is an immunoadhesin, which is
11 essentially a synthetic antibody but it's still the construct
12 of an antibody."

13 Did you make that statement?

14 A. I did.

15 Q. Let's go on to page 12.

16 A. Can I just -- I really want to make sure I clarify
17 that statement. Okay?

18 Q. No. That's okay. I'm moving on to the next
19 question, Doctor.

20 THE COURT: Just respond to the questions posed,
21 Doctor.

22 THE WITNESS: Okay. Thank you.

23 BY MR. McLAUGHLIN:

24 Q. Let's flip to page 12 of this document. There are a
25 couple of quotes attributed to you on this page. And I'd like

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1 to direct your attention to one towards the bottom where it
2 says "Dr. Csaky" -- this is attributed to you, Dr. Csaky, where
3 you say, "My hope is that we'll have agents with better
4 durability a year from now to help relieve that treatment
5 burden for our patients."

6 Do you see that?

7 A. Yes.

8 Q. Was that a true statement you made in 2021?

9 A. Yes.

10 Q. Now let's turn to the second page of this article,
11 page 2. Now, that's you pictured here in the center top?

12 A. Yes.

13 Q. Now, in connection with publishing this article, you
14 had to disclose your financial relationships and commercial
15 interests; isn't that right?

16 A. Correct.

17 Q. If we turn to page 3, it states here you're a paid
18 consultant for Regeneron Pharmaceuticals; is that right?

19 A. That's correct.

20 Q. And also Genentech?

21 A. Correct.

22 Q. And then below your name is Diana Do, MD; is that
23 right?

24 A. Correct.

25 Q. And is that the same Diana Do whose IPR declaration

KARL CSAKY, MD, PhD - CROSS

1 you relied upon in this matter?

2 A. Correct.

3 Q. You'll see that here Dr. Diana Do discloses her
4 financial and commercial interests, right?

5 A. Correct.

6 Q. And there she lists Regeneron Pharmaceuticals; is
7 that right?

8 A. Correct.

9 Q. I'm going to shift gears a little bit. Let's turn to
10 PTX 311. This should be the Heier 2012 article that you've
11 relied upon in formulating your opinions in this case.

12 So, first of all, let me take you to the back. I
13 just want to establish some information. This is on page 12,
14 where it indicates the -- who the authors are associated with,
15 which entities the authors are associated with.

16 Do you see that?

17 A. Yes.

18 Q. And the superscript 10 indicates a Regeneron
19 Pharmaceutical association; is that right?

20 A. Correct.

21 Q. And superscript 11 indicates a Bayer HealthCare
22 association; is that correct?

23 A. Correct.

24 Q. So if we turn back to page 1 of this article, there
25 are at least one, two, three, four, five authors that are

KARL CSAKY, MD, PhD - CROSS

1 Regeneron employees or associated somehow with Regeneron that
2 are authors on this article, correct?

3 A. Yes.

4 Q. And one of those is George Yancopoulos, the listed
5 inventor of the '572 and '601 patents.

6 Do you see that?

7 A. Yes.

8 Q. Then there are four authors here with associations
9 with Bayer; is that correct?

10 A. I'm assuming. I don't know those individuals, but
11 their references seem like they work for Bayer.

12 Q. Because they're indicated with the superscript 11?

13 A. Yes.

14 Q. Now, you understand that in this VIEW trial both
15 monthly ranibizumab and monthly aflibercept were evaluated head
16 to head?

17 A. Correct.

18 Q. And aflibercept was never shown to be superior when
19 dosed at the same frequency as ranibizumab; isn't that right?

20 A. Can you show me the -- I think -- can we look at the
21 article VIEW 1. I think -- do we have that -- am I allowed to
22 look at the entire article? Would that be okay?

23 THE COURT: Yes, Doctor.

24 BY MR. McLAUGHLIN:

25 Q. You don't recall, sitting here today?

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1 A. Well, I haven't -- no, I have not memorized the
2 VIEW 1-VIEW 2 results. So if I could look at the results, I
3 could refresh my memory, if that's possible.

4 Q. Sure. Let's take a look at those.

5 So I believe what you're looking for is found in
6 Table 2?

7 A. No. It would be the --

8 Q. Page 67.

9 A. -- the visual acuity results --

10 Q. Yep.

11 A. -- of the two trials, VIEW 1 and VIEW 2.

12 Q. Let's go to change in ETDRS. Do you see that?

13 A. Right. But the way we look at these is similar to
14 what I show with the PIER where we show the change in visual
15 acuity over time. I think that is part of these -- of this
16 publication. If you look at the -- there are these line
17 graphs. I'm sorry to make this complicated, but that's the way
18 we analyze this data. If you can go to --

19 Q. Sure. Why don't we look at that. That's Figure 3.

20 A. Okay. Yeah, there we go. Okay.

21 Q. Why don't we take a look at Graph C, the integrated
22 data for the VIEW 1 and VIEW 2 trials.

23 A. Well, I also want to look at VIEW 1 as well.

24 Q. So let's start by looking at Graph C. 2q4 is the
25 aflibercept monthly dosing arm, correct?

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1 A. Correct.

2 Q. And R q4 is the ranibizumab monthly dosing arm,
3 correct?

4 A. That's correct.

5 Q. And the integrated data across both those studies
6 shows that aflibercept was only -- the patients on average
7 gained 9.3 letters of visual acuity.

8 Do you see that?

9 A. Yes. 2.2 milligrams q4, 9.3, correct, yes.

10 Q. And the ranibizumab arm patients showed on average
11 gains in visual acuity of 8.7 letters.

12 Do you see that?

13 A. That's correct.

14 Q. Now, this data presented here was never considered
15 adequate enough to come to the conclusion that monthly
16 aflibercept was superior to monthly ranibizumab; isn't that
17 correct?

18 A. The integrated data was, but there was some, you
19 know, suspicion, if you look at the VIEW 1 data in particular,
20 that -- if you look in that -- remember, there were two trials,
21 VIEW 1 and VIEW 2. And if you can highlight the VIEW 1
22 results --

23 Q. I'm not asking about the VIEW 1 results. We looked
24 at the integrated data. My question was about the integrated
25 data.

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1 A. Okay.

2 Q. And based on that integrated data, aflibercept has
3 never been determined to be superior or show statistical
4 superiority when dosed monthly compared to ranibizumab monthly;
5 isn't that correct?

6 A. If you limit your analysis to the integrated data,
7 that's correct.

8 Q. I'm going to switch focus a little bit here and
9 let's -- I want to ask you some questions about some of the
10 related patents in this family that you've reviewed in the
11 process of formulating your opinions in this case.

12 So you've considered the prosecution histories of the
13 '601 and the '572 patents; is that right?

14 I can show you the covers of those. We didn't bring
15 them today because they're huge.

16 We can provide digital copies to the Court.

17 If we show you DTX 28, the cover page.

18 A. So these are -- I'm sorry. Refresh -- these are
19 the -- what documents? These are the --

20 Q. These are the prosecution histories --

21 A. Okay.

22 Q. -- that, according to your Tab B, you've reviewed in
23 connection with formulating your opinions in this case.

24 Do you recall reviewing that?

25 A. Yeah. To some degree as needed for my -- in forming

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1 my opinion, correct.

2 Q. What's shown here is the file history from the '601
3 patent. Do you see that?

4 A. Yes.

5 Q. Did you also review DTX 29? Do you recall doing
6 that?

7 A. Yes. Again, as much as I was not aware of all of the
8 details, I did a cursory review of these to begin to understand
9 how this might help form my opinions.

10 Q. And did you -- and you also reviewed DTX 33, didn't
11 you, the prosecution history for the '338 patent from this
12 family?

13 A. Inasmuch as I could understand and how it might help
14 in forming my opinion as a POSA as it related to these claims,
15 I did that review, correct.

16 Q. Okay.

17 I'd like to call up PTX 3 at this point, the '572
18 patent. Now, what's shown here is a list of related U.S.
19 applications. Do you see that?

20 A. Yes.

21 Q. And do you see there are a number of patents listed
22 there --

23 A. Correct.

24 Q. -- that are related to the '572 patent?

25 A. Correct.

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1 Q. Those include the '338? That's at the bottom.

2 A. Correct.

3 Q. This is going kind of in reverse chronological order.

4 Then next is '069. Do you see that?

5 A. Yes.

6 Q. Then '681?

7 A. Yes.

8 Q. '345?

9 A. Yes.

10 Q. And then the patent we're talking about here today,
11 the '601.

12 A. Yes.

13 Q. The '205 patent?

14 A. Yes.

15 Q. Then, of course, the '572 patent, which all of this
16 appears on the face of, correct?

17 A. Correct.

18 Q. Now, if we look at the earliest patents in this
19 chain, U.S. Patent Number 9,254,338, are you aware that Mylan
20 challenged and then the Patent Trial Appeal Board invalidated
21 claims from that patent?

22 A. No, I was not aware.

23 Q. Are you aware that the '338 patent is directed to the
24 same eight-week dosing regimen that's claimed in the '601
25 patent?

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1 MS. OBERWETTER: Objection to the foundation with
2 this witness.

3 THE COURT: Let's rewind a little bit, Counsel.

4 BY MR. McLAUGHLIN:

5 Q. I'll represent to you, Doctor, that the eight-week
6 dosing regimen was claimed in the '338 patent.

7 And then are you also aware that Mylan challenged and
8 then the Patent Trial and Appeal Board invalidated claims of
9 the '069 patent?

10 A. So, again, you know, just so we're clear, if I stated
11 or -- in my report these documents, I just want to make sure
12 I'm clear to the Court that I'm not a patent attorney. So when
13 I'm looking through these, I'm looking for help in forming my
14 opinion as an ophthalmologist, as a POSA, right, not as a
15 patent attorney litigating various aspects of patents and
16 various procedural steps.

17 So I feel I'm entering into an uncomfortable area
18 where that's not my role as an expert. I don't have expertise
19 in assigning what the import is of various decisions and how
20 this relates to the various claim constructions and things that
21 are kind of patentese, we want to call it, rather than
22 ophthalmology stuff.

23 THE COURT: Understood.

24 Repeat your question, Counsel.

25 BY MR. McLAUGHLIN:

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1 Q. Actually, why don't we do this.

2 Can we pull up DTX 4135 and put it next to DTX 9007.

3 You see on the left-hand document it says,

4 "Determining all challenged claims unpatentable"?

5 Do you see that?

6 A. Correct.

7 Q. Under "Judgment"?

8 A. Correct.

9 Q. And this is with respect to the 338 patent?

10 A. Yes.

11 Q. And then on the right-hand side, same final judgment,
12 determining all challenged claims unpatentable? And that's
13 with respect to the '069 patent?

14 A. Correct. That's what's stated here.

15 Q. So is it safe to assume, then, that you've not
16 factored these decisions into your analysis in this case?

17 A. I was asked kind of to -- specifically to look at the
18 '572 and '601 patents in particular as an expert witness. And
19 so I did not go back into the patent history of the various
20 issues that are within the Court's purview. And so no, I did
21 not do an extensive legal analysis of these types of documents,
22 the implications, what the rulings mean. That's not what I
23 did.

24 I was looking through these and seeing if there was
25 anything that might help. And, again, recognizing the

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1 limitations of my knowledge base, my review was very cursory.
2 So this is really not -- my area of expertise is not,
3 surprisingly, patent law.

4 Q. Let's go to DTX 9015.

5 This relates to the '205 patent, which is directed to
6 monthly dosing of aflibercept. Do you see at the top here it
7 says, "I hereby disclaim the following complete claims in the
8 above-identified patent, 1, 2, and 3"?

9 A. I see that written.

10 Q. Were you aware that Regeneron, rather than contest
11 Mylan's IPR petition, chose to disclaim all claims of the
12 '205 patent?

13 A. Again, I was -- I'm not aware -- and these are,
14 again, documents that I may have used very cursorily in my
15 report. But I'm not aware or I'm not really perhaps
16 experienced enough to make any comment about what the
17 implications, what's happening here, who are the parties, what
18 this means in terms of disclosures. This is really not
19 something that I would feel is in the area of my expertise.

20 Q. Let's move on to DTX 6444. This is Docket Number 433
21 from this case, titled "Regeneron's Stipulation Regarding
22 Summary Judgment and Claim Narrowing."

23 So looking at the second bullet, the stipulation
24 states, "Regeneron accepts summary judgment of invalidity of
25 Claims 5 and 6 and 9 of U.S. Patent Number 10,888,601."

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1 Do you see that?

2 A. I see that.

3 Q. And those were claims that you've previously opined
4 are all valid; isn't that right?

5 A. I opined at the time -- when I reviewed these
6 documents at the time, my working constructs were -- I was
7 instructed on which claims were being contested, and I made my
8 opening report based off that. And so I was told, I think, at
9 some point that there was some changes in the visual acuity
10 outcomes, as I was told. And that's the extent to which I then
11 went back and said -- looked at my opinions and looked at,
12 again, the -- kind of the sections and my perspectives kind
13 of -- you know, in the absence of these claims.

14 Q. Turning to DTX 405, this is another patent disclaimer
15 filed by Regeneron in connection with the '601 patent.

16 Did you know that, prior to this litigation,
17 Regeneron had disclaimed Claims 3, 4, 13, 14, 22, 29, and 30 of
18 the '601 patent?

19 A. Again, I'm not -- I can't comment on any of these. I
20 wasn't involved in the litigation. I wasn't involved in the
21 discussions. This is not something that I'm privy to or can
22 offer or render an opinion or any statement in this regard.

23 Q. So you did not incorporate these developments into
24 your opinions in this case, correct?

25 A. No. I was simply told to -- here were the specific

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1 claims that were now under considerations, and went back into
2 my reports and looked at how I had constructed my arguments as
3 it related specifically to the claims that we've been
4 discussing during this trial.

5 Why and how it came to be that those were, I was not
6 privy to any of those discussions and to the reasons for those
7 decisions.

8 Q. So now that we've gone through some of the things
9 where invalidity is decided or not contested, let's focus on a
10 few elements that you think are contested.

11 So let's start with your Slide 30, PDX 8, and talk
12 about the '572 patent, Claim 6.

13 A. Sure.

14 Q. The only thing you've pointed to as a disputed
15 element is the isotonic solution element; is that correct?

16 A. For the anticipation analysis, that's correct.

17 Q. And you did not offer any opinions here on isotonic;
18 is that correct?

19 A. I deferred all of my opinions to Dr. Trout.

20 Q. All right. Let's turn to the September 14th, 2009,
21 DME press release. This is DTX 3198. You can go to page 2.

22 Your only complaint with respect to this reference is
23 that it expressly says three loading doses rather than five
24 loading doses; is that right?

25 A. That's correct. The major -- when I reviewed this

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1 press release as it related to the five loading doses, I did
2 not see a five-loading-dose regimen outlined here.

3 Q. But you admit that there is a 2-milligram as-needed
4 regimen after three monthly loading doses, correct?

5 A. Correct.

6 Q. There's also a 2-milligram monthly arm, correct?

7 A. There is a 2-milligram monthly arm, correct.

8 Q. So Regeneron went with a 2-milligram
9 every-single-month arm despite these systemic side effects that
10 you were talking about earlier today, correct?

11 A. So I think, again, it's critical to put this in
12 context, right? Well, for one thing, this is a --

13 Q. That was a yes-or-no question, Doctor.

14 You opined earlier today that there were systemic
15 side effects that would have discouraged somebody from going
16 from three loading doses to five; isn't that right?

17 A. That's correct.

18 Q. What Regeneron did was design an arm of their
19 Phase II trial that was straight monthly dosing; isn't that
20 correct?

21 A. That is correct.

22 Q. It's also true, when you were discussing the Lalwani
23 reference, what she did or what she described was the doubling
24 of doses, correct, in the treatment of DME?

25 A. Yes. If I recall, it was a doubling from .5 to 1.

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1 It may have been .3 to .5. I can't recall the details of the
2 result. It was an increase in the dose, for sure.

3 Q. That's despite these supposed concerns about systemic
4 side effects; is that correct? That she made that proposal?

5 A. Well, I don't know -- I mean, these considerations at
6 the time -- first of all, we were focusing on ranibizumab. And
7 so we had some data from ranibizumab, but the -- as I recall,
8 she would -- she did not recommend continued dosing with
9 multiple high doses of ranibizumab. I don't think that was
10 part of the strategies.

11 And the issues of safety still existed. I mean,
12 we're still in the -- in this period of time when we're trying
13 to navigate what exactly is happening as it relates to patients
14 and their potential for stroke and heart attacks when getting
15 intravitreal anti-VEGF injections.

16 Q. And in view of those concerns, in Lalwani they still
17 recommended the doubling of ranibizumab doses, correct?

18 A. Yes.

19 Q. Now, I want to talk to you about the -- this
20 hypothetical -- a hypothetical prn protocol. So I'm going to
21 take you to PDX 1.124. This may be a slide that you've seen
22 before. And I want to talk about the prn dosing for DME as it
23 relates to the press release, DTX 3198, okay, as if you were
24 one of the clinical inventor investigators in that study.

25 Do you understand?

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1 A. Correct.

2 Q. So I want you to assume for purposes of my next set
3 of questions that we're going to be using the row here that
4 says 2q prn. Do you see that?

5 A. 2q prn, correct.

6 Q. So you don't dispute that in the press release were
7 described three monthly loading doses, correct?

8 A. Correct.

9 Q. So that's a dose at Week 0, one at Week 4, one at
10 Week 8; is that correct?

11 A. That's correct.

12 Q. Then at Week 12, according to the DA VINCI protocol,
13 the clinical trial subject would come into the office for
14 evaluation at Week 12; isn't that right?

15 A. That's correct.

16 Q. And you performed an assessment on that subject,
17 right?

18 A. Correct. Along with OCT and vision and a full
19 examination, correct, to assess activity or no activity of the
20 macula in terms of dryness or not.

21 Q. And then upon performing that assessment, if the
22 patient meets the re-treatment criteria, you would provide an
23 injection at that visit, correct?

24 A. Correct. If it met the -- typically on these prn
25 trials, there are strict criteria that dictate when you could

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1 not re-treat, right? So there are -- whether it was a little
2 bit of fluid, maybe not; if there was more fluid, maybe yes.
3 So there's these criteria that investigators would use during
4 these prn visits that will then inform us as to whether or not
5 we should or should not inject.

6 Q. Right. So this patient came in, they met the
7 re-treatment criteria, they got an injection at Week 12. Okay?

8 A. Correct.

9 Q. The subject comes back to your office at Week 16.
10 You perform the assessment. And once again, the subject meets
11 the re-treatment criteria. You inject at that visit, correct?

12 A. If they met the injection criteria, then you would
13 inject.

14 Q. Okay. It's now Week 20. And as before, the subject
15 returns to your office for an evaluation, but here now the
16 retina looks dry. The patient doesn't meet any of the
17 re-treatment criteria. You withhold an injection; is that
18 correct?

19 A. You would not inject at that visit, correct.

20 Q. And that brings us to Week 24, where once again the
21 subject comes in for their monthly visit. If they meet the
22 re-treatment criteria, you administer an injection; is that
23 correct?

24 A. That's correct.

25 Q. And that's one scenario that any competent

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1 ophthalmologist could work out under the 2q prn regimen; isn't
2 that correct?

3 A. If you mean the regimen that a competent
4 ophthalmologist would have said is three loading doses plus
5 prn, you can't look into the future and say if a patient will
6 or will not need an injection. That's why it's a conditional
7 injection, right?

8 So an ophthalmologist would have said, question mark,
9 does that person need an injection? Question mark, does that
10 person need an injection? So that would have been the protocol
11 that an ophthalmologist would have designed under a prn dosing
12 regimen.

13 Q. And what we see here is one scenario in which that
14 would have happened. And what we're looking at are five
15 monthly injections, correct?

16 A. We see -- again, we see injections being given on a
17 conditional basis, right? So I think --

18 Q. That wasn't the question, Doctor. I'd like for you
19 to answer my question.

20 What we're seeing here are five monthly injections,
21 correct?

22 A. These are injections, if the patient meets prn
23 criteria, that they would receive injections on a monthly
24 basis.

25 Q. Now, Dr. Csaky, before the patent's issued here, you

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1 had used Avastin to treat AMD; isn't that right?

2 A. That's correct.

3 Q. And you recognized back then even that some patients
4 may need more injections for DME; isn't that right?

5 A. That's correct.

6 Q. So let's turn to DTX 9014.

7 This is a January 2010 article from *EyeNet* titled
8 "Avastin: New Hopes and Hesitations." Now, if we go to
9 page 4, there's a quote that's attributable to you, Dr. Csaky,
10 where you say, "Avastin is becoming standard of care for AMD."

11 Do you see that?

12 A. Correct.

13 Q. And you go on to say, "Sometimes you have to give
14 more injections for DME."

15 Do you see that?

16 A. So I just want to make sure we qualify, "standard of
17 care for AMD if you use the definition of what the community is
18 doing."

19 Q. Was this a true statement that you made in front of
20 your peers at this meeting in January of 2010?

21 A. Yes.

22 Q. So you managed to figure out how to give more
23 injections even without any FDA-approved label for Avastin for
24 ophthalmic use; isn't that right?

25 A. Again, in this scenario it's -- in this construct

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1 during this period of time, as I was talking about, where we
2 were actively interrogating patients, right, using OCT,
3 determining how many injections, what the degree of fluid was,
4 with the caveat again that with DME we had a little bit more
5 wiggle room. So yes, we could, depending on that individual
6 patient, change and manage their strategy on this kind of
7 personalized approach.

8 Q. And then you go on to comment about the use of
9 Avastin further. This is from page 1, where you say, "We don't
10 know how to use Avastin. We don't know when to stop it. We
11 don't know if the dose is correct."

12 Do you see that?

13 A. Correct. And --

14 Q. The article goes on to say, "Who will respond? Do
15 you give seven injections and then stop? It's all seat of the
16 pants, and it's made more implicated because we don't have
17 guidelines."

18 You said that, correct?

19 A. Remind me of the date of this.

20 Q. January of 2010.

21 A. Right. So again --

22 Q. You said those words, correct, Doctor?

23 A. I did say those words.

24 Q. All right. I'm going to shift gears a little bit
25 here.

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1 Do you recall providing opinions pertaining to the
2 written description of the claims of the '601 and '572 patents?

3 A. I did.

4 Q. And in connection with providing your opinions on
5 written description support regarding the five monthly
6 injection DME-DR claims, you relied on Example 5; is that
7 right?

8 A. Can I pull up the patent to remind myself what
9 Example 5 is?

10 Q. Sure. Actually, why don't we bring up your -- call
11 up a snippet from your report, DTX 2027, page 224,
12 paragraph 406.

13 Here you state, "Example 5 clearly identifies the
14 treatment of DME using a similar dosing regimen," correct?

15 A. Can I just have one second to find the patent? Would
16 that be all right?

17 Q. Sure.

18 THE COURT: What exhibit tab is the patent available
19 at, Counsel?

20 MR. McLAUGHLIN: Should be PTX 1.

21 BY MR. McLAUGHLIN:

22 Q. Do you have that, Doctor?

23 A. Yes, I have it. Thank you so much.

24 Q. Example 5 shows up on page 17 of PTX 1.

25 A. I'm sorry. Example 5, we're on page 17, correct?

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1 Q. We're on page 17 of the PTX number, Column 14.

2 A. Correct. Yes. I see that now.

3 Q. Towards the top, Example 5.

4 A. Yes.

5 Q. You understand this to be a recitation of the
6 DA VINCI Phase II clinical trial?

7 A. That's correct.

8 Q. Is it still your opinion that Example 5 clearly
9 identifies the treatment of DME using a similar dosing regimen
10 to those that are claimed?

11 A. This is an example that -- in the specifications as
12 one of several areas in the specification that outlines the
13 treatment of DME.

14 Q. Do you recall using Example 7 of the '572 patent to
15 illustrate that the specification provides various examples of
16 a finite number of secondary doses?

17 A. I'm sure I did if you're going to bring it up for me.

18 Q. Okay.

19 Why don't we pull up DTX 2027, page 211,
20 paragraph 378. You state here, "The patent specification
21 provides various examples of regimens with a finite number of
22 secondary doses."

23 Do you see that?

24 A. Correct.

25 Q. You state that "Example 7 discloses dosing regimens

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1 having two, three, four, five, six, and seven secondary doses."

2 Do you see that?

3 A. Correct.

4 Q. I want you to keep that statement in mind, and I want
5 to turn to PTX 722, which I believe you've seen before. This
6 is the October 1st, 2007, *Retinal Physician* article. Do you
7 recognize this document?

8 A. Yes.

9 Q. And if we go to page 1 and we look at this comment
10 from Dr. Hariprasad where he describes one of the ways that he
11 treats AMD, he states that "I treat with ranibizumab monthly
12 until optical coherence tomography (OCT) shows the macula to be
13 completely free of fluid. Some patients reach that point after
14 two injections. Others require as many as eight injections."

15 Do you see that?

16 A. Correct.

17 Q. So he talks about starting off loading doses with as
18 few as two, as many as eight; isn't that right?

19 A. Well, he's defining these injections in order to
20 achieve using OCT a macula which is free of fluid.

21 Q. Right. And, actually, I'm going to come back to
22 that.

23 Let's use the parlance of the '601 and '572 patents
24 and its use of the term "secondary doses." Okay?

25 A. Sure.

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1 Q. So using that definition, what he's talking about is
2 anywhere from one to seven secondary doses; isn't that correct?

3 A. In the context of evaluating patients, he's
4 defining -- again, the minute you start using conditions
5 like -- he even says, "I use OCT to demonstrate the macula to
6 be completely free of fluid." Then in -- my perception of this
7 is he is not necessarily in this sense using a fixed-dosing
8 approach; he's using a prn approach or a regimen that requires
9 that he create a dry macula.

10 Q. And in that context he identified one to seven
11 secondary doses, correct? Yes or no.

12 A. Yes.

13 Q. And that same article articulated the concept of
14 eight-week dosing intervals, correct, as explained by
15 Dr. Brown?

16 A. No.

17 Q. That's not an eight-week dosing interval that we're
18 looking at right there?

19 A. No.

20 Q. "I give three monthly injections and see them in
21 eight weeks."

22 Do you see that?

23 A. Correct.

24 Q. So that's an eight-week interval that he's seeing the
25 patients; isn't that correct?

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1 A. He's seeing them; he's not necessarily treating them.

2 Q. In the act of seeing them, he's going to evaluate
3 them. And if they need an injection at that eight-week mark,
4 the patients are going to get that injection, correct?

5 A. Well, it depends.

6 Q. It depends on what?

7 A. So, for example, if I see --

8 Q. It depends on the OCT readings, correct?

9 A. OCT and vision. And so in doing my -- like I said,
10 this conditional evaluation, what happens is -- for example,
11 let's say there was fluid. Could very well be that at that
12 step I start to rethink my diagnosis. I start to think about
13 doing additional testing.

14 So this approach of seeing them first -- and it's
15 critical that he says I see them -- or that I treat them and
16 see them, but I see them, is exactly what's meant by this
17 personalized approach. You're seeing these patients. And then
18 based off what you see, you can make a treatment decision.
19 There is situations -- I'm just asking -- I mean --

20 Q. Are you making a statement, or are you answering my
21 question, Doctor?

22 THE COURT: We need to get back to a
23 question-and-answer setup here.

24 THE WITNESS: Sure.

25 BY MR. McLAUGHLIN:

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1 Q. We're going to be here for a very long time.

2 A. I'm sorry. So say that again.

3 Q. Let me take you to the very next sentence in his
4 statement. He says, "If fluid is absent at that visit, I give
5 another injection."

6 Do you see that?

7 A. Yes.

8 Q. Thank you.

9 THE COURT: Counsel, why don't we take a break at
10 this point.

11 MR. McLAUGHLIN: Sure.

12 THE COURT: We'll take ten minutes.

13 Doctor, you are still off limits for conversation.

14 But we'll take ten minutes and resume at that point.

15 Thank you all very much.

16 (A recess was taken from 2:35 p.m. to
17 2:51 p.m.)

18 THE COURT: Counsel, you may continue.

19 MR. McLAUGHLIN: Thank you, Your Honor.

20 BY MR. McLAUGHLIN:

21 Q. Let's go to DTX 3089.

22 Doctor, this is a Chun reference from 2006 reporting
23 on ranibizumab in DME. I'd like to take you to page 3.

24 Can you confirm that -- and I want to go to the
25 visual acuity and central retinal thickness measurements

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1 section of this on page 3.

2 Can you confirm that this reference reports the
3 low-dose group gained a mean of 12 letters?

4 A. Yes.

5 Q. Let's move on to DTX 4069.

6 This is the Nguyen 2009 reference looking at
7 ranibizumab again in the treatment of DME. If we look at the
8 abstract, this involved 126 participants, correct?

9 A. Yes.

10 Q. And under the results it's reported that the patients
11 in Group 1 achieved 7.24 letters in visual acuity gain,
12 correct?

13 A. Yes.

14 Q. Let's go to DTX 3096.

15 This is a DRCRN 2010 article. This is a report of
16 the design and outcome of a clinical trial using ranibizumab in
17 the treatment of DME.

18 If we go down to the results, you see that patients
19 gained on average nine letters in visual acuity?

20 A. Yes. The ranibizumab and deferred laser group gained
21 nine letters.

22 Q. And it further reports that no systemic events
23 attributable to study treatment were apparent.

24 Do you see that?

25 A. Yes.

KARL CSAKY, MD, PhD - CROSS

1 Q. Let's get on to DTX 4215.

2 It's the Arevalo reference from 2007.

3 In this reference under "Participants," it reports
4 there are 110 eyes that were assessed.

5 Do you see that?

6 A. Yes.

7 Q. Then this study reports in the "Results" section that
8 55.1 percent improved by greater than or equal to two ETDRS
9 lines of BCVA.

10 Do you see that?

11 A. Yes.

12 Q. That's the same as a ten-letter gain?

13 A. Yes.

14 Q. Now, I want to ask you a little bit about PrONTO. I
15 know that's been a topic of discussion today.

16 Let's pull up DTX 3215.

17 This is the Engelbert 2010 reference. And let's go
18 to page 2, where the Engelbert authors were commenting on the
19 PrONTO study on the left-hand column.

20 And they note -- towards the bottom of that paragraph
21 that begins "the PrONTO study," they note about midway there,
22 "As a result of the PrONTO study, PrONTO-style dosing has
23 become popular in the retina community."

24 Do you see that?

25 A. Yes.

KARL CSAKY, MD, PhD - CROSS

1 Q. So now I'd like to turn to paragraph 352 of your
2 responsive expert report. This is DTX 2027 at pages 201 and
3 202.

4 Do you recall providing a chart along with your
5 opinions that described the ranibizumab clinical trial dosing
6 regimens?

7 A. Yes.

8 Q. So it's the case, though, that the prn PrONTO-style
9 protocol that had become popular and has shown visual acuity
10 gains was omitted from your chart on this page; isn't that
11 correct?

12 MS. OBERWETTER: Objection. Outside the scope of
13 direct.

14 THE COURT: How is this related to the direct,
15 Counsel?

16 MR. McLAUGHLIN: This goes -- all he did today was
17 talk about prn and PrONTO, and this goes right to the heart of
18 that matter.

19 THE COURT: Overruled.

20 THE WITNESS: So this graph is --

21 BY MR. McLAUGHLIN:

22 Q. I'm not asking you what it is; what I'm asking you is
23 you left PrONTO off this graph, correct?

24 A. I did not make this graph.

25 Q. And you didn't endeavor to correct the graph to add

KARL CSAKY, MD, PhD - CROSS

1 PrONTO?

2 A. I did not add PrONTO to this graph.

3 Q. All right. Now I want to turn to talking about the
4 q12 regimen that you've talked about today. And you've
5 provided an opinion in your opinion that Genentech repeatedly
6 tried and failed to demonstrate that Lucentis could be used
7 effectively on extended dosing regimens, right?

8 A. I indicated there were several trials on quarterly
9 following three monthly doses that did not get to the same
10 visual acuity as monthly dosing.

11 Q. But you are aware that the FDA approved Lucentis for
12 12-week dosing, are you not?

13 A. Yes.

14 Q. And that's in the Lucentis label, correct?

15 A. That's correct.

16 Q. Since 2006?

17 A. That's correct.

18 Q. It's not your testimony that the FDA would approve a
19 drug dosing regimen that it deemed a failure, right?

20 A. That's correct.

21 Q. Let's go to the Mitchell reference. That's DTX 4061.

22 And I'd like to draw your attention to page 6.

23 What's shown here, as indicated in the Figure 3 legend, is a
24 subpopulation study of the PIER trial patients. I'd like to
25 direct your attention to the top line with the triangles.

KARL CSAKY, MD, PhD - CROSS

1 Now, according to this substudy, 40 percent of
2 initial responders in the PIER study were able to maintain the
3 gains from the loading-dose phase; isn't that correct?

4 A. That's correct.

5 Q. So for these 40 percent of patients that were able to
6 maintain their vision while receiving far fewer injections in
7 their eyes, this was certainly not a failure, correct?

8 A. Unless you were -- happened to be in the other groups
9 that lost vision, then you're --

10 Q. I'm asking you about the 40 percent of the patients
11 that were in this arm that showed the ability to maintain
12 vision while receiving far fewer injections. They would not
13 have considered that a failure, would they?

14 A. If you happened to be fortunate enough to be in that
15 group in this one study, then this would not have been a
16 failure.

17 Q. And you agree that the PIER 12-week regimen was a
18 fixed-interval dosing regimen, correct?

19 A. Correct.

20 Q. Now let's go back to Dixon. That's DTX 0204.

21 I'm going to ask you a little bit more about Dixon.
22 Let's see what the prior art was saying about the CLEAR 2
23 trial, the Phase II trial aflibercept.

24 So let's get to page 5 of Dixon.

25 While we're waiting for Dixon to come up, I'll ask

KARL CSAKY, MD, PhD - CROSS

1 you this: You understand that there were several treatment
2 arms in the CLEAR-IT 2 trial, right?

3 A. Correct.

4 Q. And one of those arms involved the administration of
5 four monthly injections followed by prn dosing?

6 A. That's correct.

7 Q. Do you recall that?

8 A. Yes.

9 Q. Now, if we go to page 5 of Dixon in the right-hand
10 column, there's a paragraph that begins "data from the Phase II
11 study."

12 A. Correct.

13 Q. This states, "Data from the Phase II study of VEGF
14 Trap-Eye were positive," correct? It says that?

15 You see that, Doctor?

16 A. Yes, I see it says "were positive." Correct?

17 Q. And it also goes on to say, "Results from the
18 noninferiority Phase III trials will establish its efficacy
19 versus ranibizumab."

20 Do you see that?

21 A. Yes.

22 Q. Let's look and see what else Dixon disclosed about
23 the CLEAR-IT 2 regimen and results.

24 Do you recall providing testimony today about the
25 CLEAR-IT 2 study design?

KARL CSAKY, MD, PhD - CROSS

1 A. Yes.

2 Q. But in that discussion you didn't touch on the
3 CLEAR-IT 2 results, did you?

4 A. No.

5 Q. All right. Let's go to page 4 of Dixon and
6 Section 2.6.2. And the Phase II section there on the left.

7 So you would agree --

8 Actually, let's go to the next paragraph, the one
9 just below this, where it says, "Patients initially treated
10 with 2 milligrams of aflibercept, or VEGF Trap-Eye, monthly
11 achieved mean improvements of 9.0 letters."

12 Do you see that?

13 A. Yes.

14 Q. And 29 percent of those same patients achieved
15 greater than or equal to 15 ETDRS letters at 52 weeks.

16 Do you see that?

17 A. Yes.

18 Q. It also reports that the median time to first
19 reinjection in all groups was 110 days.

20 Do you see that?

21 A. Yes.

22 Q. That means that after the loading dose phase, the
23 median time to patients receiving their first -- the next first
24 injection was 110 days, right?

25 A. In all the groups, correct.

KARL CSAKY, MD, PhD - CROSS

1 Q. That's almost four months, correct?

2 A. Almost four months, correct.

3 Q. And Dixon cites to Reference 45 of the Dixon
4 reference, correct, for this clinical trial data?

5 A. Correct. That's the 45 reference.

6 Q. Okay.

7 Why don't we pull up DTX 3173.

8 And this is entitled "VEGF Trap-Eye in Wet AMD
9 CLEAR-IT 2: Summary of One-Year Key Results."

10 Do you see that?

11 A. Yes.

12 Q. And it's indicated this was presented on
13 September 28th, 2008?

14 A. Yes.

15 Q. Let's turn to page 6. This section that's
16 highlighted here, that's the arm that received four monthly
17 injections of aflibercept, correct?

18 A. Yes.

19 Q. Followed by prn treatment?

20 A. Yes.

21 Q. Let's see what happened to those patients. Let's go
22 to page 12. If we highlight the Row 2 2 mg q4, what this
23 reports is that these patients needed on average only 1.6
24 injections over the course of that prn dosing period from
25 Week 12 to Week 52, right?

KARL CSAKY, MD, PhD - CROSS

1 A. Yes.

2 Q. And the range is indicated as 0 to 4, meaning that
3 one or more patients required no injections between Week 12 and
4 Week 52, correct?

5 A. Yes.

6 Q. Let's go to slide -- or page 13 of this document.

7 And again, the 2 mg q4 arm, the second row, indicates
8 that the median number of days to first reinjection was 150 in
9 this arm.

10 Do you see that?

11 A. Yes.

12 Q. That's about five months, is it not?

13 A. Yes.

14 Q. Let's jump to page 19 of this document. You
15 understand that the fewer than 15 letters lost is a common
16 primary end point in these types of clinical trials?

17 A. Yes.

18 Q. And in this clinical trial, the 2q4 arm showed that
19 100 percent of the patients in that arm hit that end point,
20 correct?

21 A. Yes.

22 Q. Let's go to page 26. "Safety: Serious Adverse
23 Events" is the title of this slide. It says, "Systemic serious
24 adverse events: None deemed to be drug-related."

25 Do you see that?

KARL CSAKY, MD, PhD - CROSS

1 A. Yes.

2 Q. Let's jump to the conclusions slide, page 28.

3 "VEGF Trap-Eye achieved clinically meaningful and
4 durable vision improvement over one year."

5 Do you see that?

6 A. Yes.

7 Q. Up to nine mean letters gained in Week 52?

8 A. Yes.

9 Q. And up to 160 microns reduction in central retinal
10 lesion thickness, correct?

11 A. Yes.

12 Q. I want to shift gears a bit here and pull up a
13 DTX 917. This is a November 22nd, 2010, email from -- looks
14 like somebody called newsdesk@broadcast.shareholder.com to
15 George Yancopoulos.

16 Do you see that?

17 A. Yes.

18 Q. And it states, "Today announced" -- I'm sorry.
19 Regeneron and Bayer "today announced that in two parallel
20 Phase III studies in patients with neovascular form of
21 age-related macular degeneration (wet AMD) all regimens of VEGF
22 Trap-Eye (aflibercept ophthalmic solution), including VEGF
23 Trap-Eye dosed every two months, successfully met the primary
24 end point compared to the current standard of care,
25 ranibizumab, every month."

KARL CSAKY, MD, PhD - CROSS

1 Do you see that?

2 A. Yes.

3 Q. And then going down further where it says "About VEGF
4 Trap-Eye."

5 Do you see that section on page 2?

6 A. You have to highlight it for me, please.

7 Q. It states there on November 22nd, 2010, that "VEGF
8 Trap-Eye is specially purified and contains iso-osmotic buffer
9 concentrations allowing for injection into the eye."

10 Do you see that?

11 A. Yes.

12 Q. This is what is disclosed here?

13 A. Yes. It says that it's an iso-osmotic buffer
14 concentration.

15 Q. Let's jump to DTX 918, page 1.

16 This is an email from the same date, November 22nd,
17 2010, that reports that more than 33 million -- there were more
18 than 33 million views of that morning's announcement.

19 Do you see that?

20 A. Yes.

21 Q. So if the person of ordinary skill in the art needed
22 to have these Phase III results to ensure the need was solved,
23 those results were publicly known before the earliest filing
24 date for the '572 and '601 patents, correct?

25 A. This would have been shared with those individuals

KARL CSAKY, MD, PhD - CROSS

1 who were seeing this report, correct.

2 Q. All right. Dr. Csaky, you've reviewed Regeneron's
3 '758 patent in offering your opinions in this matter, correct?

4 A. Correct.

5 Q. If we could pull up DTX 4213.

6 Would you agree that the cover page of this document
7 states this patent term extension petition is with respect to
8 7,374,758 U.S. patent number at the top there?

9 A. Yes.

10 Q. And if we go to page 2 of this document, do you
11 agree, looking at Bullet 1, that Regeneron identified Eylea as
12 the relevant approved product covered by the '758 patent?

13 A. Yes.

14 Q. Then turning to page 4, Bullet 9.

15 Let's go down a little bit further where we see the
16 claims.

17 Regeneron stated to the patent office that at least
18 the following claims of the '758 patent claim a method of using
19 the approved products, Claims 1 and 2.

20 Do you see that?

21 A. Yes.

22 Q. When you were looking at questions of nexus in this
23 case, did you consider that fact?

24 A. Again, I'm not sure I included a comprehensive
25 understanding and perspective of nexus as it relates to claims.

KARL CSAKY, MD, PhD - CROSS

1 I looked at this simply from the viewpoint of a POSA as whether
2 or not this was informing us about the claims.

3 Q. Okay. Let's go to another document, DTX 3501. We'll
4 go to page 1, the cover here.

5 This indicates that this relates to U.S. Patent
6 Number 7,070,959. Do you see that?

7 A. Yes.

8 Q. This is another patent term extension petition. Do
9 you understand that the '959 patent expired last Friday?

10 A. No, I did not.

11 Q. And when you were looking at questions of nexus, did
12 you consider this document?

13 A. Again, I don't think I went into a complete detail of
14 nexus as I was making my opinions on the -- from the POSA's
15 perspectives on patents that were under consideration.

16 Q. Let's go to another document, DTX 4956.

17 This is a Regeneron 10-K form filed with the SEC in
18 March 2005.

19 Do you see that?

20 A. Yes.

21 Q. Are you aware that in March 2005 Regeneron filed a
22 Form 10-K with the SEC publicly disclosing that Regeneron was
23 starting clinical trials of aflibercept through intravitreal
24 injection in mid-2005?

25 A. No.

KARL CSAKY, MD, PhD - CROSS

1 Q. If we could turn to another document, PTX 1027.

2 So you mentioned your publication coauthored with
3 Dr. Diana Do in your direct exam. Do you remember that?

4 A. Yes.

5 Q. You talked about these systemic safety risks
6 associated with aflibercept?

7 A. Correct.

8 Q. So if we turn to page 9 of this document, can you
9 confirm that when you wrote this paper you -- both you and
10 Dr. Do reported that this study had been supported by research
11 funding from Genentech?

12 A. Did we report that?

13 Q. You did report that, did you not?

14 A. Yes, I did report that.

15 Q. So you were receiving -- so at the time that you were
16 talking about potential risks of using aflibercept, you were a
17 paid consultant with Genentech, correct?

18 A. Yes, but --

19 Q. All right. Next --

20 THE COURT: Yes is good enough for now, Doctor.
21 Thank you.

22 BY MR. McLAUGHLIN:

23 Q. Let's take a look at DTX 2027.

24 This morning at around 9:47 a.m. you talked about
25 justification of striking references from Dr. Albini's slide

KARL CSAKY, MD, PhD - CROSS

1 for loading doses.

2 A. Yes.

3 Q. That a POSA won't apply any results from CRVO or AMD
4 to DME. Do you remember that?

5 A. Yes.

6 Q. Why don't we take a look at DTX 2027, your responsive
7 expert report in this case, page 213.

8 And in the middle of paragraph 382 here's what you
9 say:

10 "The POSA would have understood that the
11 specification defined angiogenic eye disorders as any disease
12 of the eye which is caused by or associated with the growth or
13 proliferation of blood vessels or by blood vessel leakage
14 according to the common characteristic of their etiology and
15 thus their ability to be treated by anti-VEGF therapy."

16 Do you see that?

17 A. Yes.

18 Q. So your report you said that when you're looking at
19 angiogenic eye disorders, which includes AMD and DME and DR,
20 you said that a POSA would have understood that they had a
21 common etiology; namely, they're able to be treated by
22 anti-VEGF therapy. Correct?

23 A. Yes, but --

24 THE COURT: Yes is good enough for now, Doctor.

25 BY MR. McLAUGHLIN:

KARL CSAKY, MD, PhD - CROSS

1 Q. Let's turn to PTX 1145.

2 This is the Schmidt-Erfurth publication that you were
3 talking about earlier today. At the time that she wrote this
4 publication, are you aware that she was running the VIEW 2
5 clinical trial for Regeneron?

6 A. She was involved, as far as I recall, in the -- part
7 of the -- I think, one of the VIEW trials.

8 Q. And you talked about there being no reasonable
9 expectation of success that a POSA could use these regimens to
10 maximize vision gains.

11 Do you recall saying that?

12 A. And "these regimens" would be?

13 Q. The claimed regimens that are at issue in this case.

14 A. Yes.

15 Q. Let's use the '601 patent Claim 11 as an example.

16 Does the '601 patent Claim 11 -- actually, I'll
17 withdraw that.

18 Actually, I want to bring you to DTX 5431.

19 I believe this is another publication that you were
20 presenting information about earlier today, the Shahraki
21 publication?

22 A. Yes.

23 Q. Let's go to page 11 of that document.

24 A. Yes.

25 Q. Let's see what the authors say here.

KARL CSAKY, MD, PhD - CROSS

1 So starting with the "Shenasi and colleagues"
2 comment, they say, "Shenasi and colleagues evaluated the effect
3 of subconjunctival bevacizumab immediately after the excision
4 of primary pterygium. They concluded that the combination
5 therapy is well tolerated, but it cannot significantly reduce
6 the recurrence of pterygium."

7 Do you see that?

8 A. Yes.

9 Q. Now let's go to the first page of that Shenasi
10 reference that they refer to there, DTX 9030.

11 MR. McLAUGHLIN: And we have copies.

12 MS. MAZZOCHI: May I approach?

13 THE COURT: You may.

14 BY MR. McLAUGHLIN:

15 Q. Let us know when you have that in front of you,
16 Doctor.

17 A. I do have that in front of me.

18 Q. Let's go to the first page, the "Methods" section.

19 A. Uh-huh.

20 Q. Here it says that bevacizumab was being injected into
21 the eye, correct?

22 A. Into the -- under the "Methods" section in the first
23 page?

24 Q. Correct, about halfway through this paragraph.

25 "Subconjunctival bevacizumab, 1.25 milligrams,

KARL CSAKY, MD, PhD - CROSS

1 injected immediately after surgical excision."

2 Do you see that?

3 A. Correct. That was not into the eye.

4 Q. So that was a direct injection into the eye?

5 A. It's not into the eye.

6 Q. I'm sorry. I didn't hear that?

7 A. That's not into the eye.

8 Q. What is that?

9 A. That's into the conjunctiva.

10 Q. And the conjunctiva, that's the surrounding
11 tissues --

12 A. Correct.

13 Q. -- around the eye?

14 A. Correct. You don't enter into the eye.

15 Q. It's not intravitreal?

16 A. At this point it's not intravitreal. That's correct.

17 Q. And the conclusion was still that this administration
18 of bevacizumab cannot significantly prevent the recurrence of
19 pterygium, correct?

20 A. Correct. This study did not show that.

21 Q. Now, let's turn to the other one that you relied
22 upon, the Kasetsuwan paper.

23 I believe this is DTX 9031. And if we blow up the
24 methods section and the purpose.

25 Let's go about halfway down where it begins

KARL CSAKY, MD, PhD - CROSS

1 "Topical" -- I'm sorry. Also under purpose.

2 "This study was designed to assess the efficacy and
3 tolerability of topical bevacizumab."

4 Do you see that?

5 A. Yes.

6 Q. And if we go down into the methods section, it
7 states, "Topical bevacizumab and placebo were applied in the
8 respective groups four times daily for three months."

9 Do you see that?

10 A. Yes.

11 Q. That is not a method as claimed in the claims of the
12 '601 or '572 patents, correct?

13 A. As far as -- it is not intravitreal.

14 Q. And it's not on the same schedule, correct?

15 A. It's not on the same schedule.

16 Q. Let's look at the next reference that the Shahraki
17 publication referred to.

18 This is DTX 5431. This is at paragraph 11 -- I'm
19 sorry -- page 11.

20 This is the Shahraki reference, and it mentions on
21 page 11 a Hwang and Choi article.

22 Do you see that?

23 A. Sure. Yes.

24 Q. What they report here about that study is that they
25 compared the recurrence rates of pterygium removal surgery

KARL CSAKY, MD, PhD - CROSS

1 associated with topical MMC, cyclosporine, and bevacizumab.

2 And what they reported is that they observed no difference

3 between the control group and the group that received topical

4 bevacizumab.

5 Do you see that?

6 A. Yes.

7 Q. And then the last reference that the Shahraki

8 publication mentions -- this goes over onto the next page. And

9 it has a citation of 148.

10 Do you see that?

11 A. Yes.

12 Q. What they report there is that "In a recent study,

13 two different concentrations of topical bevacizumab were used

14 following pterygium removal of 90 patients, and the recurrence

15 rates were compared between the groups. Pterygia recurred in

16 13.3 percent in the 5 mg/mL group, while no recurrence was

17 observed in the 10 mg/mL group. Thus, the authors concluded

18 that the 10 mg/mL concentration of topical bevacizumab is more

19 effective than the 5 mg/mL dose in preventing pterygium

20 recurrence."

21 Do you see that?

22 A. Yes.

23 Q. So, again, that is not an intravitreal injection of

24 bevacizumab, is it?

25 A. At this stage it is not an intravitreal injection.

KARL CSAKY, MD, PhD - CROSS

1 Q. Let's go to page 20 of DTX 5431. And there's a
2 reference to -- a reference number 148 which cites to an author
3 Motarjemizadeh.

4 THE COURT: Would you mind spelling that for the
5 record, counsel?

6 MR. McLAUGHLIN: Absolutely. That's
7 M-O-T-A-R-J-E-M-I-Z-A-D-E-H.

8 THE COURT: Thank you.

9 MR. McLAUGHLIN: We're going to mark that paper as
10 DTX 9032. Let's pull that up on the screen.
11 BY MR. McLAUGHLIN:

12 Q. If we take a look at this one, at the abstract, what
13 we see again is that bevacizumab was given topically, correct?

14 A. Correct.

15 Q. And not only that, but it was given topically four
16 times a day for one week, right?

17 A. Yes.

18 Q. And the low dose didn't work; only the high-dose
19 group did?

20 A. Yes. The 10 mg/mL concentration was more
21 efficacious.

22 Q. We can agree that Claim 6 does not permit dosing
23 regimens of topical administration four times a day for a week,
24 right?

25 A. That's correct.

KARL CSAKY, MD, PhD - CROSS

1 Q. Now, you also mentioned that you believed aflibercept
2 would work for PVR. Do you recall that?

3 A. Yes.

4 Q. Let's take a look at what we will mark now as
5 DTX 9033, "Efficacy of Intravitreal Injection of Bevacizumab in
6 Vitrectomy for Patients with Proliferative Vitreal Retinopathy,
7 Retinal Detachment: A Metaanalysis of Prospective Studies."

8 Do you see that on the screen?

9 A. Yes.

10 Q. And if we go to the conclusion on the first page, can
11 you confirm that the conclusion there reads, "Based on the
12 available evidence, intravitreal injection of bevacizumab in
13 vitrectomy for patients with PVR-related retinal detachment did
14 not decrease retinal redetachment rate or improve visual
15 acuity," correct?

16 A. That's what it states.

17 Q. This was published in 2018; is that right?

18 A. That's correct.

19 Q. Let's take a look at a couple more. Let's start with
20 DTX 9034. This is a Tousi reference, "Intravitreal Injection
21 of Bevacizumab in Primary vitrectomy to Decrease the Rate of
22 Retinal Redetachment: A Randomized Pilot Study."

23 And if we can go to the abstract.

24 So, again, this was an intravitreal injection of
25 bevacizumab, correct?

KARL CSAKY, MD, PhD - CROSS

1 A. It is intravitreal bevacizumab.

2 Q. And if we look at the conclusion there, it says, "Our
3 preliminary results show neither benefit nor any harm from
4 intervention in both anatomic and visual outcomes."

5 Do you see that?

6 A. Yes.

7 Q. Let's take a look at DTX 9035. This is a Falavarjani
8 reference.

9 And I can spell that again. That's
10 F-A-L-A-V-A-R-J-A-N-I.

11 This relates to the "Intrasilicone Oil Injection of
12 Bevacizumab at the End of Retinal Reattachment Surgery for
13 Severe Proliferative Vitreal Retinopathy."

14 Here again, if we take a look at the abstract,
15 bevacizumab was injected, correct?

16 A. Yes.

17 Q. It was injected into the silicone -- I'm sorry --
18 injected into the silicone oil at the end of retinal
19 reattachment surgery for rhegmatogenous retinal detachment.

20 Do you see that?

21 A. Correct.

22 Q. All right. If we go to the conclusion, it states
23 here that "intrasilicone injection of bevacizumab at the end of
24 vitrectomy for RRD with severe PVR does not eliminate the risk
25 of postoperative PVR."

KARL CSAKY, MD, PHD - REDIRECT

1 Do you see that?

2 A. Yes.

3 MR. McLAUGHLIN: I have no further questions. Pass
4 the witness.

5 THE COURT: Redirect?

6 REDIRECT EXAMINATION

7 BY MS. OBERWETTER:

8 Q. All right. Good afternoon, Dr. Csaky.

9 A. Good afternoon.

10 Q. I have a few additional questions based on some of
11 the questions that Mr. McLaughlin had for you.

12 First of all, if I can direct you back towards the
13 beginning of the cross-examination, you had some questions
14 about what was marked as DTX 9024, which was a roundtable
15 discussion that I believe you participated in.

16 Do you still have DTX 9024 in front of you?

17 A. Just please project it. If I have to look for it,
18 it's going to be a problem.

19 Q. I'm not sure we actually have it loaded onto our
20 system as it was not a produced document.

21 THE COURT: Do you know in which binder or stack that
22 might be? I'll join the doctor's position on finding
23 something.

24 MS. OBERWETTER: I do not know, unfortunately, which
25 binder it was in.

KARL CSAKY, MD, PHD - REDIRECT

1 THE COURT: What's the exhibit number again?

2 MS. OBERWETTER: It's DTX 9024. And I'm sorry we're
3 doing this old school.

4 THE WITNESS: DTX --

5 MS. OBERWETTER: I believe it was Volume 2.

6 THE COURT: Yeah, Volume 2, Madam Clerk indicates.

7 Thank you.

8 The smaller of the two binders, Doctor.

9 Bear with us at the front of the room, please. Thank
10 you.

11 BY MS. OBERWETTER:

12 Q. And if it's helpful, it has the picture that
13 Dr. Csaky was not enamored of. And it's called "Unmet Needs
14 for Patients with AMD."

15 THE COURT: It's in cross exhibits, Volume 2, 9024.

16 THE WITNESS: 9024. Yes, that's my mug. Okay.

17 BY MS. OBERWETTER:

18 Q. Do you have it, Dr. Csaky?

19 A. Yes, I do have it.

20 Q. Mr. McLaughlin directed your attention to the bottom
21 of page 2 and the top of page 3 of that document and had some
22 questions about one of your comments about durability.

23 Do you recall that?

24 A. Yes.

25 Q. And do you recall that one of the potential responses

1995

KARL CSAKY, MD, PHD - REDIRECT

1 to that offered by the panelists was the port delivery system?

2 A. Yes.

3 Q. What's a port delivery system and what has happened
4 to that?

5 A. Yeah. So the port delivery system is -- was a new
6 technology that was developed by Genentech. It's essentially
7 a -- basically a piece of plastic that goes into the eye, and
8 it allows the injections to go through this little port rather
9 than going through the skin of the eye.

10 We surgically place it. And the idea is that this
11 little device can contain ranibizumab for longer periods of
12 time and therefore increase the durability as it slowly
13 releases ranibizumab.

14 Q. Is that device currently in regular and active use by
15 a large number of doctors?

16 A. No. It's been recalled by the FDA because of
17 problems with manufacturing. And the device actually has
18 issues with consistency and was a probable safety concern.

19 Q. And the other reference in that paragraph I believe
20 was to a drug called faricimab. How long after Eylea was
21 approved did faricimab come out?

22 A. Faricimab was just approved as of February of last
23 year.

24 Q. I'm going to change topics a little bit. And I'd
25 like to direct your attention to some questions that

KARL CSAKY, MD, PHD - REDIRECT

1 Mr. McLaughlin had for you about whether aflibercept is an
2 antibody.

3 Do you remember those questions?

4 A. Yes.

5 Q. Can you explain what is an immunoadhesin and whether
6 aflibercept is a, quote, antibody?

7 A. Yes. So I happen to -- I actually worked on
8 immunoadhesins. I actually made these. And so the idea is
9 that they are a purely synthetic recombinant protein. Yes,
10 they have a synthetic portion of the antibody, but they're not
11 generated in any form or fashion like an antibody.

12 You make these in a purely genetic way. And so the
13 construct has a portion that is -- has some sequences that are
14 similar in the Fc portion; but unlike being made like an
15 antibody is being made, you make these purely with recombinant
16 DNA technology. And then of course the other portion is purely
17 recombinant. So it's completely different than a naturally
18 occurring or even any type of modified antibody.

19 So that's a very important distinction that I
20 actually happen to have personal experience with.

21 Q. Thank you.

22 I'd like to change topics a little bit and take a
23 look at the Heier 2012 reference, which was PTX 311, please.

24 And this one we should have -- we should be able to
25 put up on the screen. And if we could take a look at that page

1997

KARL CSAKY, MD, PHD - REDIRECT

1 marked 8 that had the tables that Mr. McLaughlin asked you
2 about. You recognize this as the Heier reference, Dr. Csaky?

3 A. Yes.

4 Q. And we'll advance forward to page 8.

5 Mr. McLaughlin had some questions for you about the
6 integrated table and what that showed. Could you please
7 comment on what the VIEW 1 table that you wanted to comment on
8 shows?

9 A. Yeah. I think one of the interesting aspects -- and
10 it's one of the things that Regeneron was actually looking at.
11 If you look at the VIEW 1 results, what you actually see at the
12 top line is the 2-milligram aflibercept given every month. And
13 what you see is that says 10.9 letters of gain, and in the
14 exact same trial, that's the top line there. And,
15 interestingly, if you look at the ranibizumab same regimen
16 every four weeks, it actually is almost three letters worse.

17 So there was some interesting initial data from
18 VIEW 1 that there could be the possibility that aflibercept
19 was, in fact, better than ranibizumab.

20 Q. Okay. Was the primary benefit the extended interval?

21 A. Yes. So the ultimate -- because of the ultimate
22 outcome and the fact that it was not inferior, the actual, as
23 it went to the label, was this idea of extended fixed dosing.

24 Q. Okay.

25 We can take that document down.

1998

KARL CSAKY, MD, PHD - REDIRECT

1 I want to go back to the September 2009 press release
2 that Mr. McLaughlin asked you about.

3 If we can pull up DTX 3198 again. And, again, if we
4 look at the second page of this document and pull out the DME
5 paragraph there toward the top.

6 Mr. McLaughlin had some questions for you about the
7 2-milligram monthly arm. Do you remember that?

8 A. Yes.

9 Q. Can you please comment on whether the use of the
10 2-milligram monthly arm in the Phase II trial would have
11 affected the reasonable expectation of success as to safety?

12 A. Again, in these kinds of trials, there's several
13 limitations, right? One is the fact that there was a
14 restriction. In this study in particular, some of the
15 inclusion criteria included restricting patients who
16 potentially were at risk for developing strokes and heart
17 attacks. So, again, there was a reduction in the type of
18 profile that we're having.

19 And the other thing that's really important to
20 remember is in these trials there's data safety monitoring
21 boards. And these review the data very, very carefully. And
22 if there's any even hint of a safety concern, that arm gets
23 stopped.

24 So in the context of a trial, as we're trying to
25 decipher signals -- small signals, big signals -- the decision

1999

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1 to include this in a trial carries with it lots of restrictions
2 and boundaries that really relates to ensuring the safety of
3 this type of 2-milligram monthly dosing.

4 Q. Thank you.

5 We can take that document down.

6 I'd like to talk about another document that
7 Mr. McLaughlin showed you. And, again, I think this one you
8 may need to fish out of your pile. It's DTX 9014. And it's
9 that article printed in color that says "Avastin: New Hopes
10 and Hesitations."

11 THE COURT: 9014?

12 MS. OBERWETTER: Yes, Your Honor.

13 THE COURT: I have 9015. There it is.

14 MS. OBERWETTER: It sounds close.

15 THE COURT: It does sound close.

16 Yeah, same binder, Doctor, second smaller binder.

17 THE WITNESS: Thank you.

18 DTX -- say that again.

19 BY MS. OBERWETTER:

20 Q. It's 9014, and it's that article printed in color.

21 A. Yes, yes, yes. I got it. Thank you.

22 Q. So I'm going to direct you to the bottom of the first
23 page of the article. And it's one of the paragraphs that
24 Mr. McLaughlin directed you to that contained one of your
25 quotes. It's the one that includes the phrase "it's all seat

KARL CSAKY, MD, PHD - REDIRECT

1 of the pants."

2 Can you please explain what you were -- what that
3 paragraph of this article is about.

4 You have me on the first page. You're looking down
5 toward the bottom right of the first page.

6 A. I got it. Here we go.

7 So, again, this is now -- we've had some beginning
8 experiences with Avastin. We don't have any clinical trial
9 guidelines yet. This was in 2010. So we don't have any
10 guidelines about the whole idea behind Avastin. And so I think
11 the point of Avastin, even more so than with ranibizumab, we
12 had very little guidelines as to, A, how effective it was, what
13 type of approaches we should be using in patients.

14 So I think it's fair that, with Avastin in
15 particular, we were really trying to kind of work out and
16 figure out what were treatment regimens and approaches that we
17 could use with Avastin since we really had only had it for five
18 years, and we were beginning to get kind of some -- we didn't
19 really have lots of guidelines.

20 So we were all a little bit -- not just me, but I
21 think all of us were a little bit undirected. And we were
22 trying to figure out exactly what was the full potential for
23 Avastin.

24 Q. And how much experience was there with aflibercept at
25 this point in time in clinical practice?

KARL CSAKY, MD, PHD - REDIRECT

1 A. None.

2 Q. I'd like to talk about a different document. And
3 this one, I think we can put up on the screen. It's PTX 722.
4 And this is the October 2007 reference that Mr. McLaughlin
5 showed to you.

6 There's a quote that he showed to you on the first --
7 I believe it was on the first page that we looked at earlier.

8 If we can highlight or pull out those -- yes. Thank
9 you. That is exactly the paragraph I was looking for.

10 And just to clarify for the record, is this a
11 reference to a prn dosing strategy?

12 A. Yes.

13 Q. And how can you tell that?

14 A. So very simply. I mean, you look at these
15 qualifiers, when the macula is completely free of fluid, when
16 the macula is dry. So, again, these are all indicators that
17 this OCT machine was being used and that in this case the
18 physician was using those tools -- it even says that -- to make
19 treatment determinations.

20 Q. Okay.

21 We can take that document down.

22 Mr. McLaughlin had a series of questions for you
23 using the word "nexus."

24 Do you recall that generally?

25 A. Yes.

KARL CSAKY, MD, PHD - REDIRECT

1 Q. Were you able to tell from his questions exactly what
2 nexus he was asking you about?

3 A. No.

4 Q. I'm going to change topics a little bit. And I'd
5 like to talk about some of the references that arose toward the
6 end of the examination. And, in particular, Mr. McLaughlin
7 asked you a series of questions about pterygium.

8 Do you recall those?

9 A. Yes.

10 Q. You recall those additional references?

11 A. Yes.

12 Q. Did the additional references that were provided to
13 you by Mr. McLaughlin affect the point that you were making
14 about angiogenic eye disorders?

15 A. No.

16 Q. And why not?

17 A. No, because the point of these diseases is -- and of
18 course they are much more complete and comprehensive review
19 articles and ongoing trial results.

20 And the point of this was to indicate that these are
21 angiogenic eye disorders and they could be treated with an
22 anti-VEGF agent. Whether we're using topical or, down the
23 road, some form of intravitreal is still to be determined, but
24 the point is that these references -- there are, of course,
25 many more. My colleagues -- in particular, my cornea

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1 colleagues -- are very excited about using anti-VEGF agents in
2 the treatment of pterygia.

3 Q. And Mr. McLaughlin also asked you some questions
4 about PVR.

5 A. Yes.

6 Q. And my question is the same. Do the additional
7 references affect your point about angiogenic eye disorders in
8 light of what you know about how aflibercept is being used?

9 A. No. I mean, I found an article -- an article,
10 clinical trial, that showed that intravitreal bevacizumab was
11 effective, right? And, again, if you look at the work of
12 Andrius Kazlauskas and his work with the clinicians at the
13 University of Chicago, Illinois, there was an ongoing trial --
14 actually, the beta trial -- that was in bevacizumab for PVR.

15 So there's been a lot of interest in interrogating
16 with some success in the biology in particular of VEGF and
17 anti-VEGFs in PVR. It's really good science. And so there's a
18 lot more that we could add to this -- to the repository of
19 articles that support my opinion.

20 Q. I'd like to take a look at -- I'm going to change
21 topics a little bit. I'd like to take a look at PTX 1027,
22 which is that article that you coauthored with Dr. Diana Do.

23 If we could pull that back up.

24 Mr. McLaughlin had some questions about a passage
25 toward the end of the article where he pointed to who

2004

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1 participated in funding some of the work for the article.

2 Can you please provide the context and explanation
3 for how this article came to be.

4 A. Yes. I mean, this is something that Diana and I
5 talked about doing. It's not uncommon for us to reach out for
6 kind of writing support. You know, we write the manuscript and
7 then we need somebody to help kind of wordsmith it. And so the
8 key thing that every journal wants to see -- and I think this
9 is the key point. Both authors were involved in the design and
10 conduct of the study, collection of data management analysis
11 and interpretation of data and preparation, review, and
12 approval of the manuscript. That was left up completely to
13 Diana and I to write this in the way that we thought
14 represented the state of the knowledge when we wrote this
15 article.

16 Q. And what was going on in the art at the time that
17 made you interested in writing this article?

18 A. Yes. It's exactly this point, that there was already
19 some data, if we'd looked at ongoing trials, SAILOR, for
20 example showed a slight difference in stroke rates between .5
21 and .3. There was this concern -- Bob Avery had started to
22 look at systemic levels following an intravitreal injection.

23 And then we had this molecule, aflibercept, that
24 again had these higher affinities and potentially higher
25 duration in the systemic circulation. So we wanted to really

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1 call attention to our colleagues. And, again, it's not
2 something that we typically think about in our day-to-day
3 lives. And suddenly here we were faced with giving new
4 medicines into old people, into diabetics who potentially were
5 sick. And we really wanted to make sure that we raised the
6 specter for everybody to be aware of this potential issue.

7 MS. OBERWETTER: Nothing further, Your Honor.

8 THE COURT: Recross?

9 MR. McLAUGHLIN: Just one question, Your Honor.

10 THE COURT: I'm going to hold you to that.

11 MR. McLAUGHLIN: Understood.

12 RECROSS-EXAMINATION

13 BY MR. McLAUGHLIN:

14 Q. Dr. Csaky, you just made reference to some various
15 articles, references, clinical studies. However, today,
16 despite having multiple opportunities to do so, you've not been
17 able to identify anything from the published medical literature
18 that showed intravitreal aflibercept dosed on the Claim 6
19 schedule that actually worked to treat formed corneal
20 neovascularization, proliferative vitreal retinopathy, pannus,
21 or pterygium in humans, correct?

22 A. That's correct.

23 MR. McLAUGHLIN: Thank you.

24 Thank you, Your Honor.

25 Thank you, Dr. Csaky.

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1 THE COURT: Rerredirect?

2 MS. OBERWETTER: No, Your Honor. Only exhibits if we
3 should do that at this point.

4 THE COURT: Yeah. Let's go ahead and do that. If I
5 could ask you, Ms. Oberwetter -- you can remain seated if you'd
6 like. Just get closer to a mic so we can hear you clearly.
7 And slowly, of course, the newest local rule we have.

8 Doctor, if you'll bear with us for one moment.

9 MS. OBERWETTER: Yes. We have DTX 212, which I
10 believe we previously used on day two. And we probably
11 misspoke and called it PTX 212, but it's DTX 212.

12 DTX 3105, DTX 3112, DTX 3186, PTX 821, PTX 841,
13 PTX 1027, PTX 1143, PTX 1145, PTX 1146, PTX 1155, PTX 1447,
14 PTX 1794, PTX 3225, and DTX 9014.

15 THE COURT: Seeing no objections from your own table,
16 Counsel.

17 Any objections to any of those from the adverse
18 party?

19 MR. McLAUGHLIN: No objection, Your Honor.

20 THE COURT: Without objection, each of those
21 identified by Ms. Oberwetter will be hereby admitted.

22 (DTX 3105, DTX 3112, DTX 3186, PTX 821, PTX 841,
23 PTX 1027, PTX 1143, PTX 1145, PTX 1146, PTX 1155, PTX 1447,
24 PTX 1794, PTX 3225, and DTX 9014 were admitted.)

25 THE COURT: Exhibits from Mylan.

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1 MR. McLAUGHLIN: Yes, Your Honor. I tried to
2 deduplicate as counsel was reading them off. I apologize if I
3 repeat any.

4 DTX 9, DTX 10, DTX 12, DTX 28, DTX 29, DTX 33,
5 DTX 405, DTX 917, DTX 918, DTX 2027, DTX 2733, DTX 3082,
6 DTX 3089, DTX 3096, DTX 3051, DTX 4069, DTX 4135, DTX 4213,
7 DTX 4215, DTX 4956, DTX 9007, DTX 9008, DTX 9009, DTX 9013.

8 DTX 9014, that might have already been read in.

9 DTX 9015, DTX 9022, DTX 9024, DTX 9030, DTX 9031,
10 DTX 9032, DTX 9033, DTX 9034, DTX 9035, PTX 1027.

11 And then -- actually, I'm having to actually withdraw
12 one of these, DTX 2027.

13 THE COURT: Off the list.

14 MR. McLAUGHLIN: Off the list. Thank you.

15 THE COURT: Thank you, Mr. McLaughlin. Does that
16 comport with the rest of your table's list?

17 It seems so. Outstanding.

18 Any objections from the adverse party?

19 MS. OBERWETTER: No objection, Your Honor.

20 THE COURT: Without objection, the list -- with 2027
21 being withdrawn?

22 MR. McLAUGHLIN: 2027.

23 THE COURT: 2027 being withdrawn. Otherwise,
24 Mr. McLaughlin's list, without objection, is hereby deemed
25 admitted.

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1 (DTX 9, DTX 10, DTX 12, DTX 28, DTX 29, DTX 33,
2 DTX 405, DTX 917, DTX 918, DTX 2027, DTX 2733, DTX 3082,
3 DTX 3089, DTX 3096, DTX 3051, DTX 4069, DTX 4135, DTX 4213,
4 DTX 4215, DTX 4956, DTX 9007, DTX 9008, DTX 9009, DTX 9013,
5 DTX 9015, DTX 9022, DTX 9024, DTX 9030, DTX 9031, DTX 9032,
6 DTX 9033, DTX 9034, DTX 9035, and PTX 1027 were admitted.)

7 THE COURT: Doctor, thank you, sir. You may step
8 down. Thank you very much. Whatever's there, leave. We'll
9 tidy up.

10 Why don't we take a ten-minute break. We'll let
11 everyone reshuffle in here. I'd ask folks to use that time
12 wisely and efficiently to distribute binders and the rest. I'm
13 assuming we're going to do Dr. Trout next; is that correct?

14 MR. BERL: Correct, Your Honor.

15 THE COURT: All right. Let's take ten while we
16 rearrange the courtroom. If I could ask counsel to grab
17 whatever's left here from Dr. Csaky and pass out the rest, and
18 then we'll get started with Dr. Trout. Thank you all.

19 (A recess was taken from 3:50 p.m. to
20 4:05 p.m.)

21 THE COURT: Yes?

22 MS. MAZZOCHI: A quick housekeeping matter, Your
23 Honor. I know that you said that, as we got closer to the end
24 of the trial days, people would either be happy with or angry
25 with the keeper of the time. The way in which we've been

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KARL CSAKY, MD, PHD - RECROSS

1 calculating things, just based on Your Honor's average trial
2 day, et cetera, by our estimates, defendants have about three
3 hours left; plaintiffs have about 90 minutes left.

4 If we were to subtract out some of the time that
5 plaintiffs have indicated they want to use for deposition
6 designations, we can lower that a bit more.

7 Since there was an agreement for an even split
8 between the parties in terms of time and we've been -- we've
9 tried to be very judicious to make sure we have enough time for
10 a full and effective cross-examination at the end, we just want
11 to make sure that we're going to be able to get our full time
12 to do the complete cross-examination of Dr. Csaky.

13 THE COURT: Trout?

14 MS. MAZZOCHI: I'm sorry. Trout. Apologies.

15 THE COURT: Yeah, I would assume we'll start and stop
16 Dr. Trout, resume tomorrow with him. And then I know we've yet
17 to talk about -- how long are the videos?

18 MR. BERL: Your Honor, I actually have some good news
19 in that regard. We've decided, in view of how the evidence
20 came in, we are not going to play any of those videos. So
21 Dr. Trout is the last witness. I think we have some
22 differences from the calculations. Honestly, I don't really
23 think it matters. We're going to finish tomorrow.

24 THE COURT: Indeed we are.

25 MR. BERL: They'll have the time that they need.

2010

KARL CSAKY, MD, PHD - RECROSS

1 THE COURT: We don't have any choice.

2 Yeah. Okay. Noted. Understood.

3 MS. MAZZOCHI: Thank you.

4 THE COURT: Let me ask this before we get started.

5 Any issues if we resume tomorrow at 8:30 a.m. to get a running
6 start on the day?

7 MR. BERL: No issues at all.

8 THE COURT: All right. And for those lucky
9 associates in charge of ordering lunch and the rest, I will
10 know in the morning if we're taking another early lunch
11 tomorrow based on the weather forecast and my 11-year-old
12 daughter's softball schedule tomorrow. So I'll let everybody
13 know as soon as I can tomorrow what our outlook looks like.
14 But let's get started at 8:30 tomorrow and hit the ground
15 running.

16 With all that, Regeneron may call its next witness.

17 MR. BERL: Your Honor, Regeneron calls Bernhardt
18 Trout.

19 THE COURT: Doctor, if you wouldn't mind repeating
20 from last week, I believe.

21 THE WITNESS: Yes, Your Honor.

22 **BERNHARDT TROUT, PHD, PLAINTIFF'S WITNESS, SWORN**

23 THE COURT: Thank you, sir. Once you're comfortable,
24 if you wouldn't mind adjusting that mic.

25 With that, you may proceed.

2011

BERNHARDT TROUT, PHD - DIRECT

1 DIRECT EXAMINATION

2 BY MR. BERL:

3 Q. Good afternoon, Dr. Trout.

4 A. Good afternoon, Mr. Berl.

5 Q. We're here to talk about validity today. Did you
6 evaluate validity from the perspective of the person of
7 ordinary skill?

8 A. Yes, I did.

9 Q. Okay.

10 Can we put up Demonstrative 2 on the screen.

11 Can you read into the record your definition of the
12 person of ordinary skill.

13 A. Yes.

14 "The POSA would have held an advanced degree such as
15 a master's in a biopharmaceutical science or related discipline
16 such as chemical engineering and several years of experience in
17 the development of biologics product. Alternatively, the POSA
18 could have a PhD in such discipline and less experience."

19 Q. Did you meet the definition of a person of ordinary
20 skill in 2006?

21 A. Yes, I did.

22 Q. How so?

23 A. Well, I actually had a PhD then, and I had been doing
24 relevant research since 1998, at least. So I met that
25 definition.

BERNHARDT TROUT, PHD - DIRECT

1 Q. Do you understand Mylan's definition of the POSA to
2 differ substantially from yours?

3 A. No, not much.

4 Q. Would any of your opinions be different if Mylan's
5 definition were used instead of yours?

6 A. No.

7 Q. And did you apply the Court's claim constructions in
8 your validity analysis?

9 A. Yes, I did.

10 Q. I'd like to ask about some background issues before
11 we get into the prior art itself.

12 What is aflibercept?

13 A. Well, aflibercept, as we've heard for the past couple
14 weeks, is what's known as a fusion protein. So it's made up of
15 three different pieces of three different proteins. And we
16 could call it a Frankenstein molecule because it's a nonnatural
17 molecule.

18 Q. Let's look at PTX 1826, the Aruffo article. Did you
19 review this article in connection with your work in the case?

20 A. Yes, I did.

21 Q. And if we look at page 1 and blow up one excerpt,
22 beginning with "fusion proteins" and "these proteins consist,"
23 can you explain what Aruffo is telling us.

24 A. Yes. And I guess just to be clear, it continues,
25 "These proteins consist of the constant regions of

2013

BERNHARDT TROUT, PHD - DIRECT

1 immunoglobulin, typically mouse or human, fused to an unrelated
2 protein or protein fragment."

3 So basically what I said, they're nonnatural proteins
4 that are made by fusing various parts of other proteins.

5 Q. And what are the parts of the aflibercept fusion
6 protein?

7 A. So one of the parts is what's called the constant
8 domain of an antibody, so a piece of an antibody. And then
9 there are two other parts from two different receptor proteins.

10 Q. You heard Dr. Rabinow testify last week about a
11 fusion protein and an antibody being largely the same thing.

12 Do you agree?

13 A. No, I don't agree.

14 Q. How are fusion proteins different from antibodies?

15 A. Well, as I've been emphasizing, fusion protein is
16 made of different pieces of other proteins. It's not natural.
17 Antibodies have evolved over time or are part of nature.

18 Q. Were fusion proteins known as of 2006?

19 A. Yes.

20 Q. Were any commercially available?

21 A. Yes.

22 Q. Let's look at one of the slides shown by Dr. Rabinow.
23 It was his Slide 47.

24 Let's put that on the screen.

25 Do you remember this chart you put up of stable

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1 protein formulations?

2 A. Yes, I do.

3 Q. Did Dr. Rabinow identify any fusion protein drug
4 products on this slide?

5 A. No. And as a matter of fact, each of those is
6 highlighted because they're all antibody, noting that
7 ranibizumab is an antibody fragment, a piece of an antibody.

8 Q. And the next one in the chart, that's bevacizumab, is
9 that also called Avastin?

10 A. Yes. That's correct.

11 Q. And is that a fusion protein or an antibody?

12 A. No. That's an antibody.

13 Q. Now, do fusion proteins and antibodies have the same
14 properties?

15 A. No.

16 Q. Okay.

17 Let's bring up the Fast reference. That's PTX 1835.

18 Did you review this article in connection with your
19 work on the case?

20 A. Yes, I did.

21 Q. And if we go to page 15. And we'll also show an
22 excerpt from page 19 below it, beginning in the paragraph that
23 starts "intact antibodies."

24 Can you explain the relevance of the Fast disclosure?

25 A. Yes. And I've highlighted, I think, the relevant

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1 pieces of that section.

2 "In comparison with native IgG proteins" -- like the
3 ones on the previous slide -- "wherein interdomain interactions
4 presumably here evolved to provide mutual stabilization, fusion
5 proteins may lack such stabilizing interdomain stabilization."

6 And then a little skip there, but goes on to say,
7 "This has been seen in other artificial fusion proteins as
8 well."

9 And this referenced the Souillac, which is a bit more
10 of a technical article.

11 Q. What is this conveying with respect to the relative
12 expected stability of antibodies on the one hand compared to
13 fusion proteins on the other?

14 A. Well, this is conveying that the skilled person or
15 the person of ordinary skill in the art would expect that
16 fusion proteins could be less stable than antibodies.

17 Q. And the Souillac reference that's cited for this
18 proposition, in what year was that published?

19 A. That was published, as highlighted here, in 2005.

20 Q. And the proposition about the expected relative
21 stability of fusion proteins compared to antibodies, would that
22 have been consistent or inconsistent with the POSA's thinking
23 as of 2006?

24 A. That would have been consistent. This is
25 illustrative of what the POSA would expect.

BERNHARDT TROUT, PHD - DIRECT

1 Q. Now, I'd like to turn to obviousness and invalidity
2 over the prior art now, Doctor.

3 Do you understand that Dr. Rabinow testified that the
4 asserted claims of the '865 patent are invalid on three bases:
5 Fraser plus Lucentis; Fraser plus Liu; and, thirdly, Dix?

6 A. Yes.

7 Q. Do you agree with Dr. Rabinow's opinions?

8 A. No, I do not.

9 Q. Let's take them one at a time. And let's start with
10 Lucentis plus Fraser.

11 Let's take a look at 2.13.47.

12 Now, you heard Dr. Rabinow -- or did you hear
13 Dr. Rabinow testify first about Claim 1 and then about the
14 asserted claims?

15 A. Yes, I did.

16 Q. Is that how you conducted your anticipation and
17 obviousness analyses?

18 A. No, that is not. I started with the asserted
19 claims -- for example, Claim 4 here -- noting that Claim 4
20 depends on Claim 2. Claim 2 depends on Claim 1. And I looked
21 at all of that together.

22 Q. Now, in order to reference Dr. Rabinow's testimony
23 and demonstratives, I'm going to go back to his demonstratives
24 even though they address Claim 1 and the dependent claims
25 separately.

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1 Is that okay?

2 A. Okay.

3 Q. Before we get into the various limitations of the
4 claims and the details of these references, do you think a POSA
5 looking to make a formulation to treat eye diseases would have
6 selected Fraser and the Lucentis references from all of the
7 available prior art?

8 A. No.

9 Q. Why not?

10 A. Well, there was quite a bit of prior art. And
11 there's no particular reason why the POSA would be pointed to
12 those two references.

13 Q. Do you think the POSA would have any reason to choose
14 to combine Fraser and the Lucentis references of Gaudreault and
15 Shams?

16 A. No. There's no reason.

17 Q. Is that how formulation research is done, to take a
18 formulation form from one molecule and combine it with another
19 and put them together?

20 A. No, it is not.

21 Q. Is there any reason that Dr. Rabinow provided that
22 you heard to choose these references from amongst all of the
23 prior art?

24 A. No.

25 Q. Now, Doctor, I understand your opinions, but unless I

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1 specifically say otherwise, I'd like you to assume for the rest
2 of your testimony about this combination that the POSA would
3 have combined Fraser with Lucentis as Dr. Rabinow urges.

4 Can you make that assumption?

5 A. Okay.

6 Q. Now, let's go back to Claim 1 for a moment.

7 What does Claim 1 recite with respect to the claimed
8 VEGF antagonist?

9 A. Well, it's what's highlighted here. It's a VEGF
10 antagonist. But it's not just any; it's a specific one. It's
11 got to be glycosylated. And it comprises a specific sequence
12 of amino acids that is specifically defined and described in
13 the patent.

14 Q. Let's go to Dr. Rabinow's Demonstrative 51.

15 And what did Dr. Rabinow rely on to meet those
16 limitations in his Fraser plus Lucentis combination?

17 A. Well, Dr. Rabinow relied on this disclosure in Fraser
18 which says VEGF Trap R1R2.

19 Q. And does Fraser disclose the limitations that we're
20 discussing relating to the VEGF antagonist in Claim 1?

21 A. No, it doesn't. It doesn't disclose this sequence.

22 Q. Do you recall that Dr. Rabinow relied on Holash as
23 somehow being incorporated into Fraser?

24 A. Yes.

25 Q. And if we look at the next -- does Fraser incorporate

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1 Holash?

2 A. No. Holash is just one of the many references in
3 Fraser.

4 Q. Now, I understand your opinion there, but I'd like to
5 look at Holash nevertheless. That's DTX 3549. And we've shown
6 part of page 2 of the Holash reference.

7 Does that disclose the amino acid sequence recited in
8 Claim 1 of the '865 patent?

9 A. No, sir, it does not. It just discloses this
10 schematic here which does not disclose or relate the sequence.

11 Q. Are these disclosures from -- are these the
12 disclosures from Fraser and Holash that Dr. Rabinow relied on
13 to meet these claim limitations about the amino acid sequence
14 of aflibercept?

15 A. Yes.

16 Q. And to be clear, do either disclose the claimed amino
17 acid sequence?

18 A. No, neither do.

19 Q. And did you highlight in red boxes for the
20 disclosures that don't meet the claim limitations in
21 Dr. Rabinow's demonstrative?

22 A. Yes, I did, right here on the screen.

23 Q. Now, do you recall Dr. Rabinow discussing the
24 Papadopoulos reference, DTX 3619?

25 A. Yes, I do.

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1 Q. Do you understand Papadopoulos to be part of either
2 of Dr. Rabinow's obviousness combinations?

3 A. It is not.

4 Q. Do any of the references in Dr. Rabinow's obviousness
5 combinations cite or discuss Papadopoulos?

6 A. No.

7 Q. Now, Doctor, did you prepare a demonstrative exhibit
8 summarizing the fusion proteins disclosed by Papadopoulos?

9 A. Yes, I did.

10 Q. And were those sequences voluminous in Papadopoulos?

11 A. Yes.

12 And the summary, Your Honor, is here in this table,
13 all the different -- I just have the names here. You can
14 imagine each of those sequences is about a page or longer. But
15 the Papadopoulos discloses all of those.

16 MR. BERL: And for the record, this is marked as
17 DTX 3619A.

18 BY MR. BERL:

19 Q. Doctor, can you explain what is shown here.

20 A. Yes.

21 So this is a list that I've prepared. On the right
22 side are different names as disclosed in Papadopoulos. On the
23 left side are the figures that are in Papadopoulos. Those
24 figures actually contain the sequences listed out.

25 Q. Doctor, there are a lot of letters on this table.

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1 I'd like to discuss a couple of them with you. What is Flt1,
2 or Flt1?

3 A. Yes.

4 So that, Your Honor, might be new in terms of the
5 abbreviation, but all it means is the same as this VEGR1.
6 Biologists may have a certain sense of humor in naming
7 different proteins, but that's just the VEGF R1.

8 Q. So that's VEGF Receptor 1?

9 A. Yes. Correct.

10 Q. And there's also something in here that's referenced
11 as Flk1. What's Flk1?

12 A. Well, again, Flk1 is just another name for the VEGF
13 Receptor R2. So the Flt and the Flk together are the R1R2.

14 Q. And we saw earlier that there was a description in
15 the references that Dr. Rabinow testified about to VEGF R1R2.

16 Do you remember that?

17 A. Yes.

18 Q. And how many fusion proteins does Papadopoulos
19 describe that fall within that categorization?

20 A. Well, it describes these two. I've just highlighted
21 in the table, the small reproduction of the table, the two that
22 I just mentioned. And here on the upper right side is where
23 they are in the text. And, again, it tells you that R1R2 are
24 just the Flt1 and the Flk1.

25 Q. And are you showing on the right-hand side part of

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1 page 60 of DTX 3619, the Papadopoulos reference on about
2 lines 4 to 5?

3 A. Yes. That's correct.

4 Q. Do these two fusion proteins that are denoted R1R2
5 have the same sequence or different sequences?

6 A. They have different sequences.

7 Q. How do you know?

8 A. Well, I did a comparison. I talked about a different
9 comparison last week that I did. But I did a comparison here
10 using the same National Institute of Health software. And I
11 showed that the sequences, as we say, do not align. In other
12 words, they're different.

13 Q. How would the POSA interpret the references to VEGF
14 Trap R1R2 in the literature such as Fraser?

15 A. Well, the POSA would interpret them as meaning a
16 multiplicity of different sequences.

17 Q. Now, the claims also require that the VEGF antagonist
18 is glycosylated; is that right?

19 A. Yes. Correct.

20 Q. Very briefly, Dr. Trout, what is glycosylation again?

21 A. Very briefly, it's the addition of carbohydrate
22 groups, or kind of extended sugar groups, to various sites in
23 the protein.

24 Q. And why does glycosylation matter?

25 A. Well, I think it could be a number of reasons. But

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1 for the standpoint here, I think it matters because, if a
2 molecule is glycosylated, it makes it bigger, more voluminous.

3 Q. You said that proteins can be glycosylated at certain
4 sites; is that right?

5 A. Correct.

6 Q. Now, if those sites are present, if those amino acids
7 are present, will the protein always be glycosylated?

8 A. Not necessarily, no. Not always, I should say.

9 Q. And let's look at the Sinclair reference. That's
10 PTX 1773. Did you review this reference?

11 A. Yes, I did.

12 Q. And let's look at page 2 of that reference beginning
13 with the sentence that says, "Most naturally occurring
14 consensus sequences in secreted proteins are not glycosylated."

15 What is this conveying as relevant to your opinions?

16 A. Well, it's conveying, again, what a POSA would know
17 and what I just stated, which is that not all proteins are
18 glycosylated.

19 Q. And is that true even if they have the sites that
20 would potentially permit glycosylation?

21 A. Yes. That's correct.

22 Q. Let's turn back now to Dr. Rabinow's slides and focus
23 on the glycosylated requirement.

24 Now, does Fraser teach that VEGF R1R2 is
25 glycosylated?

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1 A. No, it does not.

2 Q. Does Fraser say anything about glycosylation?

3 A. No, it does not.

4 Q. Did you hear Dr. Rabinow refer to Papadopoulos with
5 respect to glycosylation?

6 A. Yes.

7 Q. Did Papadopoulos describe glycosylation of the
8 sequence recited in the '865 patent claims?

9 A. No.

10 Q. Is that disclosed anywhere in the prior art, as far
11 as you know?

12 A. Not as far as I know. Not as far as I've seen.

13 Q. Now, if we go back to Papadopoulos at page 82 of the
14 reference, what sequence did Papadopoulos disclose the
15 glycosylation of?

16 A. Well, as I've showed here in this excerpt that there
17 are five possible glycosylation sites. And it describes a
18 different molecule or different fusion protein than the one in
19 the '865 patent.

20 Q. So to be clear, what we have here at line 20 in
21 Papadopoulos at page 82 of the exhibit, is -- that protein
22 that's identified with the glycosylation sites, is that
23 aflibercept or is that a different protein?

24 A. No. That's different protein. Again, I did a
25 comparison between that and aflibercept. And this one is not

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1 the same.

2 Q. Would you know from the glycosylation of a different
3 protein that the protein in the claims of the '865 patent,
4 aflibercept, would be glycosylated?

5 A. No, you would not.

6 Q. Now, let's look at the claims of the '865 patent
7 again and, in particular, if we could look to Claim 14 on
8 page 13 of the reference.

9 Doctor, what does Claim 14 require?

10 A. Well, it requires glycosylation at these specific
11 sites. There are five sites in sequence ID Number 4. These
12 are asparagine sites, and they're numbered right here.

13 Q. Does Papadopoulos teach the glycosylation of
14 aflibercept at those sites recited in Claim 14 of the '865
15 patent?

16 A. No, it does not.

17 Q. As far as you're aware, is that disclosed in any
18 prior art that's been advanced by Dr. Rabinow?

19 A. No, it does not.

20 Q. Does Holash -- also I recognize not part of the
21 obviousness combination -- teach glycosylation at these
22 residues?

23 A. No, it does not.

24 Q. I'd like to shift to a different topic, Dr. Trout.
25 I'd like to talk about retinal penetration and aflibercept.

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1 A. Okay.

2 Q. Based on the prior art as a whole, what kind of
3 molecule would the POSA have wanted to use for intravitreal
4 injection?

5 A. Well, the POSA would have wanted to use a relatively
6 small molecule relative to aflibercept, for example, because of
7 the limit of going through the various membranes to reach the
8 retina.

9 Q. Now, Mylan's combination of Lucentis and Fraser
10 relies on the Gaudreault reference as one of the Lucentis
11 references, correct?

12 A. Yes.

13 Q. Okay. We've placed on the screen part of page 6 of
14 the Gaudreault reference. That's Exhibit PTX 1839.

15 What does Gaudreault teach with respect to retinal
16 penetration?

17 A. Well, it teaches what I've basically just said,
18 highlighted here, "Notably, penetration of ranibizumab into the
19 retina is critical for its clinical use. Retinal penetration
20 suggests the availability of ranibizumab to inactivate VEGF at
21 the site of AMD."

22 Q. Now, let's go back to page 1 of Gaudreault,
23 Exhibit 1839 and beginning with this paragraph that starts
24 "ranibizumab."

25 Can you explain what Gaudreault is teaching a person

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1 of ordinary skill as it relates to retinal penetration?

2 A. Yes. So, again, with respect to ranibizumab, I'll
3 just focus on that larger highlighted portion of this excerpt.

4 "Ranibizumab has also been shown to penetrate all
5 layers of the rabbit retina, the first demonstration of retinal
6 penetration of an anti-VEGF therapy intended for AMD."

7 Q. And was it the understanding -- what did the POSA
8 understand about why ranibizumab was being developed by
9 Genentech? For what kinds of diseases was it being developed?

10 A. Well, for anti-VEGF diseases; in other words,
11 diseases of angiogenesis.

12 Q. Where in particular?

13 A. In the eye, of course, yes.

14 Q. Now, if we go further down on page 1 of the
15 reference, Gaudreault, 1839, was the size of ranibizumab
16 disclosed to be relevant for that purpose?

17 A. Yes. Extremely relevant.

18 Q. What is Gaudreault saying in that regard?

19 A. Well, again, just right below what I had read before,
20 the "ability" -- that is, for retinal penetration -- "has been
21 attributed to the small molecular size (48 kilodaltons) because
22 a full-length antibody, trastuzumab (148 kilodaltons) was not
23 able to penetrate all the retinal layers of rhesus monkeys."

24 It continues, "The small molecular weight of
25 ranibizumab probably also contributes to its demonstrated

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1 ability to penetrate the retina."

2 Q. What is that conveying?

3 A. Okay. All that sort of technical terms basically
4 says if you have a relatively small molecule, 48 kilodaltons --
5 I understand that's a weight, but it can also be reflected in
6 the volume. So it's a small molecule. That can penetrate the
7 retina -- or layers to get to the retina, I should say; whereas
8 larger molecules, like antibodies or aflibercept, were thought
9 not to be able to get through to the retina.

10 Q. What is molecular radius that's being described here
11 by Gaudreault?

12 A. Okay. So that is the important term here. That's
13 basically the size of the molecule. So it's related to the
14 molecular weight in kilodaltons, but it's the size. And that's
15 what's, at the end of the day, most important.

16 Q. Does glycosylation affect a protein size?

17 A. Yes, it does.

18 Q. And in what way?

19 A. Well, again, glycosylation means that carbohydrates
20 are added, they're extended carbohydrates. So they're going to
21 be added to these sites, extend out, and increase the effective
22 volume.

23 Q. Was ranibizumab glycosylated?

24 A. No.

25 Q. Now, Gaudreault was a Genentech paper. Did

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1 literature from other researchers inform your opinions as to
2 the issue of size and retinal penetration?

3 A. Yes.

4 Q. And let's look at the Gbate reference. That's
5 PTX 576. Did you review this article?

6 A. Yes, I did.

7 Q. And what did it disclose with respect to retinal
8 penetration?

9 A. Well, here I've just highlighted an excerpt. It
10 says, "The internal limiting membrane" -- that's the membrane
11 to get from the vitreous to the retina, "that membrane is
12 impermeable to" -- and then it talks about linear molecules,
13 which aren't so important for this situation.

14 But what it also talks about are globular molecules
15 greater than 70 kilodaltons. So the larger macromolecules
16 would have a longer retention time, possibly weeks, but their
17 effect on the retina after an intravitreal injection is
18 limited.

19 Q. Did you look at other references as well?

20 By the way, was that pages 8 and 9 of
21 Exhibit PTX 576?

22 A. Yes.

23 Q. Did you look at other references as well?

24 A. Yes.

25 Q. Okay.

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1 And let's put up the Jackson reference. That's
2 PTX 1842.

3 Did you rely on Jackson in connection with your
4 opinions?

5 A. Yes, I did.

6 Q. Okay.

7 And if we can put up page 1 of Jackson in the
8 conclusion.

9 What is it disclosing?

10 A. Well, sort of the beginning of the conclusion here,
11 "In humans, the inner and outer plexiform layers are sites of
12 high resistance to the diffusion of large molecules, resulting
13 in an REL of" -- about 76, 77 kilodaltons -- it says 76.5.

14 And REL is the retina exclusion limit.

15 Q. And did you prepare a demonstrative to help show the
16 relative sizes of aflibercept compared to ranibizumab?

17 A. Yes, I did.

18 Q. Okay. And if we take a look at that, that's
19 Demonstrative 4 on the screen.

20 Can you explain how these compare.

21 A. Yes.

22 And, Your Honor, I'll just focus on the middle and
23 the right one.

24 So this is the aflibercept that we've been talking
25 about. It's about 115 kilodaltons, remembering that the

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1 retinal exclusion limit is in the 70s. It's close enough.
2 Ranibizumab, on the other hand, is 48 kilodaltons, so below
3 that limit.

4 Q. Now, Doctor, as of the priority date, was the
5 efficacy of larger VEGF R1R2 proteins like aflibercept in
6 treating retinal diseases compared by the intravitreal route
7 and the subcutaneous systemic route?

8 A. Yes.

9 Q. Let's take a look at the Saishin article,
10 Exhibit 1785, and at the time at the Ferrara review article,
11 Exhibit 701.

12 Did you review both of these references?

13 A. Yes, I did.

14 Q. Now, Ferrara, is that a review article?

15 A. Yes.

16 Q. And what is a review article?

17 A. Oh, a review article is an article that summarizes
18 what's already in the literature. It typically does not
19 include new results, but it's an analysis of results that are
20 already in the literature.

21 Q. And does it generally reflect the conventional wisdom
22 in the field at the time?

23 A. Yes.

24 Q. Okay.

25 So if we look to -- if we can put up the

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1 demonstrative showing both of those together.

2 On the left-hand side, do we have Figures 1 and 2 of
3 Saishin, PTX 1785?

4 A. Yeah, we do.

5 Q. And on the right-hand side, do we have Ferrara at
6 page 5, also page 862?

7 A. Yes. Yes.

8 Q. And Ferrara is PTX 701.

9 Can you explain first what the left-hand side shows,
10 Saishin, and then what the right-hand side, Ferrara, is saying
11 about it?

12 A. Yes, I can.

13 And, Your Honor, you've seen this perhaps a couple
14 times before.

15 So this is a comparison of the effect of the VEGF
16 Trap. Well, the first one is without the VEGF Trap and the
17 second one is with it. And this is subcutaneous injection; in
18 other words, not intravitreal injection. And I think the
19 analogy was used before this is like golf, not basketball. You
20 want to have as low a score as possible.

21 And that's compared here with the intravitreal
22 administration. And so this is, again, the baseline. You can
23 see a much lower differential here versus subcutaneous.

24 Q. And what was said about this data in the literature?

25 A. Well, so Ferrara, in referencing this -- we can turn

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1 to the screen here -- says, "The limited efficacy occurred in
2 spite of the high binding affinity of the VEGF Trap for VEGF.
3 And it may be due, at least in part, to the existence of a
4 barrier to the transretinal penetration of large molecules such
5 as the VEGF Trap."

6 Q. Does this reflect what the POSA would have thought at
7 the priority date?

8 A. Yes. Exactly.

9 Q. And does Ferrara analyze the Saishin reference and
10 account for the details of its experimental design?

11 A. Yes. Clearly, Ferrara looked at it closely and
12 analyzed it and led to that conclusion, which would be the
13 conclusion of a POSA.

14 Q. Doctor, on the basis of these data, if the POSA
15 wanted to use a VEGF R1R2 Trap like aflibercept to treat
16 retinal diseases, what kind of administration would the POSA
17 have used?

18 A. Well, if it's going to be the VEGF Trap, the POSA
19 would have used subcutaneous or some kind of systemic
20 injection.

21 Q. Would the POSA who made that choice have practiced
22 the claims of the '865 patent?

23 A. No.

24 Q. Does the '865 patent require intravitreal
25 administration?

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1 A. Yes, it does.

2 Q. Now, were there risks and drawbacks associated with
3 intravitreal injection?

4 And we'll bring up on the screen PTX 576 again, the
5 Ghate reference, at page 8.

6 A. Yes. And, again, just highlighted this one sentence
7 from Ghate.

8 "It is also the most invasive and the route with the
9 most serious complications," referring again to intravitreal
10 injection right here in the header.

11 Q. And does it further in the next sentence explain one
12 or more of those complications?

13 A. Yes. In the next sentence it talks about the various
14 complications and the rates varying from 0.15 percent to as
15 high as 0.87 percent.

16 Q. And it talks about endophthalmitis. Do you
17 understand that to be infection inside the eye?

18 A. Yes. I wasn't going to go into the details of that
19 term; but yes, my understanding is an infection. But it's a
20 very serious infection.

21 Q. Now, does Saishin teach anything about the
22 appropriate formulation for aflibercept?

23 A. No.

24 Q. Does Saishin indicate anything with respect to
25 whether the VEGF Trap stays in native conformation in a

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1 formulation?

2 A. No, nothing.

3 Q. Now, if the POSA had decided to treat retinal
4 diseases using an intravitreal injection, on the basis of all
5 of the information you've reviewed, what molecules would the
6 POSA have wanted to use, what kind of molecules?

7 A. Well, the POSA would have wanted to use smaller
8 molecules such as ranibizumab.

9 Q. Was there also a VEGF Trap that fit into that
10 category?

11 A. Yes, there was.

12 Q. If we bring up Demonstrative 6.

13 You've labeled now a third molecule in the
14 demonstrative as Mini-Trap. Can you explain what that is.

15 A. Yes. The Mini-Trap is another molecule that
16 Regeneron was working on.

17 And, Your Honor, you've already seen these two. So
18 this is our favorite molecule here, aflibercept, and this is
19 the ranibizumab.

20 The Mini-Trap is just this top part of aflibercept
21 with a bottom part cut off to make it smaller. So it's about
22 the same size as ranibizumab, maybe even slightly smaller.

23 Q. And did you look at literature relating to the
24 Mini-Trap?

25 A. Yes, I did.

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1 Q. Okay.

2 Let's pull up Exhibit 1757.

3 Do you understand this to be the Daly application?

4 A. Yes. That's correct.

5 Q. And can you explain what Daly is disclosing here on
6 page 11, paragraph 48.

7 A. Yes.

8 At the top it's referring to this Mini-Trap,
9 nonglycosylated and glycosylated. And then it says this
10 Mini-Trap has optimized characteristics for local intravitreal
11 delivery, i.e., shorter serum half-life for faster clearance,
12 and minimizing unwanted systemic exposure.

13 In addition, due to its smaller size, the Mini-Trap
14 has the ability to penetrate through the inner limiting
15 membrane, ILM, in the eye, and diffuse through the vitreous to
16 the retina/retinal pigment epithelial RPE layer, which will
17 help to treat retinal disease.

18 Q. Doctor, on the basis of the prior art as a whole,
19 would the POSA who wanted to use intravitreal injections of a
20 VEGF Trap have wanted to use aflibercept or the Mini-Trap?

21 A. No, the Mini-Trap, the smaller molecule.

22 Q. And was that designed specifically for intravitreal
23 delivery into the eye?

24 A. Yes, it was.

25 Q. Now, we've heard a lot about Avastin during this

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1 trial. Wouldn't that have taught to use a large molecule for
2 intravitreal injection?

3 A. No.

4 Q. Now, Dr. Rabinow addressed the Avery reference.
5 That's DTX 2264. And for now I want you to assume that Avery
6 is prior art.

7 Let's turn to page 368 of Avery. What is the article
8 conveying to the person of ordinary skill?

9 A. Well, it's conveying, as you see in these two
10 excerpts that I've highlighted -- this is in the discussion
11 section -- "We acknowledge the shortcomings of this study:
12 retrospective design, limited number of patients, nonstandard
13 visions, and limited follow-up."

14 And then it further says in the same paragraph a
15 little ways down there, "However, the visual results of this
16 study are difficult to interpret."

17 Q. And did the Ferrara reference you've been discussing,
18 PTX 701, did that address Avery's findings as well?

19 A. Yes, it did.

20 Q. Okay.

21 And if we can pull that up again at page 8.

22 What did Ferrara have to say?

23 A. Well, Ferrara says, "Although intriguing, these early
24 findings are difficult to compare with data from rigorous
25 double-masked controlled Phase III trials."

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1 And then it continues. It's talking about
2 ranibizumab, among others. And then it says, "It is noteworthy
3 that initial uncontrolled Phase I or II studies with pegaptanib
4 or verteporfin photodynamic therapy suggested a considerably
5 greater benefit in AMD patients than that eventually
6 demonstrated in randomized Phase III studies, further
7 emphasizing the difficulty of interpreting early clinical
8 results."

9 Q. So in view of all the references, including Saishin
10 and Avery, what did Dr. Ferrara ultimately suggest and conclude
11 in his 2006 review article?

12 A. Well, Dr. Ferrara concluded, again, what the person
13 of ordinary skill in the art would understand, which is that
14 that person of ordinary skill in the art would be turned to use
15 the smaller molecules like ranibizumab and others.

16 Q. And so the record's clear, that excerpt that you were
17 discussing on page 8 a moment ago from Ferrara, and it had the
18 Footnote 114, was Ferrara discussing the Avery reference there?

19 A. Oh, yes. And you can see that on the right on the
20 slide, the same Avery reference, correct.

21 Q. And that's the Avery reference that Dr. Rabinow
22 discussed last week at trial?

23 A. Yes.

24 Q. Now, I'd like to shift again, Dr. Trout, and discuss
25 the concentration required by the claims.

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1 What is the concentration that all of the asserted
2 claims require?

3 A. Well, of the aflibercept, it's highlighted here,
4 40 mg/mL.

5 Q. And let's go back to the prior art on which
6 Dr. Rabinow relied, Fraser at DTX 729 on the second page.

7 Does Fraser teach 40 mg/mL of VEGF Trap?

8 A. No, not at all. Fraser teaches, as underlined here,
9 24.3 mg/mL.

10 Q. Did you hear Dr. Rabinow's testimony that the POSA
11 would have used the 40 mg/mL concentration from the Lucentis
12 references if we look at Slide 93 of Dr. Rabinow's
13 presentation?

14 A. Yes, I heard him say that.

15 Q. Now, let's look at the Lucentis references. Do you
16 recall that Dr. Rabinow relied on two Lucentis references,
17 Shams and Gaudreault?

18 A. I do recall.

19 Q. Let's take a look at Shams first. That's DTX 726.
20 And we're showing on the screen page 32 of the exhibit.

21 What does Shams teach regarding the concentration of
22 ranibizumab?

23 A. Well, just what's highlighted here regarding that
24 concentration, 6 mg/mL or 10 mg/mL.

25 Q. And just to be clear, is that 40?

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1 A. No.

2 Q. And I think this was discussed last week, but what
3 was the purpose for which Shams was using this ranibizumab?

4 A. Oh, so Shams is disclosing clinical approaches to
5 using ranibizumab, so clinical trials.

6 Q. And let's look at Gaudreault, PTX 1839, and we'll
7 look at page 2.

8 What concentrations does Gaudreault discuss?

9 A. Well, Gaudreault discusses 10 mg/mL and 40 mg/mL.

10 Q. Would Gaudreault have taught the POSA to use 40 mg/mL
11 of aflibercept, Dr. Trout?

12 A. No, sir. On the contrary, Gaudreault teaches away
13 from that. You can see some excerpts here. Actually, if we go
14 back to the previous -- previous one.

15 Thank you.

16 It says that at the 2000 micrograms, that's the
17 40 mg/mL, it causes, at that concentration, moderate to severe
18 inflammation; whereas it is not moderate to severe at the
19 10 mg/mL.

20 Q. And you're reading from pages 2 and 3 of Gaudreault,
21 Exhibit 1839?

22 A. Yes.

23 Q. And how would the person of ordinary skill in the art
24 have interpreted the findings of Gaudreault with respect to the
25 10 mg/mL compared to 40 mg/mL concentrations of ranibizumab?

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1 A. Well, that person again would understand that the 40
2 mg/mL is problematic from an immune response standpoint versus
3 the 10 mg/mL. And this would teach the person away from the
4 40 mg/mL. And I emphasize the bottom two. It basically lasted
5 two to eight days, so seven days.

6 Q. Why do you say that it lasted seven days?

7 A. Well, it says that the inflammation was present at
8 day two. It was a monkey study. The eyes were monitored
9 throughout. So it was present at day two but had completely
10 resolved by day eight.

11 Q. And is that good news or bad news?

12 MR. RAKOCZY: Your Honor?

13 Objection, Your Honor. He obviously has testified
14 about it from the protein formulation perspective. The witness
15 is not an ophthalmologist; so I don't think he's qualified to
16 talk about good or bad from a clinical standpoint here.

17 THE COURT: Understood. Sustained.

18 BY MR. BERL:

19 Q. Doctor, let's take a look -- well, what happened to
20 the 40 mg/mL dose of ranibizumab?

21 A. Well, it wasn't used going forward.

22 Q. Now, I think we had another excerpt that we put on
23 the screen from a moment ago from Gaudreault. Can you explain
24 the relevance of the sentence beginning after administration of
25 500 micrograms per eye?

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1 A. Yes. This is another point from Gaudreault focusing
2 on the 500 micrograms per eye. Again, in the table, you can
3 see that corresponds to 10 mg/mL. And Gaudreault is saying
4 that the retinal exposure was greater than 3,000-fold larger
5 than the retinal exposure to VEGF.

6 So -- and it says suggesting that this ranibizumab
7 dose provides maximum inhibition of VEGF. So the 10 mg/mL
8 dose, according to Gaudreault, provides maximum inhibition. So
9 you don't get more if you go higher anyway.

10 Q. Doctor, are you aware of any use of 40 mg/mL of
11 ranibizumab after Gaudreault?

12 A. No, I'm not.

13 Q. Now, how does the potency of ranibizumab compare to
14 the potency of aflibercept?

15 A. Well, aflibercept has a much higher potency than
16 ranibizumab, 10 to 100 times more. I think I said in my
17 report, 20 times more, so significantly more.

18 Q. Now, if the POSA had relied on ranibizumab as
19 Dr. Rabinow suggests, how would the POSA have applied the
20 teachings of Gaudreault and Shams regarding ranibizumab to the
21 concentration of aflibercept?

22 A. Well, if anything, the POSA would choose a lower
23 concentration. Again, as I said, aflibercept is much more
24 potent than ranibizumab. Even accounting for the difference in
25 the size or the weight, there would be much lower concentration

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1 based on Gaudreault of the aflibercept, much less than the
2 10 mg/mL.

3 Q. Now, let's take a look at Ferrara 2004.

4 Just for the record, this is a different Ferrara
5 article. It's PTX 1838.

6 Did you review this article as well?

7 A. Yes, I did.

8 Q. Okay. And if we look to page 7 of the article, can
9 you explain what Ferrara is disclosing here and how it's
10 relevant to the consideration of an appropriate concentration
11 to use.

12 A. Certainly.

13 So Ferrara -- and, again, different from the Ferrara
14 that we just talked about a little while ago, it's referring to
15 the VEGF Trap again and is basically just relating what I said
16 earlier and what the POSA would know. Because of the fact that
17 this not a natural molecule, it's completely constructed, the
18 junctions between the various structural elements in such
19 multicomponent molecules can generate an immune response,
20 which, again, I think I talked about this last week too, is
21 something that the formulator is very concerned about.

22 Q. What would the relevance of this discussion in
23 Ferrara 2004, Exhibit 1838, have had on the concentration that
24 the POSA would have wanted to use for an intravitreal
25 injection?

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1 A. Well, it would teach the POSA to use a low
2 concentration. Again, it's going to be much lower than the
3 10 mg/mL to try to minimize the risk of such an immune
4 response.

5 Q. Let's take a look at the Wang reference. That's
6 PTX 1556.

7 And we'll blow up part of page 1.

8 What is Wang teaching here, and how does it relate to
9 the protein concentration that the person of ordinary skill
10 would have wanted to use?

11 A. Well, Wang here -- again, this is a review article.
12 It says, "Increasing protein concentration generally increases
13 protein aggregation."

14 Q. And so how would that be relevant to the POSA who's
15 trying to choose a concentration to use for intravitreal
16 injection?

17 A. Well, it would teach the POSA to use as low a
18 concentration as possible, again teach away from these higher
19 concentrations like 40 mg/mL. Again, aggregation can cause
20 serious problems, as the formulator would understand, not only
21 in -- you don't want to inject aggregates as such into the eye,
22 but also the possibility of these immune responses.

23 Q. Okay.

24 And for the record, this is page 9 of PTX 1556, the
25 Wang reference.

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1 Doctor, in view of the -- all of the prior art that
2 you reviewed, what would the POSA have thought in terms of an
3 appropriate concentration of aflibercept for intravitreal
4 injection if the POSA had wanted to use aflibercept for
5 intravitreal injection?

6 A. Well, the POSA would choose a concentration probably
7 lower than that of ranibizumab, so lower than 10 mg/mL.

8 Q. What would the POSA have thought about the idea of
9 using 40 mg/mL?

10 A. Well, the POSA would be taught away from using
11 40 mg/mL. In other words, it wouldn't be a good idea.

12 Q. Now, I'd like to turn to a new topic, which is
13 polysorbate 20.

14 Doctor, if we pull up the claims again, do all of the
15 asserted claims require polysorbate 20?

16 A. Yes, they do.

17 Q. And do you understand Dr. Rabinow in his combination
18 to have relied on Gaudreault and Shams for this limitation?

19 A. Yes.

20 Q. And what do the references -- well, let's first look
21 at Gaudreault.

22 And, again, this is page 2 of Gaudreault. What does
23 Gaudreault teach with respect to its formulation and
24 polysorbate 20?

25 A. Well, Gaudreault teaches, as we have here -- this is

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1 the formulation in the first -- or the top excerpt and the
2 highlighted one -- highlighted sentence for polysorbate, which,
3 again, I think Your Honor noted correctly that Tween 20 is a
4 synonym for polysorbate. It teaches 0.05 percent.

5 THE COURT: I've been right about this for the last
6 couple weeks, Doctor, if you ask all them out there.

7 Oh, come on. That was funnier.

8 MR. BERL: No comment. Too tired to laugh, Your
9 Honor.

10 THE COURT: Limping to the finish line, but I thought
11 that was better than that.

12 THE WITNESS: That was funny from up here.

13 THE COURT: Thank you.

14 BY MR. BERL:

15 Q. Doctor, did Genentech proceed with this formulation
16 that has .05 percent polysorbate?

17 A. No, Genentech did not.

18 Q. Let's take a look at the Shams reference. And,
19 actually, we'll look at Dr. Rabinow's discussion of the Shams
20 reference in regards to this limitation. What does Shams teach
21 with respect to its formulation and polysorbate 20?

22 A. Okay. So this is a cutout or excerpt on the bottom
23 right, again, from Dr. Rabinow from Shams. And you can see
24 highlighted here 0.01 percent polysorbate 20.

25 Q. And what is the concentration, Doctor, required by

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1 Claim 4 of the '865 patent?

2 A. Claim 4 is about 0.03 percent to about 0.1 percent
3 polysorbate 20.

4 Q. And Dr. Rabinow put the .01 percent polysorbate 20
5 from Shams in green and colored also in green the
6 about .03 percent to about .1 percent in Claim 4.

7 Do you agree with his analysis that Shams teaches
8 that concentration required by Claim 4 of polysorbate 20?

9 A. No, because Shams teaches 0.01 percent, which doesn't
10 fall in the range of polysorbate from Claim 4.

11 Q. What concentration did Genentech ultimately use for
12 Lucentis?

13 A. 0.01 percent.

14 Q. Now, let's discuss Fraser, the last reference in this
15 combination. Again, that's DTX 729.

16 Does Fraser say anything about intravitreal
17 administration?

18 A. No.

19 Q. What concentration of Tween 20 or polysorbate 20 does
20 Fraser disclose, looking at page 2 of the reference?

21 A. 0.01 percent.

22 Q. Now, reading --

23 A. I apologize. Sorry to interrupt.

24 0.1 percent -- added an extra zero.

25 0.1 percent, for the record.

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1 Q. My last case in West Virginia was all about something
2 0.001 percent, and everyone throughout the trial kept adding
3 and subtracting zeros throughout the entire time. So the
4 record was a mess. Thank you for correcting yourself.

5 Now, Doctor, reading Dr. Rabinow's combination as a
6 whole, the Lucentis plus Fraser, and assuming the POSA combined
7 those references contrary to your opinion, what concentration
8 of polysorbate would the POSA have preferred to use?

9 A. Well, if one were going to do that, it would be
10 0.01 percent.

11 Q. Why?

12 A. Well, that's what the Shams teaches, and that's what
13 it recommended for the clinical trials. And, in fact, that's
14 what finally Genentech used.

15 Q. And the clinical trial that Shams is discussing, is
16 that a systemically administered drug as in 729, Fraser, or is
17 that an intravitreal trial?

18 A. No. Shams teaches intravitreal clinical trials.

19 Q. And would that have been more relevant to the POSA
20 than formulations like Fraser?

21 A. Yes. Of course.

22 Q. Now, let's turn to the next limitation of the claim,
23 the 98 percent native conformation as measured by
24 size-exclusion chromatography limitation.

25 Do any of Fraser, Gaudreault, or Shams teach the

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1 98 percent native conformation limitation?

2 A. No, they do not.

3 Q. Did Dr. Rabinow present any evidence that any of the
4 formulations in Fraser, Gaudreault, or Shams achieved the
5 98 percent native conformation limitation?

6 A. No, he did not.

7 Q. Now, did either of the Gaudreault formulations go
8 into clinical trials?

9 A. No, they did not.

10 Q. You mentioned before that Shams went into clinical
11 trials. Does that mean that it met the 98 percent native
12 conformation requirement?

13 A. No, it does not.

14 Q. Why not?

15 A. Well, there's no indication -- it might be stable
16 enough for clinical trials, but there's no indication that it
17 met the 98 percent limitation here.

18 Q. Did either Gaudreault or Shams teach that the
19 ranibizumab formulations had 98 percent native conformation?

20 A. No, they did not.

21 Q. Now, even if one somehow believed that the Shams
22 formulation or the Gaudreault formulation had 98 percent native
23 conformation of ranibizumab, would the POSA have expected that
24 the same formulation with aflibercept would have 98 percent
25 native conformation?

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1 A. Based on that of ranibizumab, no.

2 Q. Why not?

3 A. They're different molecules. They're going to behave
4 differently. And as I mentioned, aflibercept is this fusion
5 protein. It's not a natural molecule. So, if anything, if one
6 were -- had that information and were to do the comparison, one
7 would expect it to be less stable.

8 Q. Let's take a look at Wang again. That's Exhibit
9 1556. And we'll look at page 7 of the article.

10 What -- in this Section 2.3.1 in the sentence
11 beginning "mutation of one amino acid," what is Wang teaching
12 here?

13 A. Well, maybe just to read the whole sentence,
14 "Mutation of one amino acid in a peptide or protein can
15 dramatically increase the aggregation propensity."

16 That's just one. If we're talking about completely
17 different molecules, that can make them substantially different
18 in terms of --

19 Q. Was there one amino acid difference between
20 ranibizumab and aflibercept or a lot more than one difference?

21 A. A lot more than one.

22 Q. Now, let's move on to discuss the pH limitation and
23 in particular the pH limitation found in Claim 9 of the '865
24 patent.

25 And that says about 6.2 to 6.3; is that right?

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1 A. Yes. Correct.

2 Q. Does the Fraser plus Lucentis prior art, even if
3 combined, teach using the required pH range of Claim 9?

4 A. No, they do not.

5 Q. Now, if we look at Shams and Gaudreault again now
6 side by side -- Gaudreault, 1839, and Shams, 726 -- what are
7 the pHs used in those formulations that Dr. Rabinow relies on?

8 A. Well, the Gaudreault is in the upper left here. That
9 pH is 5.0. The Shams is kind of the bottom right, and that pH
10 is 5.5.

11 Q. Does that meet the limitation of about 6.2 to 6.3?

12 A. No. Neither do.

13 Q. Now, the third reference here, Fraser, if we -- we
14 looked at that a moment ago. That had a pH of 6.0; is that
15 right?

16 A. Correct.

17 Q. Would the POSA have just used that pH?

18 A. No.

19 Q. Why not?

20 A. Well, because, first of all, the POSA, in
21 investigating a formulation for the '865 patent, would
22 investigate that for aflibercept with intravitreal
23 administration in mind, whereas Fraser doesn't teach
24 intravitreal administration.

25 Q. Did Dr. Rabinow ever identify which precise

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1 formulation in his combination the POSA would have used if
2 combining Fraser, Gaudreault, and Shams?

3 A. No, he did not.

4 Q. If you assume Dr. Rabinow's hypothesis that the POSA
5 would have substituted aflibercept into the ranibizumab
6 formulation, what pH would the POSA have used?

7 A. Well, the ranibizumab is at 5.5. So if one were
8 going to do that, it would be 5.5.

9 Q. What if you performed experimentation to find a
10 different pH, as Dr. Rabinow suggests?

11 A. Well, then, that would be a whole formulation study,
12 a whole investigation.

13 Q. Would you end up with the same formulation, or at
14 that point do you have a different formulation than the one
15 you'd have if you combined the references?

16 A. Well, then, you have likely a different formulation.
17 You're doing a whole research project at that point.

18 Q. Now, let's turn to the turbidity limitation. And we
19 can look at that in Claim 15.

20 Does that require a turbidity of 0.01 or lower at
21 OD405 after two months' storage at 5 degrees?

22 A. Yes. That's correct.

23 Q. Did Dr. Rabinow present any evidence that a
24 40-milligram formulation of aflibercept would achieve the
25 claimed level of turbidity in view of Fraser, Gaudreault, or

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1 Shams?

2 A. No, he did not.

3 Q. Have you seen any such disclosure or teaching in
4 those references?

5 A. No.

6 Q. Can you conclude that the Shams formulation meets the
7 turbidity limitation of Claim 15 on the basis of a disclosure
8 for use in a clinical trial?

9 A. No.

10 Q. Is the turbidity limitation synonymous with stable?

11 A. No.

12 Q. Is the 98 percent native conformation limitation
13 synonymous with stable?

14 A. No.

15 Q. Why do you say no to those questions? Why not?

16 A. Well, because stable doesn't mean it has to be
17 98 percent or meet this particular turbidity requirement. It
18 could be stable and not be at 90 percent and not meet this
19 turbidity requirement.

20 Q. Based on the prior art on which Dr. Rabinow relied
21 for obviousness, even if combined, would the POSA have had any
22 expectation that the formulations Regeneron claimed of the '865
23 patent would meet the turbidity limitations of the claims?

24 A. No.

25 Q. Same question for the 98 percent native conformation,

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1 would the POSA have had any expectation of success?

2 A. Same answer. No.

3 Q. Would the prior art formulations on which Dr. Rabinow
4 relied, even if combined, necessarily and always have the
5 turbidity required by the asserted claims?

6 A. No. There's no reason to think that.

7 Q. And how about for 98 percent native conformation?

8 A. Again, no reason to think that either.

9 Q. Is the claimed protein concentration relevant to
10 turbidity?

11 A. Yes.

12 Q. How so?

13 A. Well, again, generally, the higher concentration
14 leads to a higher aggregation propensity, hence higher
15 insoluble aggregates and hence higher turbidity.

16 Q. Did Dr. Rabinow point to any prior art turbidity data
17 on 40 mg/mL of aflibercept?

18 A. No.

19 Q. Did Dr. Rabinow point to any turbidity data on
20 40 mg/mL of ranibizumab?

21 A. No.

22 Q. In your view, Dr. Trout, are the asserted claims
23 obvious over the combination of Fraser and Lucentis?

24 A. No.

25 Q. Now, we're done with Fraser and Lucentis.

1 MR. BERL: I can keep going, Your Honor. I'm at your
2 pleasure.

3 THE COURT: Let's call it a day. Let's do that.

4 Is that all right with you, Doctor?

5 THE WITNESS: Yes, as long as you give the order that
6 the attorneys can't talk with me.

7 THE COURT: Motion granted.

8 Yes, Doctor, because you remain midstream on your
9 testimony, even though you've come and gone once but you're
10 considered midstream again by our rules, you are prohibited
11 from contact with other humanoids about your testimony here.

12 So you're welcome. You can go ahead and step down,
13 sir. Have a lovely evening in quiet solitude.

14 THE WITNESS: Thank you.

15 Thank you, Your Honor.

16 THE COURT: You're welcome.

17 Everybody okay with starting at 8:30 tomorrow?

18 MR. BERL: Absolutely.

19 THE COURT: Let's do that. And we'll sprint through
20 the tape at that point, as they say.

21 Anything we need to take up from Regeneron's
22 standpoint at this juncture?

23 MR. BERL: Not from Regeneron, Your Honor.

24 THE COURT: Mr. Rakoczy, anything from Mylan?

25 MR. RAKOCZY: Nothing from Mylan.

1 THE COURT: Okay. And we anticipate at this point
2 that Dr. Trout will be the last witness; is that correct?
3 Anybody being called by Mylan on the back end?

4 MR. RAKOCZY: Not as far as we know. He'll be the
5 last one.

6 THE COURT: Okay. Al right. Well, let's do that.
7 We'll see everyone at 8:30 tomorrow morning. And, again, my
8 promise to be prompt with notifications about any change in the
9 lunch run schedule tomorrow. Apologies for any heart
10 palpitations I gave everybody.

11 With that, everybody have a pleasant evening, and
12 we'll see you all tomorrow morning.

13 Thank you very much.

14 (Proceedings concluded at 5:07 p.m.)
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CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 22, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 22nd day of June 2023.

/s/Cindy L. Knecht

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Official reporter, United States
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District of West Virginia