prior art makes the invention obvious is also required, neither of which have been disclosed.

So I'll sustain the objection. Again, we can proceed and leave the unconnected bodies of testimony out there. The Court will not draw that connection. And so I'll just say that now. But objection sustained.

You may proceed, Counsel.

MR. HUNT: Just to be clear, Your Honor, we're free to proceed and discuss the disclosure of the Liu reference and then we can tie it together appropriately in a few minutes, correct?

THE COURT: "Appropriately" being the key word, but otherwise, yes. But, again, I just want to make sure that I'm quite clear. The Court will not take up the invitation to put a bow on something that should have been wrapped and presented in opening disclosures.

MR. HUNT: Understood, Your Honor.

BY MR. HUNT:

Q. If we could please turn to Slide 55. And we're looking on the right-hand side at another disclosure from the Liu reference, Dr. Rabinow.

If you could please describe for the Court what is disclosed at DTX 730, page 35.

A. Liu is describing high-concentration antibody formulations. He is describing a particular formulation that

contains a histidine buffer, a trehalose stabilizer, a polysorbate 20 component, at pH of 6. He discloses that protein concentrations of 40 to 150 mg/mL have been studied and are stable and that formulations also containing trehalose or sucrose stabilizers in a concentration range of 20 to 350 millimolar are also stable as well as a polysorbate concentration range of .01 percent to .1 percent.

In specific, he is directing attention to a table where he is describing an 80 mg/mL antibody formulation comprising histidine and trehalose and showing that, over a period of 24 months, the -- well, at three months and beyond, that -- at 5 degrees, the -- by size-exclusion chromatography, the percent monomer exceeds 98 percent to meet the claim limitation of the '865.

Q. If we could please move to Slide 56.

Dr. Rabinow, on Slide 56 have you set forth the combinations of prior art references that you contend render Claim 1 of the '865 patent obvious?

A. Yes.

Q. And is there intended to be any relation on this slide between the claims on the left and the references on the right?

A. Yes.

Q. Okay. So let's just briefly summarize your opinions.

Could you please summarize your opinion regarding the

obviousness of Claim 1 in view of Lucentis in combination with Fraser?

A. Yes. Claim 1 of the '865 would be obvious in view of Lucentis plus Fraser.

Q. And separately, can you summarize your opinion regarding obviousness of Claim 1 in view of Fraser in combination with Liu?

A. Yes. Claim 1 of the '865 would be obvious in view of Fraser plus Liu.

Q. Now, would the person of ordinary skill in the art have a reasonable expectation of success in combining the disclosures that we've discussed today of the Lucentis prior art -- that is, Shams and Gaudreault -- with the disclosures of Fraser?

A. Yes.

Q. And similarly, would the person of ordinary skill in the art have a reasonable expectation of success when combining the disclosures that we have discussed today of Fraser in combination with Liu?

A. Yes.

Q. Turning to Slide 57, do you have an opinion as to whether the person of ordinary skill in the art would have been motivated to combine her knowledge of Lucentis with Fraser?

A. Yes. It would be provided by Saishin, DTX 2751, page 1, where it is disclosed that VEGF Trap R1R2 is a fusion

protein and, further, that it -- subcutaneous or a single intravitreous injection of Vermont VEGF Trap R1R2 strongly suppressed choroidal neovascularization in mice with laser-induced rupture of Bruch's membrane.

And that, therefore, it is concluded that VEGF Trap R1R2 may provide a new agent for consideration for treatment of patients with choroidal neovascularization and diabetic macular edema. And this is back in 2003.

Q. And this disclosure from Saishin, Dr. Rabinow, is at DTX 2751, page 1?

A. Correct.

Q. And did you rely on DTX 2751, the Saishin reference, for purposes of your analysis?

A. Yes.

Q. If we could please turn to Slide 58.

Is there anything else that supports your opinion regarding the person of ordinary skill in the art's motivation to combine her knowledge of Lucentis with Fraser?

A. Saishin at DTX 2751, page 7, discloses further that VEGF Trap R1R2 deserves consideration as a potential treatment for two complications of diabetic retinopathy: retinal neovascularization and macular edema. It emphasizes again that a single intravitreous injection of VEGF Trap R1R2 markedly suppressed the development of choroidal neovascularization over the course of two weeks. And, concurrently, additional

preclinical studies should explore modes of local delivery to the eye that can be used adjunctively or as an alternative to systemic administration. This is DTX 2751 at page 7.

Q. Thank you, Dr. Rabinow.

Now, we just discussed your opinions regarding the motivation to combine Lucentis with Fraser. Is it also your opinion that Saishin, DTX 2751, provides a motivation to combine Fraser and Liu?

A. It does.

Q. Is there any additional disclosure in Saishin besides what you've already described that is relevant to the motivation to combine Fraser with Liu?

A. Well, it's clear -- I'm sorry. Could you repeat that.

Q. Yeah.

I'm just looking for confirmation that your opinion with regard to motivation to combine Lucentis and Fraser is the same for Fraser and Liu; is that correct?

A. It is. It also provides a reasonable expectation of success to do so as well.

Q. And that's the Saishin reference, correct?

A. That is correct.

Q. Is there anything else about the knowledge of the person of ordinary skill in the art that would provide the person of ordinary skill in the art a reasonable expectation of

success in combining Lucentis and Fraser?

A. There is knowledge that Lucentis at the time that we were discussing had been used in humans. And, therefore, safety studies would have been conducted as well as stability studies.

Q. Thank you, Doctor.

I would like to now discuss your anticipation opinions with regard to the Dix '226 patent. Have you prepared some slides to assist in your presentation of anticipation to the Court?

A. Yes.

Q. Okay.

Mr. Gibson, next slide, please, Slide 60.

Dr. Rabinow, what have you included on this slide to assist in your anticipation analysis?

A. So as before, I list out the individual claim limitations of Claim 1 of the '865. And on the right side is displayed Dix '226, the cover page to page 2.

Q. This one is a little less wieldy because we're only talking about one reference, correct?

A. Yes.

Q. Shall we march through it?

A. Please do.

Q. All right.

If we could turn to Slide 61, please.

How does Dix '226, DTX 13, disclose the initial limitations of Claim 1?

A. Dix discloses a formulation inhibiting vascular endothelial growth factor, VEGF, on page 4. And the -- it states that it is suitable for injection. He discloses a lyophilized formulation is reconstituted with sterile water suitable for injection; so that implies that there is a vial involved, which meets one of the claim limitations of Claim 1. And the POSA would understand as of the date of Dix that ophthalmic formulations as well as cancer formulations were being considered for VEGF medicaments.

Q. Would the person of ordinary skill in the art also understand from the disclosures of Dix that intravitreal administration is a possibility?

A. Yes, certainly, because that was being done already for other VEGF antagonists.

Q. If we could please move to Slide 62.

How does the Dix '226 patent relate to the VEGF antagonist limitations of Claim 1?

A. So Dix discloses a VEGF antagonist fusion protein in a Chinese hamster ovary, or CHO, cell, comprising a polynucleotide of amino acids 27 to 457 of sequence ID Number 4, wherein said fusion protein binds vascular endothelial growth factor.

So this directly discloses the claim limitation of

essentially the essential wording of Claim 1 on the left-hand side of the screen, and it certainly discloses a vascular endothelial growth factor antagonist. And it confirms it on -- so that was -- I read that on DTX 13, page 13. And on page 6 it confirms this by stating that, again, VEGF antagonist is expressed in a CHO cell line. And it comprises, again, amino acids 27 to 457 of sequence ID Number 4 and is glycosylated at asparagine residues 62, 94, 149, 222, and 308. This is at DTX 13, page 6.

Q. If we could turn, please, to Slide 63.

Which Claim 1 elements have you highlighted from Dix '226, DTX 13, on this slide, Doctor?

A. These are formulation claim elements.

Q. And could you please describe the formulation elements that are disclosed in DTX 13 --

A. Yes.

Q. -- as they relate to Claim 1 of the '865 patent?

A. Right.

So it states at DTX 13, page 4, a polysorbate may be present. And this meets the organic cosolvent limitation using Regeneron's infringement contention definition.

It also -- on that same page of Dix, for a buffer he divulges -- discloses 1- to 10-millimolar phosphate buffer, 1- to 10-millimolar citrate buffer. And few lines down, he further discusses a 5-millimolar phosphate buffer and

5-millimolar citrate buffer. And, furthermore, on DTX 13, page 7, he also discloses 10-millimolar phosphate.

And a stabilizing agent as a claim element of Claim 1 is disclosed by 20 percent by sucrose on page 7 of Dix. It's mentioned multiple times on pages 4 and 7, sucrose.

Q. If we could turn to Slide 64.

Dr. Rabinow, how does DTX 13, the Dix '226 patent, relate to the stability elements of Claim 1?

A. So DTX 13 at page 7 displays Table 1, which shows the percent VEGF Trap native conformation values of a 50 mg/mL protein formulation stored at 5 degrees at three months where the value is 98.8 percent, which exceeds the claim limitation of at least 98 percent VEGF in native conformation following storage at 5 degrees for two months as measured by size-exclusion chromatography.

Q. I just want to make sure that I'm clear. The Table 1 in DTX 13, page 7, that you display here, Doctor, indicates that the data is reflecting percent VEGF Trap native configuration.

Do you see that?

A. I do.

Q. Would a person of ordinary skill in the art have an understanding of whether there's a difference between native configuration and native conformation as reflected in Claim 1?

A. They're essentially equivalent.

Q. And does DTX 13, the Dix '226 patent, also disclose that the stability data reflected in Table 1 was measured by a particular analytical method?

A. It was size-exclusion chromatography.

Q. Turning to Slide 65, can you summarize your opinion regarding the Dix '226 reference as it relates to your anticipation analysis of Claim 1 of the '865 patent?

A. Yes. Dix '226 anticipates all of the claim limitations of Claim 1 of the '865 and therefore anticipates Claim 1.

Q. And your testimony, just so that it's clear, is that the Dix '226 patent discloses each and every limitation of Claim 1, correct?

A. That's correct.

Q. Now I'd like to move to your anticipation opinions with regard to the dependent claims.

If we could go to Slide 66, please.

Do you have opinions regarding the dependent claims as it relates to the Dix '226 patent --

A. Yes.

Q. -- DTX 13?

A. Yes. The Dix '226 anticipates Claims 4, 7, 9, 11, and 14 through 17.

Q. Let's go to Slide 67 and first look at Claim 2 of the '865 patent.

What have you highlighted on Slide 67 relating to the concentration limitations of Claim 2 of the '865 patent?

A. Dix --

THE COURT: One second, Doctor.

Yes, Counsel?

MR. TRASK: Your Honor, I object to the passage at the bottom of this slide. It's outside the scope of his expert reports. The 40 mg/mL prelyophilized solution is discussed nowhere in either of the doctor's reports.

THE COURT: Understood.

Counsel?

MR. HUNT: Your Honor, I'd need a minute to take a look through the report, but the Dix '226 patent is very clear from day one that there has been anticipation argument that Dix '226 patent, DTX 13, is prior art for all that it discloses. And there is and can be no argument that plaintiff has not been put on notice of this anticipation theory that the Dix '226 patent anticipates the claims of the '865 patent.

So, with that, Your Honor, if you'll permit me a moment, I'll take a look through the expert report.

THE COURT: Understood. Okay, Counsel.

MR. TRASK: If I may while he's looking.

So to be clear, the top box discloses a range of 10 to 50 mg/mL of fusion protein. That's disclosed in the doctor's report, and we don't object to that.

There's several paragraphs in the report which I can point counsel to -- paragraph 124 of the opening report, paragraph 8 of the reply report -- where that passage is disclosed, the 10 to 50 range. We disagree that's a disclosure of 40, but it's disclosed and they can rely on it. The 40 mg/mL prelyophilized solution is nowhere in the report. Counsel is free to look, of course.

THE COURT: But that's from the Dix reference, correct?

MR. TRASK: It's in the Dix reference, but it was never discussed. And there are sections in the report purporting to state where Dix discloses 40 mg/mL. That passage is discussed nowhere in the report.

THE COURT: Understood.

At this point, objection will be overruled. Counsel of course will be free to probe that particular issue on cross and likewise address it in posttrial submissions.

But for now, objection overruled.

MR. HUNT: Thank you, Your Honor.

BY MR. HUNT:

Q. If we could go to Slide 68, please. How does DTX 13, the Dix '226 patent, disclose the polysorbate limitations of Claims 2, 4, and 5 of the '865 patent, Dr. Rabinow?

A. On page 4 it discloses polysorbate may be present. That addresses that claim element of Claim 2 where it

discloses -- comprises polysorbate. The range in Dix is .05 to .15 percent polysorbate 20, which overlaps the claim limitation of .03 percent to .1 percent polysorbate 20 of Claim 4 as well as the limitation of Claim 5 of .1, .01, to 3 percent polysorbate 20.

So Dix discloses the presence of polysorbate 20 as well as its ranges, which address Claims 2, 4, and 5.

Q. If we could turn to Slide 69.

How does DTX 13, the Dix '226 patent, relate to the buffer limitation of dependent Claim 7?

A. The buffer limitation is 5- to 25-millimolar buffer. Dix discloses 1- to 10-millimolar phosphate buffer, 1- to 10-millimolar citrate; and a few lines down, 5-millimolar phosphate buffer, 5-millimolar citrate buffer on page 4 of DTX 13.

Q. And with respect to the added limitation of Claim 9 of the '865 patent, Dr. Rabinow, on the next slide, what is expressly disclosed in Dix '226, DTX 13?

A. On pages 4 and -- well, on page 4 it discloses pH 6.25, which lies in the interval of the Claim 9 limitation of pH about 6.2 to 6.3. And, furthermore, on page 7 of Dix it discloses pH of about 6 to 6.5, which similarly overlaps the range of 6.2 to 6.3, the claim limitation of Claim 9.

Q. If we could go to DDX 4, Slide 71, what does Dix '226, DTX 13, disclose regarding the additional stabilizing

agent limitations of Claims 10 and 11?

A. On page 4 of Dix, it is stated that the formulation contains sucrose, which addresses the claim element of -- the stabilizing agent comprises a sugar of Claim 10.

Claim 11 goes beyond that and specifies that the sugar is selected from the group consisting of sucrose, et cetera. And sucrose is specifically disclosed on page 4. So that addresses claim -- the Claim 11 limitation as well.

Q. And, Dr. Rabinow, are these the same two passages of Dix that we looked at on the prior slide?

A. Yes.

Q. And I just -- I want to make the record clear. You referred to page -- DTX 13, page 4. And I think that that same page number was reflected here, but on the prior slide the second callout was referred to as DTX 13, page 7. Do you understand that the second callout on this page is also at DTX 13, page 7?

A. Yes.

Q. If we could please move to Slide 72.

Now, Dr. Rabinow, you may have mentioned this earlier in connection with the VEGF antagonist elements of Claim 1, but what does Dix '226, DTX 13, disclose regarding the glycosylation characteristics of Claim 14 of the '865 patent?

A. Dix discloses the fusion protein comprises amino acids 27 to 457 of sequence ID Number 4 and is glycosylated at

asparagine residues at 62, 94, 149, 222, and 308. So it fully discloses the claim element of Claim 14.

Q. And that is at DTX 13, page 6, correct, Doctor?

A. That is correct.

Q. Finally, let's discuss the stability limitations in the dependent claims of the '865 patent. On DDX 4, Slide 73, what have you highlighted here from DTX 13, the Dix '226 patent?

A. Dix discloses in Example 1 on page 7 that turbidity was measured at OD405 and furthermore provides data at three months of a formulation stored at 5 degrees. And the turbidity value is zero, thus meeting the claim limitation of a turbidity of .01 or lower at OD405 after two months storage at 5 degrees.

Q. Now, turning to Slide 74, what does DTX 13, the Dix '226 patent, disclose regarding formulation stability over time?

A. In Table 9 on page 9 is listed the percent native configuration, equivalent as we said before to conformation, at two months' storage of 5 degrees, a value of 99.6 percent, thus meeting the claim limitation of at least 99 percent after two months at 5 degrees.

Q. And, Dr. Rabinow, does Dix tell us what analytical method is used to generate the data reflected in Table 9?

A. Yes. Size-exclusion chromatography.

Q. And Table 9 is at DTX 13, page 9, correct?

A. Yes.

Q. Turning to Slide 75, what does Dix '226, DTX 13, disclose regarding the further stability limitations of Claim 17?

A. Dix on page 7, Table 1, provides a value for percent VEGF Trap native configuration -- equivalent, as we said, to conformation -- at 24 months, 5 degrees storage, of 98.3 percent, which meets therefore the limitation of at least 98 percent of VEGF antagonist following storage at 5 degrees for 24 months as measured by size-exclusion chromatography. The same technique was used in Dix.

Q. Now, looking at Table 1 of the Dix '226 patent at DTX 13, page 7, there's a reference here to VEGF Trap.

Do you see that?

A. Yes.

Q. And would the person of ordinary skill in the art understand, or does the Dix '226 patent tell them, that VEGF Trap is in fact a VEGF antagonist fusion protein?

A. Yes.

Q. Dr. Rabinow, if we look at DDX 4, Slide 75, is it your opinion that Dix '226, DTX 13, discloses each and every limitation of the asserted claims of the '865 patent?

A. They are. It is.

Q. And, therefore, is it your opinion that the Dix '225 [sic] patent, DTX 13, anticipates the asserted claims of the

'865 patent?

A. That is correct. I agree with that.

Q. Dr. Rabinow, I'd like to now return to your obviousness analysis and specifically focus on the asserted dependent claims.

Could we please display Slide 77, Mr. Gibson.

Now, Dr. Rabinow, have you prepared a summary chart to assist you in comparing the prior art disclosures, and specifically your asserted combination of Lucentis and Fraser, and separately Fraser and Liu, to Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent?

A. Yes.

Q. Is it your opinion that Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent would have been obvious to one of ordinary skill in the art after consideration of Fraser in combination with Liu?

A. Yes.

Q. Is it also your opinion that Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent would have been obvious to one of ordinary skill in the art after consideration of the Lucentis disclosures in Shams and Gaudreault in combination with Fraser?

A. Yes.

Q. With that in mind, Doctor, I would like to proceed to discuss some of the disclosures in the prior art. And then

after that discussion, we can further revisit your obviousness combinations. Okay?

A. Fine.

Q. Turning to the next slide, Slide 78, how does Fraser, DTX 729, apply to the dependent claims of the '865 patent?

A. Fraser discloses 2-mL aliquots that were used to dose the monkeys in his study. And it is clear that, individually, solutions had to be withdrawn from 2 mL because, in certain cases, multiple vials were drawn. So that addresses the claim limitation of the vial of Claim 1 in Claim 2.

Furthermore, Fraser discloses VEGF Trap R1R2 as provided by Regeneron Pharmaceuticals, Inc., Tarrytown, New York, which addresses the claim element of Claim 2, said VEGF antagonist fusion protein.

40 mg/mL is the claim element. Fraser has 24.3 mg/mL, which, by routine experimentation in light of what the prior art was that is known by the POSA, could have been so optimized. Fraser also discloses a buffer -- I'm sorry. Let me back up.

The final claim element of Claim 2 is polysorbate, which is addressed in -- on page 2 of Fraser by the term "Tween 20." So that addresses fully Claim 2.

The disclosure of .1 percent weight-per-volume Tween 20 similarly addresses Claims 4 and Claims 5 because the .1 percent weight per volume clearly addresses Claim 4 as

well as Claim 5. It's in the interval denoted by the extremes of values. So that addresses Claims 4 and 5.

The claim element of 5- to 25-millimolar buffer of Claim 7 is disclosed by Fraser's use of the term "5-millimolar phosphate, 5-millimolar citrate." So that addresses Claim 7.

Claim 9 has a limitation of pH about 6.2 to 6.3. And Fraser discloses pH 6.0, which is about 6.2 to 6.3.

Claim 10 has a limitation of comprising a sugar, and the term "20 percent sucrose" is expressly disclosed in Fraser. So that addresses Claim 10 as well as Claim 11, which specifies the group consisting of sucrose, et cetera.

Finally, Claim 14, the claim limitation of said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residue 62, 94, 149, 222, and 308 of sequence ID Number 4 is addressed by the term that Fraser uses, "VEGF Trap R1R2 (Regeneron Pharmaceuticals)," which a POSA would know by that point referred unambiguously to a protein molecule fusion protein glycosylation pattern, amino acid sequence of that descriptor in the claim limitations of Claim 14.

Q. Thank you, Dr. Rabinow.

And if I may, especially when you're reading from a technical document, if you could please make a point to try and talk just a bit slower for the court reporter's benefit. I think everyone would appreciate it.

A. I apologize.

Q. Thank you.

Now, I want to revisit your discussion of the 24.3 mg/mL concentration that's disclosed in the Fraser reference DTX 729, page 2, that we've been discussing.

How does the 24.3 mg/mL dose in Fraser compare to the 40 mg/mL limitation in Claim 2 in light of what is disclosed in Fraser?

A. Fraser discloses a 24.3 mg/mL formulation. He uses that to dose monkeys of various sizes, and he has various doses that are given to each monkey.

The smallest dose that was administered is .1 milliliters. That was administered to his animals.

.1 mL times 24.3 mg/mL would give a dose of 2.43 milligrams to the monkeys, which is the -- conservatively the lowest dose of the series. Okay?

The POSA would know as well, for intravitreal administration for humans, that values of .05 milliliters were administered from both bevacizumab as well as ranibizumab.

So 2.43 milligrams divided by .05 mL, or say -- just because we want to be generous here, .06 mL, because we're expecting some wastage, would give you a value of 40 mg/mL.

Q. And when you indicated a moment ago, Dr. Rabinow, that I believe the person of ordinary skill in the art would want to be generous, that's with regard to the injection

volume; is that right?

A. That's correct.

Q. And why is it your testimony that the person of ordinary skill in the art might consider adding a small volume to the injection liquid?

A. There would be hang-up perhaps in the syringe.

Q. What do you mean by hang-up?

A. When you inject a volume from a syringe into the eye or anywhere else, there is residual that is left in the needle and the bore of the syringe.

Q. So looking at the disclosures of DTX 729, the Fraser reference, it's your opinion that the 24.3 mg/mL dose that is described there could actually, if used for intravitreal administration in humans, end up somewhere between 40 and 50 mg/mL?

A. Correct.

Q. Now, Dr. Rabinow, I'd like to next briefly revisit the Dix '226 patent. If we go to Slide 79.

Is it your opinion that Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent would also have been obvious to one of ordinary skill in the art after consideration of the Dix '226 patent, either alone or in combination with Liu -- I'm sorry. I apologize. Strike that. Strike that on this paper here, Your Honor. Many apologies. Let me start over.

Dr. Rabinow, next I'd like to briefly revisit the

Dix '226 patent, DTX 13. Is it your opinion that Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent would have been obvious to one of ordinary skill in the art after consideration of the disclosures of the Dix '226 patent alone in view of the knowledge of the person of ordinary skill in the art?

A. Yes.

Q. Is it for the same reasons that we discussed a few minutes ago with respect to the anticipation analysis of DTX 13, the Dix '226 patent?

A. Yes.

Q. I'd like to briefly walk through these again. If we could turn to the next slide, Slide 80.

I believe you've testified already that DTX 13, pages 4 and pages 5, explicitly or inherently disclose certain limitations of Claims 2, 4, 5, 7, 9, 10, and 11. Is that right?

A. Yes.

Q. And those relevant disclosures are at DTX 13, page 4, and DTX 13, page 5; is that correct?

A. Yes.

Q. Turning to the next slide.

THE COURT: Yes, Counsel.

MR. TRASK: Your Honor, I just wanted to note for the record Regeneron, of course, is advancing the position that the Dix '226 patent is not properly prior art under the 103(c) safe

harbor. Just for purposes of preservation, I wanted to note that we're maintaining that objection during this part of the testimony.

THE COURT: No. Understood.

You may proceed, Counsel.

MR. HUNT: Thank you, Your Honor.

BY MR. HUNT:

Q. Now, could we please pull up Slide 85.

Dr. Rabinow, could you please briefly summarize your opinion regarding the stabilizing agent limitations of Claims 10 and 11 of the Dix '226 patent, DTX 13.

A. Dixon on page 7 calls out sucrose. That's disclosed, and that meets the claim limitation of a sugar in Claim 10, and also in Claim 11 the limitation, the group consisting of sucrose, et al. So that addresses the claim limitations of 10 and 11.

Q. If we could turn to Slide 86.

I believe it's your testimony, Doctor, that the Dix '226 patent discloses the VEGF antagonist fusion protein element of Claim 14.

Could you confirm your opinion as to where that is disclosed in the Dix '226 patent, DTX 13?

A. That is disclosed on page 6.

Q. If we could next turn to Slide 86.

To briefly recap, what does Dix 226, DTX 13, disclose

regarding the stability elements of Claims 16 and 17?

A. On page 9 Dix discloses the percent native configuration at two months and by size-exclusion chromatography. That value is 99.6 percent, which meets the Claim 16 claim limitation of at least 99 percent is present in native conformation after two months at 5 degrees as measured by size-exclusion chromatography.

Dix also indicates that after 24 months at 5 degrees, there is a value of 99.3 percent native configuration. And that meets the Claim 17 limitation of at least 98 percent of said VEGF antagonist fusion protein is present in native conformation following storage at 5 degrees for 24 months as measured by size-exclusion chromatography.

Q. And if we could -- I think we need to revisit Claim 15, which oddly is on the next slide. So if we go to the next slide.

Could you please briefly describe the disclosures of Dix '226, DTX 13, with regard to the turbidity limitations of Claim 15.

A. Dixon page 7 discloses a value of zero for the three-month, 5-degree OD405 turbidity measurement, which meets the Claim 15 claim limitation of a turbidity of .01 or lower at OD405 after two months storage at 5 degrees.

Q. And if we could turn quickly to Slide 90, just to confirm -- and, again, this is only with respect to the

Dix '226 patent -- what is your opinion as to whether the Dix '226 patent discloses all of the elements of the dependent claims of the '865 patent?

A. The dependent claims are all disclosed by Dix and, therefore, are obvious.

Q. All right. Now, I'd like to turn to your opinions regarding the prior art disclosures of Lucentis.

Which two references do you rely on, Dr. Rabinow, for prior art disclosures relevant to Lucentis?

A. Shams and Gaudreault.

Q. Turning to Slide 92, please, can you explain what disclosure from Shams is shown on this slide?

A. Shams discloses a vial, which is a claim limitation of Claim 2, and --

Q. That is at DTX-- sorry. Go ahead.

A. That is at DTX 726 at page 32.

He discloses a ranibizumab, which is a known VEGF antagonist fusion protein. And he discloses polysorbate 20 as well. And while the concentration of ranibizumab is 10 mg/mL, Gaudreault discloses 40 mg/mL. So that addresses all of the claim elements of Claim 2.

Q. All right. And I want to go to Slide 93 quickly.

And this -- Dr. Rabinow, you testified a moment ago that the Gaudreault reference assisted with the 40 mg/mL concentration; is that correct?

A. That's correct.

Q. And this relevant disclosure, in your view, is at DTX 2265, page 2; is that right?

A. Correct.

Q. All right. And if we could turn to Slide 94, please.

This is the polysorbate limitation you discussed a moment ago, right?

A. Yes.

Q. And that's at DTX 726, page 32?

A. Correct.

Q. Now, turning to Slide 95, does the Lucentis prior art disclose anything about buffer amounts in the formulation?

A. Yes. Shams, on page 32, discloses a histidine buffer, 10 millimolar. So that meets the claim limitation of 5- to 25-millimolar buffer of Claim 7.

Q. And turning to Slide 96, Doctor, can you explain what the person of ordinary skill in the art would know regarding Lucentis and the stabilizing agent element of Claims 10 and 11?

A. Right. Shams discloses on page 32 trehalose, which is a sugar. So that meets the claim limitation of Claim 10 as well as Claim 11, which specifies that such sugar is selected from the group consisting of, among other things, trehalose.

Q. And now, Dr. Rabinow, I'd like to ask you about the stability elements of Claims 15, 16, and 17.

Is it your opinion that the person of ordinary skill

in the art as of June 16, 2006, would have understood the formulation disclosed in Shams or Gaudreault was stable?

A. Yes.

Q. Finally, turning to the next slide, Slide 97, Dr. Rabinow, please summarize your opinion with respect to the Lucentis prior art disclosures and the asserted claims of the '865 patent.

A. All of the asserted dependent claims are obvious.

Q. Now, I'd like to turn next to your opinions regarding the disclosures of Liu, Dr. Rabinow.

Could I please have Slide 99 on the screen, Mr. Gibson.

Dr. Rabinow, what do you show on Slide 99 with regard to the disclosure of Liu, DTX 730?

A. Liu discloses on page 9 an antibody with a specified concentration -- a disclosed concentration range of 40 to 150 mg/mL, which meets the claim limitation of 2, VEGF antagonist fusion protein is 40 mg/mL.

THE COURT: Yes, counsel.

MR. TRASK: Your Honor, I'd just like to restate our objection and renew our objection that Your Honor sustained several moments ago.

Here, of course, we have the application of Liu to Claim 2, which expressly refers to the vial of Claim 1. And we saw earlier in Claim 1 that Lucentis was being applied for a

particular limitation to check the box. So in Regeneron's view, this is an improper combination, not disclosed in the doctor's report.

THE COURT: Understood.

Any response to that, Counsel?

MR. HUNT: I believe, Your Honor, again, we're walking through the disclosures of the prior art. Dr. Rabinow has offered opinions as to why Claim 1 of the '865 patent is invalid as obvious over the combination of Fraser and Liu and, separately, Fraser and Lucentis.

The disclosure that Dr. Rabinow is discussing now, I believe Your Honor will find out in a few minutes when he summarizes his obviousness combinations, that the disclosure of Liu for Claim 2 is intended solely for discussion of the combination of Fraser and Liu. It will not be combined with Lucentis.

THE COURT: Understood.

Same ruling applies. And I'll reiterate the Court will not accept any invitation to tie the two together for the reasons already articulated. But objection sustained, for lack of a better term, I guess.

But you may proceed, Counsel.

MR. HUNT: Thank you, Your Honor.

BY MR. HUNT:

Q. Now, if we could turn next to Slide 100.

Dr. Rabinow, what from DTX 730, the Liu reference, is relevant to the elements of Claims 2, 4, and 5 concerning polysorbate 20?

A. Polysorbate is disclosed on DTX 730, page 9. That meets the claim limitation comprises polysorbate of Claim 2. The polysorbate range of .01 percent to .1 percent is disclosed also on page 9 of Liu, and that meets the claim limitation of Claim 4 of .03 to about .1 percent polysorbate 20.

And the same range disclosed by Liu of polysorbate .01 percent to .1 percent also meets the claim limitation of Claim 5 of .01 percent to 3 percent polysorbate 20.

Q. And on the next slide, 101, Dr. Rabinow, what does DTX 730, the Liu reference, disclose concerning formulation buffer concentration?

A. Liu on page 9 discloses a 10- to 100-millimolar histidine buffer, which meet claim limitation range of 5- to 25-millimolar buffer of Claim 7.

Q. And on Slide 102, Dr. Rabinow, what would the person of ordinary skill in the art know from the disclosure of DTX 730, the Liu reference, as it relates to the stabilizing agent elements of Claims 10 and 11?

A. Page 9 specifies a sugar, for example, trehalose or sucrose. And that expressly meets the claim limitation of Claim 10, sugar, as well as Claim 11, the group consisting of

sucrose, sorbitol, glycerol, trehalose of Claim 11.

Q. And finally, on Slide 103, Dr. Rabinow, what does DTX 730, the Liu reference, contain that is relevant to the stability elements of Claims 15 through 17 of the '865 patent?

A. On page 9 Liu lists the stability of a formulation, an 80 mg/mL formulation, comprising histidine and trehalose, listing out, first of all, turbidity values and using Dr. Trout's proposed deduction of what the -- the change in the value of turbidity is, subtracting the initial value from the subsequent values at different time points.

So here we would be subtracting turbidity values at time zero, storage at 5 degrees, the turbidity value of 0.20; and that subtracted from the three-month value would leave a value of zero turbidity, which would meet the claim limitation of turbidity of .01 or lower at OD405 after two months' storage at 5 degrees for Claim 15.

Q. And is it also your opinion, Dr. Rabinow, that DTX 730 of the Liu reference discloses the stability elements of Claims 16 and 17?

A. Yes.

Q. And where is that disclosure found?

A. That is also on DTX 730, page 35, of Liu in the table showing stability data for the 80 mg/mL antibody formulation. And he indicates a value of 96.8 percent size-exclusion chromatography percent monomer, which therefore would meet

the -- I'm sorry.

He -- okay. He shows a value of 99.1 percent size-exclusion chromatography percent monomer at six months and 99.0 percent after 14 months, which meets the claim limitation of at least 99 percent of said VEGF antagonist fusion protein is present in native conformation after two months storage at 5 degrees as measured by size-exclusion chromatography.

Q. And, Dr. Rabinow, just so that I'm sure the record is clear, it's your opinion that the after two-month storage at 5 degrees C limitation in Claim 16 of the '865 patent refers to any time point after two months, correct?

A. Correct. Furthermore, a value is provided of SEC data at 24 months' storage at 5 degrees, and that value is 98.8 percent. That meets the claim limitation of at least 98 percent of said VEGF antagonist fusion protein present in native conformation following storage at 5 degrees for 24 months as measured by size-exclusion chromatography for Claim 17.

Q. If we could turn to Slide 106, please.

Dr. Rabinow, is it your opinion that the dependent claims of the '865 patent are obvious in view of the combination of Fraser and Lucentis as understood in connection with the knowledge of the person of ordinary skill in the art?

A. Yes.

Q. And, separately, is it your opinion that the prior

art disclosures of Fraser in combination with Liu render the dependent claims of the '865 patent obvious?

A. Yes.

Q. If we could turn to Slide 107, please.

Would the person of ordinary skill in the art have been motivated to combine Fraser and Liu, or separately Fraser and Lucentis, to make an ophthalmic formulation suitable for intravitreal administration?

A. Yes. Saishin -- we covered this before, but Saishin at DTX 2751 at page 1 states -- discloses, "VEGF Trap R1R2 strongly suppressed choroidal neovascularization" and further down that page, "may provide a new agent for consideration for treatment of patients with choroidal neovascularization and diabetic macular edema."

Q. And so it's your testimony, Doctor, that the person of ordinary skill in the art would be motivated to combine Fraser and Liu on the basis of the disclosure of the Saishin reference, DTX 2751?

A. That is correct. And, furthermore, would have a reasonable expectation of success in doing so.

Q. And, separately, it's your opinion that the person of ordinary skill in the art would have been motivated to combine Fraser and Lucentis to make an ophthalmic formulation suitable for intravitreal administration on the basis of the disclosures of Saishin?

A. That is correct, for the same reasons.

Q. And just in case I didn't cover it before, did you rely on Saishin, DTX 2751, in support of your opinions?

A. Yes.

Q. If we can go to the next slide, please.

What specifically in Saishin is it, your opinion, provides the person of ordinary skill in the art with a motivation to combine Fraser and Liu or, separately, Fraser and Lucentis?

A. Saishin at DTX 2751, page 7, discloses, "VEGF Trap R1R2 deserves consideration as a potential treatment for two complications of diabetic retinopathy, retinal neovascularization and macular edema. A single intravitreous injection of VEGF Trap R1R2 markedly suppressed the development of choroidal neovascularization over the course two of weeks. Concurrently, additional preclinical studies should explore modes of local delivery to the eye that can be used adjunctively or as an alternative to systemic administration."

Q. And so just to summarize, Dr. Rabinow, what is your opinion with regard to the combination of the -- strike that. Let me start over.

Dr. Rabinow, what is your opinion with regard to the combination of the disclosures of Fraser and Liu with respect to the obviousness of the dependent claims of the '865 patent?

A. The dependent claims would be obvious.

Q. And, again, just to confirm separately, what is your opinion as to the disclosures of Fraser combined with Lucentis as it relates to the dependent claims of the '865 patent?

A. The dependent claims would be obvious.

Q. Thank you.

MR. HUNT: Your Honor, I have just a little bit left. This is a breaking point. I thought I'd give you the option. I can continue for -- I don't know -- maybe 15 minutes or --

THE COURT: Why don't we go ahead and take a break at this point if it's going to be that long before you transition or wrap on direct. So we'll go ahead and take our lunch break at this point.

Doctor, I've got good news for you. You get to have a quiet, secluded lunch.

THE WITNESS: Thank you, Your Honor.

THE COURT: And consistent with this Court's prior orders, they're ordered to feed you, but they can't talk to you. But during the lunch break, you're on your own, of course, because you're midstream. Nobody can converse with you about your testimony so far or the remainder of it.

But you can step down, sir. You can leave all your materials there. Have a great lunch.

Why do not we take 30 for lunch. Let's resume at 1:00 and pick up with the doctor's direct examination at that point. Thank you all very much.

(A recess was taken from 12:33 p.m. to 1:15 p.m.)

THE COURT: Counsel, are you ready to resume?

MR. HUNT: I am, Your Honor.

THE COURT: The floor is yours.

MR. HUNT: Thank you, Your Honor.

BY MR. HUNT:

Q. Dr. Rabinow, if you'll bear with me for a few minutes. As tends to happen when you give a lawyer time to think, I need to circle back on a few things. Okay?

If I could please bring up Slide 61.

Now, Dr. Rabinow, you testified earlier today regarding certain disclosures of the Dix '226 patent, correct?

A. Yes.

Q. And on the bottom of your Slide 61 is reflected DTX 13, page 5. And I believe it was your testimony that page 5 of DTX 13 discloses that the formulations are suitable for injection; is that right?

A. Yes.

Q. Is it your opinion that the Dix '226 patent inherently discloses the intravitreal administration -- I'm sorry -- the ophthalmic formulation suitable for intravitreal administration element of Claim 1?

A. Yes.

Q. If we could turn now to Slide 80, please.

And, again, I want to be clear. First, Dr. Rabinow, I'm asking only about the disclosure of DTX 13 on page 4 at the top of the slide. And I just wanted to make sure that the record is clear.

What does DTX 13, page 4, disclose regarding the concentration of the fusion protein described there?

A. From Dix?

Q. That's correct. Dix '226, DTX 13, page 4. What is the concentration disclosed on page 4 of the fusion protein?

A. 25 mg/mL.

Q. I'm sorry, sir. I'm asking you about the yellow highlight on DTX --

A. Oh, I'm sorry.

10 to 50 mg/mL.

Q. Okay. So the Dix '226 patent, DTX 13 at page 4, discloses a range of 10 to 50 mg/mL of the fusion protein; is that right?

A. Yes, that is correct.

Q. Thank you.

Now, Dr. Rabinow, do you recall earlier today we discussed the Andya reference, DTX 3492?

A. Yes.

Q. And you also testified that it's your opinion that the person of ordinary skill in the art has a reasonable expectation of success in combining Fraser and Liu; is that

right?

A. Yes.

Q. What, if anything, about DTX 3492, the Andya reference, would give the person of ordinary skill in the art a reasonable expectation of success in combining the disclosures of Fraser and Liu?

A. If I -- all right. So there were two Andya references. One dealt with a road map for formulating proteins; another one dealt with stability, I believe, of a high-concentration protein. Which Andya reference are you referring to?

Q. Yes. Doctor, I'm sorry that I was not clear. I'm deferring to DTX 3492 which is Andya 1.

A. Okay. So I believe that that refers to the road map for how you would formulate; is that right?

MR. HUNT: Mr. Gibson, could we please get Slide 13 up on the screen.

BY MR. HUNT:

Q. Is this DTX 3492 the Andya 1 reference?

A. Yes. I'm sorry. Yes, correct, it is.

Q. And so just to quickly revisit my question, what, if anything, about DTX 3492 would provide the person of ordinary skill in the art a reasonable expectation of success in combining the disclosures of Fraser and Liu?

A. There is an indication here that one can achieve

long-term stability for 12 months at 5 degrees in terms of there being no change in the percent intact protein for antibody formulations that contain -- that are formulated with trehalose and Tween 20.

Q. And is it likewise your opinion that the disclosures of DTX 3492, the Andya reference, would provide the person of ordinary skill in the art a reasonable expectation of success in combining the disclosures of the Lucentis references and Fraser?

A. Yes.

Q. Is it for the same reason as the other combination, Fraser and Liu?

A. Yes.

Q. All right.

If we could now go to -- apologies -- Slide 111, Mr. Gibson.

Dr. Rabinow, I would like to discuss certain objective evidence of nonobviousness. Do you understand that Dr. Trout has offered certain opinions in this case that there exists objective evidence of nonobviousness of the asserted claims of the '865 patent?

A. Yes.

Q. And have you formed an opinion in response to Dr. Trout?

A. Yes.

Q. And generally speaking, what is that opinion?

A. That it's a red herring, that it was already known at the time that Dr. Ferrara published this document that there was successful use of bevacizumab intravitreally so it would obviate any theoretical issue concerning the ability or nonability of large molecules like VEGF Trap to penetrate the retina.

Q. Okay. Let's go to Slide 112. And we're looking at PTX 701. Is that the Ferrara reference you were speaking of a moment ago?

A. Yes.

Q. And do you understand Dr. Trout to rely on the Ferrara reference, PTX 701, in support of his opinion on purported industry skepticism?

A. Yes.

Q. Do you agree with Dr. Trout's opinion that there would be skepticism in the industry?

A. No.

Q. Why not?

A. For a number of reasons.

Well, for one thing, Dr. Ferrara was employed by Genentech. So as an employee of Genentech, one would naturally expect that his opinions might be tainted in favor of supporting the competitive advantage of the molecules advanced by Genentech versus those of Regeneron.

Q. Let's take a quick look at PTX 701 on the next slide. Is this the portion of PTX 701 that Dr. Trout relies upon?

A. Yes.

Q. And, Dr. Rabinow, were you present for Dr. Trout's testimony earlier this week?

A. I was.

Q. Do you recall Dr. Trout's testimony wherein he compared the size of aflibercept, ranibizumab, and aspirin?

A. Yes.

Q. Do you agree with Dr. Trout and Ferrara 2006 that VEGF Trap R1R2 would have been too large to penetrate the retina?

A. No.

Q. Why not?

A. Because it had already been demonstrated prior to that in 2005 that bevacizumab, which was an even larger antibody at, I believe, 149 kilodaltons compared to the 113 kilodaltons for VEGF Trap R1R2, that bevacizumab had been employed successfully in mid-2005 intravitreal injections and had demonstrated a remarkable improvement ophthalmologically of patients who were afflicted with overzealous vascular endothelial growth factor.

Q. Now, in your opinion, would the person of ordinary skill in the art be discouraged from developing a stable

protein formulation comprising VEGF Trap R1R2 based on its size?

A. Hardly. In fact, he would be incentivized to do so.

Q. Let's take a look a little bit closer at the Ferrara paper on the screen.

In the -- on page 4 how would the industry have viewed the Ferrara 2006 review paper and specifically the disclosure that you've called out here?

A. They would have looked at the data. They would have compared the data with the dosing pattern for the two branches of the animals, which, in this case, involved a systemic administration as well as an intravitreal administration.

And it appears that there were five separate systemic administrations of VEGF Trap and there was one intravitreal administration. The five systemic inoculations inhibited neovascularization by 75 percent, which is large -- a large effect.

The one intravitreal administration of the same agent resulted in a 25 percent inhibition, which, on the surface, is, in absolute terms, a smaller number than a 75 percent inhibition, but that must be taken into consideration with the number of doses that were administered. So one might argue that, on a relative basis, the intravitreal administration demonstrated higher efficacy than the systemic.

Q. Thank you, Dr. Rabinow. I want to break that down

just a little bit.

Looking at PTX 701, page 4, the 25 percent limit -- inhibition mention that you have covered, is there a citation after that?

A. Yes.

Q. And I apologize.

A. I'm sorry. Yes. A citation to Footnote 80 to Saishin.

Q. And just after that Footnote 80 -- we'll get to that in just a minute -- the Ferrara reference suggests that there's limited efficacy. Do you see that?

A. Yes.

Q. Do you agree that the -- that there was limited efficacy of VEGF Trap R1R2 at this time frame?

A. No.

Q. So let's go to Slide 114 and take a closer look at the Saishin reference.

Apologize. If we could go ahead one more.

So have you prepared a demonstrative, Dr. Rabinow, to help compare the disclosure of Saishin with the disclosure of Ferrara?

A. I have.

Q. And on the slide, do we have the disclosure of Ferrara, PTX 701 at page 4, with the language called out to the right of it?

A. Right.

Q. Okay. And now you've added DTX 2751 at page 4. Is that the Saishin reference?

A. It is.

Q. Taking a closer look at Saishin, what is disclosed here at DTX 2751, page 4?

A. There is a plot of the choroidal neovascularization area that was measured following administration of five doses -- of subcutaneous doses of VEGF Trap R1R2 in comparison with a FC control. And there is a 75 percent reduction in the -- in the area of -- from the subcutaneous administration following five subcutaneous doses.

Q. Where do you find your support for there being five subcutaneous doses?

A. Well, it states in the yellow there "Prior to laser" -- a laser was used to cause rupture of Bruch's membrane, which is an anatomical feature of the eye.

"Prior to laser and on days" -- so that's prior; so that's day zero. And on days two, five, eight, and eleven. So that's a total of five dose administrations.

Q. And that's set forth on DTX 2751, page 4, correct?

A. Yes.

Q. Okay.

If we could advance the slides to 116, please. Oh, apologies. You can stay right there.

Now, on the right-hand side you have included DTX 2751, the Saishin reference on page 5. What is shown here?

A. So what is shown here is the result of the reduction of choroidal neovascularization in comparison with an FC control from a single intravitreous injection of VEGF Trap R1R2. There is something like a 25 percent reduction. And the statistical significance is at the same level of confidence, .0001, as that of the subcutaneous doses.

Q. So looking at DTX 2751, page 5, how many doses of intravenous VEGF Trap R1R2 were administered?

A. One.

Q. And how do you interpret the results of the graph at DTX 2751, page 5?

A. It was pretty darn effective because a single intravitreous dose suppressed choroidal neovascularization.

Q. I apologize.

I apparently may have said "intravenous" instead of "intravitreous," sir. So if you'll permit me, I'd like to restate my question.

DTX 2751, page 5, what is disclosed on that page regarding the single intravitreous injection of VEGF Trap R1R2 and its related response?

A. There was a statistically significant decrease in choroidal neovascularization of perhaps 25 percent, and that was at a very high degree of statistical confidence of P value

less than .0001, which means it was as statistically significant as the figure shown for subcutaneous administration on page 4.

Q. And if we could go to the next slide.

Have you prepared a demonstrative to show what Saishin actually disclosed?

A. Yes.

Q. If the dose frequency from Saishin, DTX 2751, pages 4 through 5, is properly reflected in Ferrara, what would the person of skill in the art understand about the number of doses of intravitreal injection?

A. That the single intravitreous injection was able to exert a, relatively speaking, much larger effect than the subcutaneous dosing because only a single intravitreous injection resulted in a 25 percent decrease, whereas it took five subcutaneous injections to achieve a 75 percent reduction.

Q. Now, Dr. Rabinow, do you agree with Dr. Trout's opinion regarding skepticism?

A. No.

Q. If we could turn to Slide 119, please.

Dr. Rabinow, do you understand that Dr. Trout has argued that the person of skill in the art would find unexpected safety and efficacy through the use of Eylea?

A. No.

Q. And why do you disagree?

A. Eylea was intentionally designed to be a superior molecule from both a safety perspective largely because its affinity for VEGF was so great. So it had -- Eylea had a 20-fold greater affinity for VEGF than did ranibizumab.

What that means is that it binds it so tightly that it prevents attachment of Eylea to the extracellular matrix around the eye; that is to say, it would result in less toxicity.

This is pointed out by Holash as early as -- I'm not sure -- 2003, I think, where he says that the development of Eylea was designed to have very high affinity so that two things were achieved. Not only did it bind extraordinarily tightly to the target VEGF, but it prevented off-target binding to anatomy -- anatomical parts of the eye that it was not intended to bind to.

And as a result of that, it would not mediate toxicity to the same level as ranibizumab. So that's the affinity/toxicity analysis.

Additionally to that, Eylea was designed intentionally to be large. It was a full antibody. It was glycosylated at five positions and at a very large molecular weight. And as a result, its pharmacokinetics were prolonged. And this is shown as early as 2000 in Papadopoulos, where he showed the PK, pharmacokinetic, curves after administration of Eylea to animals.

Q. Now, Dr. Rabinow, do the '865 patent asserted claims require that the claimed protein formulation demonstrate safety or efficacy?

A. No.

Q. Now I want to turn to Slide 119 that's on the screen. And you understand that Dr. Trout relies on the Thomas reference, PTX-1155 --

A. Yes.

Q. -- in support of his opinion that the efficacy unexpected?

A. Correct.

Q. And you disagree with this, correct?

A. Yes.

Q. Please describe your disagreement with the Thomas reference, PTX 1155.

A. Well, I see that Dr. Trout states that this unexpected safety and efficacy holds both in comparison to the closest prior art relating to Lucentis and in a comparison to any of the other prior art, whereas, in point of fact, there was enormous discussion and strategizing on the part of Regeneron to intentionally design their molecule with prolonged pharmacokinetics precisely because they could decrease the frequency of intravitreal injection, would -- which would be a tremendous improvement over the monthly administration requirements of Lucentis to give a q2 months, or every two

months, injection. It would be a phenomenal competitive advantage.

Q. I want to focus on the formulation components. Okay?

So if we could turn to Slide 120.

If we compare the formulation components between Lucentis and Eylea, what, if any, conclusion would the person of ordinary skill in the art draw regarding the contribution of formulation components to safety and efficacy?

A. He would look and -- he/she would look and observe that these were all known in the prior art. There was nothing special so that there would be no substantial impact to safety or efficacy.

Q. And if we could turn to Slide 123.

Dr. Rabinow, do you disagree with Dr. Trout's opinion regarding copying?

A. Yes.

Q. Why?

A. The formulation components for Eylea are displayed in the far right column in the lower table compared to Yesafili in the middle column. And you see that the buffer differs. There's histidine used for Yesafili versus sodium phosphate for Eylea. The surfactant, polysorbate 20, is the same. The stabilizer is different. There's trehalose used for Yesafili versus sucrose for Eylea. And Eylea in addition contains sodium chloride, which is lacking in Yesafili.

Furthermore, as we've considered the state of the art of half a dozen antibody proteins, fusion and otherwise, polysorbates were essential to include in the formulations to anticipate the common failure mode of denaturation and adsorption which occurs for all proteins. Everybody was putting polysorbate 20 or 80, preferably polysorbate 20, into their protein formulations.

Q. Dr. Rabinow, do you agree with any of Dr. Trout's supposed evidence of nonobviousness?

A. No.

Q. I'd like to now turn briefly to the next slide, 125, and discuss the '572 patent and the limited claim term of formulated as an isotonic solution in Claim 6.

A. Fine.

Q. Now, Dr. Rabinow, did you review the term "isotonic solution" as it appears in Claim 6 of the '572 patent and compare it to the disclosures of the prior art to determine whether the person of ordinary skill in the art of the '572 patent would have considered these claim elements known and/or obvious as of January 13, 2011?

A. I did.

Q. If we could turn to Slide 126.

Dr. Rabinow, did you review the Hecht reference?

A. Yes.

Q. And that's DTX 3588, correct?

A. Yes.

Q. And you relied on the Hecht reference in connection with your opinions?

A. Yes.

Q. And when was the Hecht reference published?

A. 1995.

Q. And we see that at DTX 3588 on page 3, correct?

A. Yes.

Q. Now, if we turn to Slide 127, what is the title of Chapter 89 in DTX 3588?

A. "Ophthalmic Preparations."

Q. And do you consider an intravitreal injection to be an ophthalmic preparation, Doctor?

A. Yes.

Q. If we could turn to the next slide, Slide 128.

What does Hecht teach the person of ordinary skill in the art regarding formulations of ophthalmic solutions?

A. On page 11 Hecht states that ophthalmic solutions are formulated to be sterile, isotonic, and buffered for stability and comfort. On page 13 he further discloses, given a choice, isotonicity always is desirable and particularly is important in intraocular solutions.

Further, on page 11 under "General Considerations," it is disclosed a number of requirements must be considered in the preparation of ophthalmic solutions. These include, among

other things, tonicity.

Q. Apologies, Doctor. Please continue.

A. And he states what he means by tonicity in the box at the bottom on page 13.

Q. So we've discussed a number of disclosures in Hecht. And I just want to make sure that the record is clear. That's DTX 3588 at page 11 and 13, correct?

A. Yes.

Q. If we could turn to Slide 129, please.

Dr. Rabinow, what reference is depicted here?

A. This is a 2009 reference by Dixon, "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration."

Q. And this is DTX 204, correct?

A. Yes.

Q. And you relied on DTX --

A. Yes.

Q. -- in forming your opinions?

A. Yes.

Q. If we could look at the first page of DTX 204, when was this reference published?

A. 2009.

Q. If we could turn to Slide 130, please.

What does Dixon teach the person of ordinary skill in the art regarding intravitreal injections containing aflibercept?

A. On page 3 it is disclosed VEGF Trap-Eye, which is aflibercept, is also formulated with different buffers and at different concentrations for buffers in common suitable for the comfortable, nonirritating direct injection into the eye.

Q. What would the person of ordinary skill in the art understand in or around January 13, 2011, reading the disclosure of Dixon, suitable for the comfortable, nonirritating direct injection into the eye?

A. He would understand, among other things, that it should be isotonic.

Q. Now, Dr. Rabinow, if a formulation is not isotonic, would it cause irritation in the patient when injected into the eye?

A. It could.

Q. And based on this, is it your opinion that the person of ordinary skill in the art as of January 13, 2011, would know that the formulation used in Dixon was isotonic?

A. Yes.

Q. In fact, isn't it your opinion that the person of ordinary skill in the art would expect that the aflibercept formulation used in Dixon was isotonic?

A. Yes.

Q. And would the person of ordinary skill in the art have been motivated to formulate aflibercept as an isotonic solution so that it would be nonirritating when administered to

a patient's eye?

A. Yes.

Q. And, finally, would the person of ordinary skill in the art have had a reasonable expectation of success in formulating aflibercept as an isotonic solution so that it would be nonirritating when administered to a patient's eye?

A. Yes.

Q. Now, I briefly want to touch on your deposition. Do you recall at your deposition that counsel for plaintiff asked you some questions about isotonicity?

A. Very well.

Q. Okay. And did we see that during the opening statement? Were you present for that, the opening statements here in this court?

A. Oh, yes. Yes, indeed.

Q. Did we see some of your testimony regarding isotonic solution during the opening statement?

A. I believe we did.

Q. Do you recall that questioning?

A. Yes, I did.

Q. From your deposition?

A. Oh, yes.

Q. And in what context were the questions being asked in connection with the testimony that plaintiff's counsel displayed during the opening statement?

A. I was shown a document displaying a very high hypertonic solution which was purported to be a -- for intravitreal use. And I was asked did I believe that that would have been acceptable or not.

Q. And do you consider that testimony to have been taken out of context?

A. Yes.

MR. HUNT: Your Honor, at this time I pass the witness.

THE COURT: Thank you, Counsel.

MR. TRASK: Thank you, Your Honor. May I have a moment?

THE COURT: You may. Permission granted to approach to distribute any materials.

MR. TRASK: Thank you, Your Honor.

THE COURT: Whenever you're ready, Counsel, you may proceed.

MR. TRASK: Thank you, very much, Your Honor. Andrew Trask on behalf of Regeneron.

CROSS-EXAMINATION

BY MR. TRASK:

Q. Good afternoon, Doctor. Good to see you again.

A. Good afternoon. You too, sir.

Q. Doctor, you rely on the formulation disclosed in the Fraser reference for obviousness, correct?

A. Yes.
Q. You didn't testify that Fraser anticipates the '865 patent, did you?
A. No.
Q. The study reported in Fraser involved monkeys, not humans, correct?
A. Yes.
Q. And the researchers in Fraser were studying the effects on female monkeys' ovaries, right?
A. Yes.
Q. They weren't studying the monkeys' eyes at all, right, Doctor?
A. Correct.
Q. Fraser didn't involve any ophthalmic disorder at all, did it?
A. Correct.
Q. The only method of administration disclosed by Fraser is intravenous injection, right?
A. Yes.
Q. Intravenous injection is a totally different method of administration compared to intravitreal injection, right?
A. Yes.
Q. Intravitreal injection involves injection into the eye, not the vein. You agree with that?
A. Yes.

Q. Fraser says not one word about injecting its formulation into the eye, correct?

A. Yes.

Q. Fraser also says nothing about the particular amino acid sequence of the molecule that was injected into the monkeys in that study, correct?

A. There's an inherent disclosure.

Q. The amino acid sequence is not recited in Fraser, correct, Doctor?

A. He mentions VEGF Trap R1R2.

Q. That's not a disclosure of the amino acid sequence as stated in Fraser, correct?

A. A POSA would understand what the amino acid sequence was by the term VEGF Trap R1R2.

Q. And that's based on information outside of Fraser, correct?

A. That's based upon common knowledge that a person of ordinary skill in the art would know by virtue of working in this very restricted field with very few participants, and it would be expected that he would be mindful of all of the relevant literature in this tiny area in which he was working.

Q. Doctor, every asserted claim of the '865 patent requires an organic cosolvent. You understand that?

A. Yes.

Q. You're familiar with the Court's construction of the

term "organic cosolvent" in the claims of the '865 patent, right?

A. Yes.

Q. The Court construed "organic cosolvent" to mean an organic substance added to the primary solvent to increase the solubility of the VEGF antagonist, right?

A. Yes.

Q. Now, the Fraser formulation includes polysorbate, right?

A. Yes.

Q. And that's the substance in Fraser's formulation that you believe meets the organic cosolvent limitation of the asserted claims, right?

A. Yes.

Q. Now, at your deposition in this case you took the position that, in order to answer the question of whether a substance meets the Court's construction of organic cosolvent, you've got to do an experiment in order to determine if the substance is to be considered a cosolvent or not, right?

A. Yes.

MR. HUNT: Objection, Your Honor. To the extent that counsel is intending to elicit testimony regarding infringement of the '865 patent, it's been made clear that Dr. Rabinow is not offering any opinions regarding infringement.

THE COURT: Understood. Overruled at this point.

You may proceed, Counsel.

MR. TRASK: Thank you, Your Honor.

BY MR. TRASK:

Q. Now, you're not taking that position here at trial, right?

A. Correct.

Q. But your position at deposition was that experimental data is required to prove whether or not an organic cosolvent is present, right?

A. That's what I said at the time.

Q. Now, you can't point to any data from such an experiment on the formulation disclosed in Fraser, right?

A. Correct.

Q. And you yourself didn't do any experiments on the Fraser formulation to show that its polysorbate 20 meets the Court's construction for organic cosolvent?

A. Correct.

Q. And there's no data in your report demonstrating that the polysorbate 20 in the Fraser formulation is an organic cosolvent under the Court's claim construction, right?

A. I believe I prefaced my comments here by saying "assuming Regeneron's infringement contention of the definition of polysorbate as a cosolvent," and then I proceeded to give my opinion.

So I was not -- I was not asked to consider

infringement; so I didn't have to worry about that. I'm merely assuming Regeneron's infringement contention, and then I proceeded on to do what I was being asked to do, which was to discuss invalidity and obviousness.

Q. I'll ask the question again, Doctor.

There's nothing in your report demonstrating that the polysorbate 20 in the Fraser formulation is an organic cosolvent under the Court's claim construction, right?

A. I don't know. I didn't consider that question.

Q. Fraser itself does not disclose any experimental data showing that its polysorbate 20 meets the Court's construction of organic cosolvent, right?

A. I believe that's correct.

Q. Now, when the Court issued its construction of the claim term "organic cosolvent," it adopted Mylan's proposed construction for that term, right?

A. Yes.

Q. You served your opening and reply reports in this case on the Court's schedule prior to the Court issuing its claim construction order, right?

A. Yes.

Q. And so you served two opening reports, one under Regeneron's construction, the other under Mylan's construction, right?

A. Yes.

Q. And you didn't include any data in your report under Mylan's construction showing that polysorbate 20 functions as an organic cosolvent. We just agreed to that, right?

A. Yes.

Q. And the reason that that's not in your report under Mylan's construction is that you understood from Mylan's lawyers that the construction of organic cosolvent that they urged the Court to adopt would not be accepted by the Court, right?

A. There was discussion about two differing opinions as to the claim construction, and so we wrote two reports.

Q. I'll ask the question again, Doctor.

The reason that data is not in your report under Mylan's construction is that you understood from Mylan's lawyers that the construction of organic cosolvent that they urged the Court to adopt would not be accepted by the Court, right?

A. I think I said something to that effect at the time.

Q. At the time being your deposition, correct?

A. Yes.

Q. Was that a truthful statement at your deposition, Doctor?

A. Yeah. I mean, I wouldn't lie in my deposition.

Q. You got the impression from Mylan's lawyers that Regeneron's construction was going to be accepted by the Court,

right?

A. That's what I said at the time, yes.

Q. Was that a truthful statement at the time, doctor?

A. Yes.

Q. You were so certain that Mylan's construction wasn't going to be accepted by the Court that you didn't really pay much attention to it, right?

A. Well, we paid sufficient attention to write two reports. That part is true.

Q. Doctor, you were so certain that Mylan's construction wasn't going to be accepted that you didn't really pay much attention to it. Is that true?

A. I think -- I think that's taken out of context. I think what I said was there was so much information, so much documents, patents, articles, I found it difficult, frankly, to keep up with it all; and I had all I could do to simply deal with the documents that I was given and I was being asked to study and to understand without going off on my own and doing, frankly, what Regeneron's job would have been, which is to prove their infringement contention, if that's what you're asking.

Q. Doctor, we established that you were deposed in this case, right?

A. Yes.

Q. That was back in March of this year?

A. Correct.

Q. Can we look at transcript page 241, line 7 through 22, please.

I want you to confirm, Doctor, that I'm reading this correctly from your transcript.

"Q Well, I don't know what data you're talking about, Doctor, and I don't think it's referenced in your report. Your opinion on this is at paragraph 210 of your report. So I need to know whether there's actual data you're relying on or not.

"A Let me say this. I know I have seen data where Regeneron studied citrate, phosphate, buffered, otherwise optimized R1R2 formulations both with and without polysorbate 20. Can I show that to you right now? No.

"Q It's not in your report, right?

"A No. And the reason why it's not in my report is that we didn't think, frankly, that the Mylan claim construction was going to be accepted. We didn't really pay that much attention to it."

Did I read that correctly?

A. Yes.

Q. For purposes of preparing your report, Doctor,

Mylan's lawyers instructed you to assume that Regeneron's claim construction was going to be adopted by the Court, right?

A. Yes.

Q. You were led to believe by Mylan's attorneys that the Court would adopt Regeneron's claim construction of the organic cosolvent term, right?

A. I don't know to what extent I can share what Mylan's attorneys discussed with me, but they indicated that there was a high degree of uncertainty as to which claim construction was going to be accepted. And they -- and in view of that, they asked me to write two reports and to assume two different kinds of things. So I'm not sure how else I can answer your question.

Q. I'll ask the question again, Doctor.

You were led to believe by Mylan's attorneys that the Court would adopt Regeneron's claim construction of the organic cosolvent term, correct?

A. The probability of that was -- was significant, I would say that, yeah.

Q. Can we look at the doctor's transcript at page 250, lines 8 to 14, please.

I'm going to read the question and answer, Doctor, and I'd like you to confirm whether I read it correctly.

"Q Why did you assume that the Court would adopt Regeneron's claim construction of the

organic cosolvent term?"

There was an objection. And then you answered:

"A I was led to believe that by my attorneys."

Did I read that correctly?

A. Yes.

Q. And because you were instructed by Mylan's attorneys to assume that the Court would adopt Regeneron's construction, you provided no data supporting the notion that Fraser's polysorbate is an organic cosolvent under the construction that was ultimately adopted by the Court, correct?

A. Yes.

Q. When it came to proving invalidity under Mylan's constructions, the constructions that we're here today to address, you were pulling your punches, weren't you?

A. I'm sorry?

Q. When it came to proving invalidity under Mylan's constructions, the construction at issue in this trial today, you were pulling your punches, weren't you?

A. I'm not sure what you mean by that.

Q. Let's look at the doctor's transcript at page 249, line 11 through 250, line 7.

"Q Well, in the report under Mylan's construction, you provided no data supporting the notion that Fraser's polysorbate is an organic

cosolvent under Mylan's construction, right?"

Objection.

"A I guess I was pulling my punches, wasn't I? I was assuming, really, that we were going with Regeneron's claim construction and that polysorbate was going to be declared a solvent."

Did I read that right, Doctor?

A. Yes, you did.

Q. As we just discussed a moment ago, you served two opening expert reports, one under Mylan's construction and another under Regeneron's construction, right?

A. Yes.

Q. Then Dr. Trout served an expert report responding to your opinions on validity, right?

A. Yes.

Q. In response to Dr. Trout, you only served one reply report, right?

A. Yes.

Q. And that reply report was premised on Regeneron's claim construction, right?

A. It was premised on the assumption that we were assuming Regeneron's infringement claim contention of what a polysorbate was, and I think I may have specified that.

Q. Your reply report, the only reply report you served

in this case, assumes Regeneron's claim construction proposals for the claim terms "organic cosolvent" and "native conformation" in the '865 patent, right?

A. I think I felt that, unless I phrased it that way there, we wouldn't be at trial because Regeneron wouldn't have any patent at all. They wouldn't be enabled. It means that there would not have been enablement of any cosolvent. So I naturally assumed that, all right, there's going to be a trial; let's discuss this.

Q. Let's take a look at PTX 63, please.

THE COURT: Is that PTX, Counsel?

MR. TRASK: PTX, Your Honor. Thank you.

THE COURT: Thank you.

BY MR. TRASK:

Q. This is your reply report in this case, is it not?

A. Yes.

Q. If you look at page 1 of the document.

You see in the highlighting in the middle of paragraph 3, you say that "This report discloses my opinions assuming Regeneron Pharmaceutical, Inc.'s claim construction proposal for the claim terms 'organic cosolvent' and 'native conformation.'"

Do you see that?

A. Yes.

Q. Now, further down in Footnote 3, also on page 1 of

your reply report, you said, "To the extent the Court does not adopt Regeneron's claim construction proposal or submit its own construction for either term, I reserve the right to amend and/or supplement this report accordingly."

Did I get that right?

A. Yes.

Q. You never amended or supplemented your report from that point until this time today, did you?

A. No.

Q. You don't have any opinions under Mylan's claim construction in this reply report, do you?

A. No.

Q. You understand, Doctor, that this whole trial on the '865 patent is about the asserted claims of the '865 patent as interpreted by the Court under the Court's claim construction order, right?

A. Yes.

Q. But you never submitted a reply report assuming that construction, did you?

A. I wasn't asked to opine on infringement. I accepted Regeneron's infringement contention for the definition of polysorbate 20.

Q. Doctor, you have no disclosed response to Dr. Trout's opinions that the asserted claims of the '865 patent are valid under the construction ordered by the Court, correct?

A. Correct.

Q. Turning back to Fraser, let's look at DTX 729. This is the Fraser publication.

Now, Fraser explains that the aim of the study was to evaluate the effects of transient inhibition of VEGF on pituitary-ovarian function in the macaque.

Does that sound right?

A. Yes.

Q. The macaque is a monkey, correct?

A. Yes.

Q. And as we discussed a moment ago, Fraser used an intravenous injection, right?

A. Yes.

Q. When you inject intravenously, the injected dose circulates throughout the bloodstream, right?

A. Correct.

Q. Now, you testified on direct that the POSA would have taken Fraser's dose used to evaluate the effects of transient inhibition on ovarian function in monkeys and used that as an intravitreal dose to treat ophthalmic indications, right?

A. Yes.

Q. You don't cite any evidence teaching to use an intravitreal dose based on a dose designed to inhibit VEGF in a monkey's ovaries, right?

A. No.

Q. Now, in order to do the calculations you performed to get from the information disclosed in Fraser to the claimed 40 mg/mL dose, you had to rely on a value for the dose volume administered intravitreally, right?

A. Yes.

Q. And your testimony was that, for purposes of converting Fraser's dose in a monkey for inhibiting ovarian function into an intravitreal dose for treating an ophthalmic indication, the person of ordinary skill would use a .06-milliliter intravitreal injection volume, right?

A. Yes.

Q. And you testified that you use a .06-milliliter volume to be generous, right?

A. Yes.

Q. Because that's not exactly what's disclosed in the literature, is it?

A. No.

Q. You pointed to the Gaudreault and Shams references.

A. Well, wait. Let me revise that.

It is common for manufacturers of sterile fluids, of which an intravitreal injection is an example, to have an overage in the drug container to accommodate insufficient delivery of the drug solution to the site of administration. That part is well known.

Q. You cite no literature for that proposition, right,

Doctor?

A. I mean, this is what a POSA knows, right? I mean, Baxter put in -- I can't disclose exactly what they put in, but they put in an overage. In every one of their 10,000 different codes of intravenous solution, there's an overage in there to accommodate the fact that you can't get everything out of the container.

So you want to be sure that you deliver the labeled amount of solution and you're accommodating hang-up -- hang-up in the container, in the IV tubing, in the sets, in the pumps, in the butterfly injection site, in the patient. So that part's known.

Q. The references you combined with Fraser were Gaudreault and Shams, right?

A. Yes.

Q. And those disclose a .05-milliliter injection volume, not a .06-milliliter injection volume, right?

A. Yes.

Q. If you had used that .05 injection volume disclosed in the prior art in your calculations, it wouldn't have worked out to 40 mg/mL, would it?

A. Right.

Q. And each asserted claim of the '865 patent requires 40 mg/mL, right, Doctor?

A. Right. Well, let me -- let me clarify that. We're

not talking about anticipation; we're talking about obviousness. For obviousness, a POSA is allowed reasonable experimental optimization. So a POSA would know that you don't have to get exactly 40 mg/mL or you could get there to optimize it further.

Q. Doctor, the requirement of 40 mg/mL in each asserted claim of the '865 patent means that, if the prior art references don't disclose 40 mg/mL, either expressly or inherently, then the reference can't anticipate the claims, right?

A. You're right. But we weren't talking about anticipation here. You were talking about obviousness.

Q. If we look at DDX 4.79, please. This is one of the doctor's slides.

Doctor, you presented this slide as part of your direct testimony?

A. Yes.

Q. You see for the first limitation in -- shown in the slide, Claim 2, that requires 40 mg/mL, right?

A. Yes.

Q. And you checked the box under Fraser for that limitation, right?

A. Yes.

Q. What's the concentration of aflibercept -- of VEGF Trap disclosed in the Fraser reference?

A. 24.3 mg/mL, I believe.

Q. We can take that down.

You understand, Doctor, that each of the asserted claims of the '865 patent also requires a vial for holding the formulation, right?

A. Yes.

Q. Fraser doesn't expressly disclose that its formulation is contained in a vial?

A. He's talking about an aliquot, 2-milliliter aliquots in Fraser, which means it has to be contained in something, containing a small volume of liquid. A POSA reading that would read my chapter in Remington's on packaging systems and know that a vial is the most likely candidate for such a container.

Q. You believe that the disclosure of a vial is inherent, correct?

A. Yes.

Q. You think it's probable that Fraser used a vial, right?

A. Yes. Well, a POSA reading Fraser would know that the most likely container for delivery of a liquid medication would be a vial, yes.

Q. You agree that the Fraser paper itself doesn't say that, right?

A. Yes.

Q. You're familiar with the Court's construction of the

term "native conformation" in the claims of the '865 patent?

A. Yes.

Q. In your opinion, determining whether a protein is in its native conformation under the Court's construction is based upon simply running size-exclusion chromatography, right?

A. Repeat that.

Q. In your opinion, determining whether a protein is in native conformation under the Court's construction is based upon simply running size-exclusion chromatography, right?

A. I believe the Court left that open, if I recall properly. It wasn't clear what -- if that would be sufficient or not, and so I went with the size-exclusion chromatography.

Q. I'm asking, in your opinion, Doctor, determining whether a protein is in native conformation under the Court's construction is based upon simply running size-exclusion chromatography?

A. I interpreted that that was suitable for what I had to do, yes.

Q. I'm going to ask the question one more time, Doctor.

In your opinion, determining whether a protein is in native conformation under the Court's construction is based upon simply running size-exclusion chromatography; is that right?

A. I looked at the art in which that terminology was used, and there was sufficient prior art that, in fact,

conflated native conformation with size-exclusion chromatography.

So there was certainly a case to be made that size-exclusion chromatography would have been adequate to declare that to be suitable for what we were doing.

Q. Now, Fraser doesn't disclose the at least 98 percent native conformation limitation, right?

A. Right.

Q. Claim 15 of the '865 patent requires a limitation involving turbidity, right?

A. Yes.

Q. And the requirement is that the turbidity be .01 or lower at OD405 following storage, right?

A. Yes.

Q. Fraser doesn't disclose that turbidity limitation either, right?

A. Well, I think we discussed this, that there was a declaration made by Regeneron stating that the -- a Dix formulation had, in fact -- was, in fact, the one that had been used by Fraser. And in the Dix document there was the requisite stability information for both turbidity as well as native conformation over the requisite period of time at the requisite temperature of 5 degrees.

So it was inherent in what Fraser used that we learned that that had been inherently disclosed.

Q. Doctor, if the Court rules that Dix cannot be considered for anticipation or obviousness, then you have no aflibercept data to rely on to argue that Fraser inherently discloses the 98 percent native conformation limitation, right?

A. I'm not an attorney. I can't comment on that.

Q. And if the Court rules that Dix cannot be considered for anticipation or obviousness, then you also have no aflibercept data to rely on to argue that the Fraser publication discloses the turbidity limitations of Claim 15, right?

A. Again, I'm not an attorney. I can't comment on that.

Q. All of the asserted claims of the '865 patent require that the VEGF antagonist fusion protein comprised amino acids 27 to 457 of SEQ ID4, correct?

A. Yes.

Q. You don't argue that Fraser expressly discloses that amino acid sequence. We established that a moment ago, right?

A. Yes.

Q. Your position on the Fraser patent is based in part upon the disclosure of the Dix patent, right?

A. Yes.

Q. The Dix patent is only 11 pages long, right, Doctor?

A. I don't recall.

Q. You haven't read the entire Dix patent, have you, Doctor?

A. I've read it some time ago.

Q. You didn't read it before your deposition, did you, Doctor?

A. I certainly don't recall that, no.

Q. You don't recall reading it before your deposition in full, correct?

A. I don't recall reading it or not reading it.

Q. Before alleging that an inventor's patent is invalid in light of a given document's disclosure, do you think it's important to read the whole document to fully understand its disclosure?

A. Yes.

Q. Let's look at the doctor's transcript at page 177, line 19, through 178, line 1.

Doctor, referring to the Dix patent, I asked you:

"Q There are other SEQ IDs disclosed in this patent, right?"

And you answered, "I would have to read this document in order to figure out if it were logical that it would refer to it," correct?

A. That's what's written here, yes.

Q. Now, you agree that the Dix '546 and Dix '226 patents have the same disclosures, right?

A. Yes.

Q. The Dix patent states that, "VEGF expression is

nearly ubiquitous in human cancer." Does that sound right?

A. Yes.

Q. And it explains that blocking VEGF "inhibits growth of implanted tumor cells."

Does that sound right?

A. Yes.

Q. Dix is referring to cancer in those passages, right?

A. Yes.

Q. Dix never refers to any ophthalmic indication, does it?

A. I don't believe so.

Q. It never refers to age-related macular degeneration, right?

A. I think we're talking about how a POSA would read Dix. A POSA would read Dix in light of what he knew was relevant. The history of what was going on at the time, that it was known that VEGF was useful, it may have been discovered originally in cancer, but it quickly was discussed in light of neovascularization in the retina. And people were, in fact, studying it for that purpose and injecting humans intravitreally for that.

So a person tasked with developing a -- an ocular dosage form would certainly be mindful of his surroundings.

Q. I'll ask the question again, Doctor.

Dix never refers to age-related macular degeneration,

right?

A. I don't believe so.

Q. Dix never refers to diabetic macular edema, right?

A. I believe that that's correct.

Q. Dix never refers to diabetic retinopathy, right?

A. I believe that that's correct.

Q. Dix refers to administering formulations subcutaneously and intravenously, true?

A. I believe that's correct.

Q. Dix never refers to intravitreal administration, does it?

A. I don't believe so.

Q. And as we established a moment ago, intravitreal injection is a totally different method of administration from intravenous and subcutaneous administrations, right?

A. Yes.

Q. Now, Doctor, were you in the courtroom on Monday when Mr. Berl explained that Dix can't be relied on for obviousness if Dix and the '865 patent were co-owned by Regeneron or subject to an obligation of assignment to Regeneron at the time of the '865 patent's invention?

A. I believe I heard that.

Q. You don't have any opinions on the ownership of the Dix '226 or Dix '546 patents, right?

A. That's beyond my pay grade.

Q. You don't dispute that the Dix '226 and Dix '546 patents are owned by Regeneron today, do you?

A. I'm not an attorney. I originally tried to delve into this area, and I realized that I was quickly becoming mired with all kinds of complexities. And I realized I had better stay out of this, and I would leave that to my attorneys to discuss.

So I can't really comment on, you know, specific aspects of ownership, because I realize that it's a very complex web in terms of who owns what, what was the law at which time. The law was changing. So I am aware -- I know enough to realize that I could get into real trouble if I tried to opine in that area; so I left this to my attorneys.

Q. Doctor, you don't dispute that, from September 2005 onward, the Dix '226 and Dix '546 patents were owned by Regeneron, right?

A. I believe that there are connotations about ownership that I may or may not be aware of; so I feel that I probably should not comment on that.

Q. You don't dispute that, as of September 2005 onward, all four inventors named on the Dix '226 and Dix '546 patents had an obligation to assign their inventions to Regeneron, right?

A. I understand that, but I'm not sure what that means in the context of the larger question you are asking. I'm not

an attorney.

Q. You don't have any opinions on the ownership of Regeneron's '865 patent, true?

A. There are implications of what you're asking that I believe go beyond the question that you're asking me.

Q. You don't dispute that, from September 2005 onward, the inventions in the '865 patent were owned by Regeneron, do you?

A. I don't have any comment.

Q. And you don't dispute that, from September 2005 onward, all four inventors named on the '865 patent had an obligation to assign their inventions to Regeneron, right?

A. Again, I'm not an attorney; so I can't really comment.

Q. Now, the two Dix references you're relying on are patents, right?

A. Yes.

Q. Now, are you aware that a reference patent can be considered prior art as of its provisional filing date only if the provisional application provides written description support for the claims in that reference patent?

A. I have seen that point argued and discussed. Again, I'm not an attorney, and I feel that I can't really comment on that.

Q. Okay.

Can we put up Slide 3, please.

Doctor, do you see on the screen here is a quote from the Federal Circuit's *Dynamic Drinkware* case?

A. I see this.

Q. Do you see that it says a reference patent is only entitled to claim the benefit of the filing date of its provisional application if the disclosure of the provisional application provides support for the claims in the reference patent in compliance with 112, paragraph 1?

A. Yes.

THE COURT: Yes, Counsel?

MR. HUNT: I'm sorry, Your Honor.

Objection. This entire line of questioning is outside the scope of the direct. We did not in any way open the door to a discussion of whether the Dix '226 patent was commonly owned and/or has priority. The doctor assumed for purposes of his analysis that it would be prior art, and that's the end of it.

THE COURT: Counsel?

MR. TRASK: Thank you, Your Honor.

So Mylan and Biocon are relying on the March 25, 2005, date of the Dix patent. That is the provisional date. There's an obligation under the law that, if they're going to rely on that date, they need to show written description support in the provisional application. I'm trying to

establish that the doctor didn't make that showing in relying upon that date.

MR. HUNT: Just additionally, Your Honor, to the extent that this line of questioning is attempting to elicit patent law expertise from a pharmaceutical formulator, we would object on that additional basis.

THE COURT: Understood.

I won't speak for any other courts or judges. But I, with all due respect, Doctor, wouldn't think that was binding on anyone.

Objection otherwise overruled, though with the assumption with respect to these materials are a basis of the doctor's opinions which were put at issue once disclosed and called at a witness.

You may proceed, Counsel.

MR. TRASK: Thank you, Your Honor. I'll move through this rather quickly.

BY MR. TRASK:

Q. Now, of course, you're relying on the Dix '226 and '546 patents as prior art, right, Doctor?

A. Yes.

Q. And you're relying on the March 25, 2005, filing date of the Dix patents as their prior art date, right?

A. Yes.

Q. Okay.

Let's look at the slide from the doctor's presentation, DDX 4.36.

You presented this slide during your direct examination, Doctor?

A. Yes.

Q. This is the Dix '226 patent, right?

A. Yes.

Q. And these -- the text from the Dix patents is from the issued patent, right?

A. Yes.

Q. But up at the top of the slide you have a March 25, 2005, date, correct?

A. Yes.

Q. That's the provisional filing date for the Dix application, right?

A. Yes.

Q. Do you know, Doctor, whether Example 1 shown on the slide right there is present at all in the provisional application of Dix?

A. No. I don't know.

Q. You didn't do that analysis, right?

A. I did not.

MR. TRASK: You can take that down.

BY MR. TRASK:

Q. You didn't evaluate whether the claims of the

Dix '226 patent have written description support in the disclosure of Dix's 2005 provisional application?

A. No.

Q. You didn't evaluate whether the claims of the Dix '546 patent have written description support in the disclosure of Dix's 2005 provisional application?

A. No.

Q. You don't have an opinion that the Dix '226 patent is entitled to claim the benefit of its 2005 priority date, do you?

A. I'm not an attorney. I can't comment.

Q. And you don't have an opinion that the Dix '546 patent is entitled to claim the benefit of its 2005 priority date, right?

A. Again, I'm not an attorney. I can't comment.

Q. Let's turn to Dix itself and the 40 mg/mL concentration.

In your opinion, Dix discloses 40 mg/mL, right?

A. Yes.

Q. Now, Dix has a number of formulations in its working examples towards the end of the document, right?

A. Yes.

Q. None of those formulations disclose 40 mg/mL of aflibercept, right?

A. I'd have to see it again. I don't recall.

Q. Well, I believe you have the Dix document in your binder, Doctor, if you'd like to take a look and confirm.

THE COURT: Do you know which number that is, Counsel?

MR. TRASK: Yes, Your Honor. I'm sorry. It's D, as in defendant, TX 0013.

THE COURT: Thank you.

BY MR. TRASK:

Q. The examples start at Column 7 of that patent, Doctor.

A. I don't think I have it.

THE COURT: Did you say Column 7, Counsel?

THE WITNESS: I'm sorry. Where do I --

MR. TRASK: Column 7.

THE COURT: Thank you.

BY MR. TRASK:

Q. Are you there, Doctor?

A. Yes. I'm looking over it.

I see that they're talking about a 50 mg/mL. They're talking about a 75 mg/mL. They're talking about 100 mg/mL, and they're talking about a 50 to 100 mg/mL.

These concentrations are all higher than 40 mg/mL. And in the context of what is noteworthy about stability of proteins, if you have stability at a higher concentration, that is a very good basis for assuming you're going to have

stability at a lower concentration. And 40 is not all that different from 50.

So it's hard for me to -- and I'm reciting this, I believe, in an obviousness arena, in which case there is reasonable routine experimentation that is permitted to get from 50 down to 40.

Q. The question I had asked, Doctor, was none of the working formulation in Dix's examples have 40 mg/mL of a VEGF antagonist fusion protein; is that right?

A. Right. But it states very clearly that formulations of 40 up to some very large number are envisioned in this patent.

Q. Doctor, I'm only asking you about the examples starting at Column 7.

A. I believe that's correct.

Q. Just for the record, Doctor, you agree that the working examples in the Dix patent starting at Column 7, none of those disclose 40 mg/mL of a VEGF antagonist fusion protein, right?

A. Correct.

Q. Now, you testified earlier today that Dix discloses 40 mg/mL because it discloses a range of 10 to 50 mg/mL of a VEGF-specific fusion protein antagonist, right?

A. Yes.

Q. You agree that a concentration of specifically

40 mg/mL is not expressly disclosed by that 10 to 50 mg/mL range, right?

A. Correct. But it is disclosed in the paragraph lower down where it specifically mentions 40 mg/mL in connection with a lyophilized dosage form.

Q. I didn't ask you about that, Doctor. And that's not disclosed in your report, is it?

A. I can't remember. It may have been.

Q. In your opinion, Doctor, Dix's disclosure of the 10 to 50 mg/mL concentration range is a disclosure of every possible value falling within that range, right?

A. Yes.

Q. And so the 10 to 50 mg/mL range of a VEGF antagonist is a disclosure to the POSA of 28 mg/mL, right?

A. Yes.

Q. 37.2 mg/mL?

A. Yes.

Q. 49.35 mg/mL?

A. Yes.

Q. Now, the formulations claimed in the '865 patent don't allow for 40 mg/mL of any VEGF-specific fusion protein; they require 40 mg/mL of the VEGF antagonist fusion protein comprising amino acids 27 to 457 of SEQ ID Number 4, right?

A. That's what's stated in the claims.

Q. Okay.

Can we look at P2.12.1, please.

Do you know what's shown here, Doctor?

A. It's the amino acid sequence of SEQ ID4, I believe.

Q. And in order for a VEGF antagonist to meet the limitations of the claims in the patent, it needs to meet every single amino acid in this -- shown in this diagram, right?

A. Yes.

Q. Every one of these three -- every one of these three-letter sequences is a specific amino acid residue, right?

A. Yes.

Q. And if even one of those amino acids is different, it doesn't fall within the scope of the '865 patent claims, right?

A. Yes.

Q. You can take that down.

Now, if we look at Dix '226, again, DTX 013, at Column 2, lines 20 to 24.

A. I'm sorry. Say that again.

Q. Yes. We're going to look at the Dix '226 patent at Column 2, lines 20 to 24. It's also shown on the screen.

THE COURT: That's, again, DTX 13, Counsel?

MR. TRASK: That's right, Your Honor.

THE COURT: Thank you.

THE WITNESS: Okay.

BY MR. TRASK:

Q. This is the disclosure of 10 to 50 mg/mL that you're

relying on, right?

A. Yes.

Q. This doesn't say 10 to 50 mg/mL of the long amino acid sequence that we just looked at on the screen, right?

A. I think a POSA reading this would assume we're talking about a VEGF-specific fusion protein antagonist where the SEQ ID is given.

Q. You think that a POSA would read VEGF-specific fusion protein antagonist in the Dix patent and assume that it means only the SEQ ID4 sequence that we just saw on the screen?

A. Well, it could comprise a very limited class of such compounds and denote that 10 to 50 mg/mL is a suitable concentration of them.

Q. Let's look at the same document, Column 2, lines 3 through 15. This is the immediately prior paragraph to the one we were just looking at.

And it says -- starting at the top, line 4 of the patent, it refers to a "VEGF-specific fusion protein antagonist comprising a fusion protein comprising a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and an Ig domain 3 of a second VEGF receptor and a multimerizing component."

Do you see that?

A. Yes.

Q. That's not the specific amino acid sequence of

SEQ ID4, right?

A. Right.

Q. It also says that the "VEGF-specific fusion protein antagonist, the first VEGF receptor can be FLT1 and the second VEGF receptor can be FLK1 or FLT1."

Do you see that?

A. Yes.

Q. That's not the specific amino acid sequence of SEQ ID4 that we just looked at on the screen, right?

A. Correct.

Q. And even more particularly it says the fusion protein has the amino acid sequence of SEQ ID2 or SEQ ID4.

Do you see that?

A. Yes.

Q. That's not limited to only SEQ ID4, is it?

A. Right.

Q. Okay.

You can take that down.

Dix's SEQ ID2 and SEQ ID4 are different fusion proteins. Do you agree with that?

A. They're modifications, yes.

Q. They're different fusion proteins from one another, right, Doctor?

A. There are slight differences in their sequence, yes.

Q. One of them meets the limitations of the '865 patent,

but one of them does not, right?

A. Yes.

Q. It's nevertheless your opinion that when Dix discloses 10 to 50 milligrams per milliliter of the fusion protein, that that discloses 40 mg/mL of a VEGF antagonist fusion protein having amino acids 27 through 457 of SEQ ID4, right?

A. I think it discloses both. I think that disclosure applies to both sequences.

Q. I'm going to turn now to the '865 patent. This is PTX 2, P as in plaintiff.

THE COURT: Thank you, Counsel.

Do you have that, Doctor?

THE WITNESS: I'm sorry. What was that?

BY MR. TRASK:

Q. It's PTX 2, the '865 patent.

THE COURT: It's in the defendants' binder. I think -- yeah, I think you're on the right one, Doctor.

BY MR. TRASK:

Q. Whenever you're ready, Doctor.

A. What is the DTX number?

Q. It's P as in plaintiff, Number 2.

THE COURT: About halfway through, sir.

THE WITNESS: Thank you.

Okay. I have it.

BY MR. TRASK:

Q. You're obviously familiar with this patent, right, Doctor?

A. Yes.

Q. You understand that the '865 patent claims priority to a provisional application filed on June 16, 2006, right?

A. Yes.

Q. And that June 2006 provisional application is listed right on the face of the '865 patent, right?

A. Yes.

Q. If we go to P223, please. Do you see that on the screen, Doctor?

A. Yes.

Q. This is the face of the '865 patent indicating that it claims priority to a provisional application number 60,814,484 filed on June 16, 2006, right?

A. Yes.

Q. Okay.

Can we have P243, please.

Let's look now at Column 1 of the same patent, the asserted '865 patent. This is the cross-reference to related applications section of the '865 patent, Doctor, Column 1 of PTX 2.

A. Okay.

Q. Do you see this document states that the application

is a continued application -- I'll restate that.

This states that the application is a continuation application of a number of applications, including claiming the benefit under 35 USC Section 119(e) of US Provisional Application Number 60,814,484 filed June 16, 2006?

A. Where is that particular sentence?

Q. It's in the left -- it's in Column 1 towards the bottom of PTX 2.

A. Okay. And the '484, is that what you're referring to?

Q. It's the highlighted passage on the screen.

Maybe we can blow that up for the doctor.

Do you see here in Column 1 of the '865 patent it states that it's claiming priority to the provisional application number 60,814,484 filed on June 16, 2006?

A. Yes.

Q. Okay.

We can take that down.

Now, you understand from Mylan's counsel that the earliest priority date to which the '865 patent is entitled is June 16, 2006?

A. Yes.

Q. You didn't separately analyze whether the '865 patent is entitled to its June 16, 2006, priority date, did you?

A. No.

Q. You just took the word of Mylan's counsel on that, right?

A. Yes, because I'm not an attorney.

Q. And that's the date you applied in determining what teachings made up prior art to the asserted '865 patent, right?

A. Correct.

Q. Let's turn now to the Rudge reference. This is D, as in defendants', TX 3592.

A. Okay.

Q. You relied on this reference in your direct testimony, right, Doctor?

A. Yes.

Q. And in your opinion, Rudge is prior art to the '865 patent?

A. Yes.

Q. And that's because, in your view, Rudge was published in 2005, right?

A. Yes.

Q. Okay.

Can we have DDX 4.37, please.

Let's look at this slide from your direct testimony, Doctor.

Do you see Slide 37 with the Rudge reference on it?

A. Yes.

Q. And you're citing it as a 2005 reference, both with

the copyright date at the bottom and the 2005 year at the top, right?

A. Yes.

Q. Now, Rudge -- you've read the Rudge reference, right?

A. Yes.

Q. Do you know that it cites a number of references from 2006?

A. Such as? I see one relating to Heier as an abstract. Is that what you're referring to?

Q. Are you aware that there's a number of references cited in the Rudge paper dated from 2006, Doctor?

A. I see two abstracts which could very well have been announcements of a symposium, looks like ARVO or IOVS, where very often they have -- abstracts are published in advance of the symposium.

Is that what you are referring to?

Q. Let me look at the next slide in your presentation, Slide 38. This is the passage from Rudge that you were relying upon in your direct testimony, right?

A. Yes.

Q. It says, "Initial clinical studies in human patients suffering from both AMD and diabetic macular edema and retinopathy appear quite promising," right?

A. Yes.

Q. Do you know what Rudge cites in support for this

statement?

A. I forgot.

Q. Let's take a look.

Can we have DTX 3592 at the pages 4 and 5, the paragraph spanning those two pages, pages 4 and 5 of the PDF.

This is the passage you were quoting on your slide, correct, Doctor?

A. Yes.

Q. What's cited as support for that statement?

A. 2006 references.

Q. Those weren't available in 2005, were they?

A. Nguyen was available as an abstract in 2006. Shah was also available as an abstract. As I indicated, very often abstracts are published in advance. And so I'm not sure that that's -- what you're saying is correct.

Q. Your view is that these abstracts were published online a year earlier than the date reported in the Rudge paper?

A. We're not talking a year online. It could be a few months. It could be a few months that -- you know, Rudge was published late in 2005 and he had availability to abstracts that were going to appear and had a 2006 publication date. I don't know.

Q. So you believe, Doctor, that these references dated in 2006 were, in fact, available online in 2005?

A. I'm not sure what the situation is. Okay? I'm trying to make sense of what you're presenting me with given the fact that Rudge, obviously, has a publication date of 2005, and I'm trying to make sense of what you're asking me, and I'm trying to come up with a generous -- I'm going out of my way to try to anticipate why there's a 2006 reference in these things. And I'm thinking that the most likely thing is that it refers to an abstract that may have been available online.

Q. May have been online in 2005? Is that your position?

A. Yeah.

Q. And you think that's true of all of the references cited from 2006 in that paper?

A. Well, I haven't read all of the references. I've seen about three of them that all specify abstract. So it makes me wonder if there's something peculiar going on related to abstracts for conferences that were published ahead of a conference. Very often abstracts have to be published ahead of a conference so that the participants will know if there is something of interest to them there.

Q. Let me go back to the doctor's Slide 38, please.

Doctor, you prepared this slide?

A. Yes. It was prepared for me.

Q. Did you review the slide before it was presented to the Court?

A. Yes.

Q. Did you notice that this passage was based upon citations from 2006?

A. No.

Q. You never looked to see what the source of this statement was, right?

A. Right.

MR. TRASK: Can we look at D3592.7.1, please?

THE COURT: Can you give us that number one more time.

MR. TRASK: This is just a callout for the screen.

THE COURT: No, understood, but for our record if you wouldn't mind repeating that.

MR. TRASK: Oh, sure, yes. It's D3592.7.1.

THE COURT: Thank you.

BY MR. TRASK:

Q. Here are two more references cited in the Rudge paper, right, Doctor?

A. Yes.

Q. These are the Mulay and Rixe -- if I'm pronouncing those correctly -- publications. And both of these are cited among the references in the Rudge paper, right?

A. Right. Those are both abstracts, yes.

Q. When you say these are abstracts, it's your view that, even though they say 2006, they were published online in 2005; is that right?

A. I am familiar with -- when I see something that says "Proceedings of the American Society of Clinical Oncology, Abstract" that those look like -- I don't know -- poster presentations that are going to be presented at a conference in 2006, and for that reason they may very well have a 2000 date of publication. But they would be printed well ahead of the conference time so that participants could decide whether or not there was information relevant to their interests ahead of time.

Q. Have you reviewed either the Mulay or the Rixe publication cited in the Rudge paper that you rely on?

A. No.

MR. TRASK: I'm going to pass up a couple of exhibits, Your Honor.

May I pass up the exhibits, Your Honor?

THE COURT: You may.

BY MR. TRASK:

Q. Do you have those exhibits in front of you, Doctor?

A. Yes.

MR. TRASK: For the record, I've handed up to the witness and to the Court the Mulay paper, spelled M-U-L-A-Y. This is PTX 3344. And the Rixe paper -- R-I-X-E -- PTX 3346.

BY MR. TRASK:

Q. Do you have those in front of you, Doctor?

A. Yes.

Q. Can I have PTX 3344, please.

Doctor, you see that in the Mulay paper -- this is a printout of that paper from the internet. It says it was published online on June 20, 2006.

Do you see that?

A. Yes.

Q. Can we also look at the Rixe paper, please.

You see that the Rixe paper as well was published online June 20, 2006?

A. Yes.

Q. Both of those papers were published after the June 16, 2006, priority date of the '865 patent, right?

A. Yes.

THE COURT: I'm sorry. Was that yes, Doctor?

THE WITNESS: Yes.

THE COURT: Thank you.

BY MR. TRASK:

Q. If Rudge was citing papers published after June 16, 2006, then it can't be prior art relative to the '865 patent's provisional application filing date, right?

A. Well, I guess I'm confused. I don't understand why there's a 2005 date ascribed to Rudge.

Q. It's confusing, right?

A. It is confusing.

Q. You don't cite any evidence demonstrating that Rudge

was published prior to June 16, 2006, right?

A. I just have that 2005 date that's on the -- that appears on the face of the article.

Q. If Rudge was, in fact, published after June 16, 2006, then your reliance on it for invalidity of the '865 patent wouldn't be proper, right?

A. I don't know. It depends on the reasons, you know, why that was the case. I mean, as far as this goes -- I mean, it was common knowledge of a POSA that, as early as 2005, around June 2005, intravitreal bevacizumab was administered to patients, and they got that -- this is in Avery.

So it was entirely -- made perfect sense to me that an article around 2005 would contain information that would be demonstrating positive results from VEGF Trap or VEGF antagonists that were administered intravitreally.

Q. Like to turn now to the Liu reference.

THE COURT: Is that a good transition point?

MR. TRASK: Perfect, Your Honor.

THE COURT: Why don't we go ahead and take our afternoon break, then, at this point if we're getting into a different topic.

Again, Doctor, because you're midstream, you can't speak with anyone about your testimony. I just don't want you to think anyone is being rude or discourteous to you if they flee from you during the courtroom or in the hallway.

But we'll take 15 minutes and then resume with cross of Dr. Rabinow. Thank you all.

(A recess was taken from 3:00 p.m. to 3:17 p.m.)

THE COURT: Counsel, if you're ready, you may proceed.

MR. TRASK: Thank you, Your Honor.

BY MR. TRASK:

Q. Let's turn to the Liu reference, Doctor. This is D, as in defendants', TX730. Here's the front cover of the Liu reference, Doctor. Let me know when you're there.

THE COURT: Is that in your binder, Counsel, or is that it --

MR. TRASK: It should be in the binder I handed up. I believe it's in theirs as well.

THE COURT: You said D730?

MR. TRASK: Correct. You know what? I'm wrong. It's not in the binder I handed up because it's in the binder that the doctor had on direct.

THE COURT: It is.

MR. TRASK: Apologies for that.

THE COURT: It will be in the white binder, doctor.

THE WITNESS: Okay.

BY MR. TRASK:

Q. This is one of the references that you mentioned

during your direct testimony?

A. Yes.

Q. Liu doesn't disclose intravitreal administration, does it, Doctor?

A. Liu is silent as to the method of administration, I believe. He's discussing antibody formulations.

Q. Did you say --

A. It's not an efficacy or toxicity paper; it's a formulation paper.

Q. I don't know if I heard that. Did you say Liu is silent as to the route of administration?

A. Yes.

Q. Can we have paragraph 221 from Liu, please.

Doctor, I'm at paragraph 221 of the Liu reference.

THE COURT: What page is that on, Counsel?

MR. TRASK: 29.

THE COURT: Exhibit page 29, correct?

MR. TRASK: Correct. It says .0029 at the bottom.

THE COURT: Understood. Thank you.

BY MR. TRASK:

Q. Doctor, do you see paragraph 221 of the Liu reference?

A. Yes.

Q. Liu is not silent as to the method of administration, is it?

A. Liu mentions a number of methods of administration. Looks like he's trying to cover quite a bit of real estate in terms of administration.

Q. He is covering a lot of real estate, isn't he?

A. Yes, he is.

Q. He mentions -- he or she -- mentions subcutaneous, intravenous -- this is going to test my pronunciation skills -- intraperitoneal, intramuscular, intra-arterial, intralesional, and intraarticular routes.

Do you see that?

A. Yes, I do.

Q. It also mentions topical administration and inhalation or by sustained-release or extended-release means.

Do you see all of that?

A. Yeah, I see all of that.

Q. It's almost everything but the kitchen sink, right, Doctor?

A. Pretty much.

Q. But intravitreal is not listed there, is it, Doctor?

A. No. Nor is the method of administration listed in the claims.

Q. Liu doesn't disclose aflibercept either, does it, Doctor?

A. No, certainly not.

Q. If we look at Slide 55 from your demonstrative deck

this morning, you presented this slide this morning during your direct testimony regarding the disclosure of Liu?

A. Yes.

Q. And you relied on the formulation and data shown in these passages from Liu to check the box for the claim requirement wherein at least 98 percent of the VEGF antagonist is present in native conformation following storage at 5 degrees Celsius for two months as measured by size-exclusion chromatography, right?

A. Yes.

Q. And you reviewed this slide before you presented it to the Court?

A. Yes.

Q. This slide is showing a protein formulation from Example 2 of Liu, right?

A. Yes.

Q. Did you choose whether or not to highlight particular information on this slide?

A. Yes.

Q. You didn't highlight the protein itself in this formulation, right?

A. I highlighted the parts that would enable a viewer in this court to track to what were the claim limitations of the Claim 1 of the patent.

Q. This formulation contains 80 mg/mL of E25.

Do you see that?

A. Yes.

Q. On the top right?

A. Yes.

Q. Do you see that under the word "Formulations"?

A. Yes.

Q. E25 is an antibody, right?

A. Correct.

Q. Antibody is different from a fusion protein, right?

A. No. An antibody comprises roughly 40 percent of aflibercept.

Q. You think this antibody is the same as aflibercept, Doctor?

A. This antibody has an Fc fragment that comprises 40 percent of the molecular weight of aflibercept. From that perspective, antibodies are similar in terms of molecular weights. And as we've seen from the display of half a dozen of antibodies that have been approved, both fusion proteins and non, their stabilization packages, as embodied in their formulations, are remarkably uniform.

Q. Let's look at Liu at PDF page 34. You can zoom in on the text under Example 1.

Do you see this passage from Liu explains what E25 is under the words "Example 1"?

A. Yes.

Q. Do you see E25 is an anti-IgE rhuMAB-E25?
A. Yes.
Q. That's not a VEGF antagonist, is it?
A. No.
Q. And it's not a fusion protein, right?
A. It's an antibody.
Q. Which is not a fusion protein, right?
A. 40 percent of the weight of aflibercept is an antibody. That's why we used antibodies as models for formulations. They're very similar.
Q. E25 is not aflibercept, right?
A. No, but there is a lot of overlap between the Fc fragment contained in E25 and the aflibercept molecule.
Q. If we go back to the doctor's slide, please.
Now, you highlighted stability data for the E25 antibody, right?
A. Yes.
Q. There's no stability data on this slide for aflibercept?
A. Correct.
Q. And there's no stability data on this slide for a VEGF antagonist, right?
A. Correct.
Q. You nevertheless checked the box for at least 98 percent of the VEGF antagonist being present in native

conformation, right?

A. As I explained in my expert reports, both of them, we used antibodies as models for aflibercept because 40 percent of the weight of aflibercept is comprised of the Fc fraction of a typical antibody.

So it's a good model, and as if that weren't enough, we see from half a dozen of the approved antibodies, whether fusion proteins or not, that they all involve buffers, surfactants, and stabilizing sugars. And within each of those categories, only two different choices are necessary to stabilize them. And as a result, these are all approved, which means that they all have SEC information that shows that they're stable as well as turbidity.

So this is common, common, to all proteins, certainly to all antibodies, including the antibody representation in aflibercept.

Q. Doctor, I'll ask the question again.

There's no stability data here for aflibercept, right?

A. No.

Q. You agree that different proteins have different propensities for aggregation, right?

A. That statement covers a lot of real estate in terms of the propensity for degradation.

Q. Do you agree, Doctor, that different proteins have

different propensities for aggregation?

A. Yes.

MR. HUNT: Your Honor, this is outside the scope of the direct. We didn't have any discussion of protein aggregation.

THE COURT: Where are we in the scheme of things, Counsel, in terms of being related to the direct?

MR. TRASK: Sure. This was a slide shown on direct. The doctor checked the box for the claim limitation about native conformation, which is a measure of aggregation. And so I'm trying to establish that the data that the doctor pointed to here is not aggregation data for the VEGF antagonist in the claims.

THE COURT: Understood. Overruled.

BY MR. TRASK:

Q. I'm not sure if I got an answer to that question, Doctor. You agree that different proteins have different propensities for aggregation, right?

A. Yes.

Q. Just because one protein has a given native conformation at a specific condition, the person of ordinary skill wouldn't expect that a different protein will have the same native conformation at that condition, right?

A. Correct.

Q. I'd like now to turn to the Lam reference. This is

D -- defendants' -- TX 3556. This one too is in defendants' binder, the direct binder.

Doctor, do you see the Lam application shown on the screen?

A. I do.

Q. You discussed this paper in your direct testimony?

A. Yes.

Q. You're relying on this publication for purposes of your opinions?

A. Yes.

Q. This is a patent about antibody formulations, right?

A. Yes.

Q. I think we've established this, but aflibercept is not an antibody, correct?

A. No. What I said was that 40 percent of the weight of aflibercept matched the Fc part of an antibody, that there is a very high degree of identicality of an antibody with aflibercept.

It is for that reason that we consulted the antibody formulation literature, particularly that of Genentech, which develops and approves these molecules as models for what to expect from aflibercept.

Q. It's a simple question, Doctor. Is aflibercept an antibody?

A. It has a very high resemblance to an antibody. It

looks like an antibody. If you look at the diagram of what aflibercept was that Dr. Yancopoulos presented, it showed a wide receiver with two arms and a rather solid trunk standing up there and taking up a large amount of real estate inside of an airplane and being able to hold a football on two sides. It's a Y shape. That is what an antibody is.

Q. I'll ask the question again, Doctor. It's a simple one, I think.

Is aflibercept an antibody?

A. Yes. Absolutely.

Q. Do you know if Lam describes routes of administration?

A. I don't know.

Q. Take a look at D3556.39.1, please.

I'm on page 39 of the Lam reference, looking at the screen here. Do you see the section called administration of the formulation?

A. Yes.

Q. Were you aware that this passage existed in the Lam reference?

A. I think I read over it, and I saw that he was trying to cover a lot of administration real estate, in fact, all of the known methods of administration.

Turns out that intravitreal was rather recent compared to when this patent came out, and for that reason it

didn't make it into his list.

Q. Pretty long list here, right, Doctor?

A. It's a pretty long list, but he did not anticipate intravitreal because it is, in fact, prior art.

Q. Prior art wouldn't have anticipated intravitreal administration, right?

A. I think very few people at that time would have.

Q. If we turn to the doctor's slide Number 17, please.

Doctor, you helped prepare this slide?

A. Yes.

Q. This is a slide showing disclosure from the Lam reference we just looked at, right?

A. Yes.

Q. And you reproduced some information here from the Lam reference about the rhuMAB-CD20 antibody, right?

A. Yes.

Q. That's not aflibercept, right?

A. Correct.

Q. Now, you highlighted some of the ingredients of this formulation in the text on the right of your slide, correct?

A. Yes.

Q. You did that highlighting?

A. I worked with the presentation people who highlighted that to indicate what are the areas that would enable us to compare to the claim elements of the '865.

Q. I noticed you didn't highlight 0.9 percent benzyl alcohol. That's listed as one of the ingredients in this formulation you're relying on, right?

A. Correct.

Q. Do you think it's a good idea to inject 0.9 percent benzyl alcohol into the eye, Doctor?

A. This Lam is not -- I didn't choose this reference as a model for what to administer to the eye. I chose this reference as what kind of an antibody and associated formulation elements would provide knowledge to the POSA about stability. So there's a linkage between formulation antibody on the one hand and stability on the other.

The formulation element -- benzyl alcohol is an antimicrobial agent, and we would not -- I'm not looking to this as a model, for example, for what to administer to the eye. I'm looking at it as a model for what to expect for stability from this kind of a API.

Q. You agree that this formulation is not a good idea to administer to the eye intravitreally, right?

A. I wasn't proposing it for that.

Q. Do you agree with me?

A. I don't understand the question. I was using this as an indicator of what to expect for stability from an antibody. It had nothing to do with administration to the eye; so I'm not sure why you're bringing that up.

Q. Doctor, do you have an opinion on whether the formulation shown here in Lam is a good idea to administer to the eye intravitreally?

A. I'm not sure about benzyl alcohol. I'd probably have a question about that, but that's not why I brought this data up, and it does not affect the conclusions that I drew.

Q. You'd defer to an ophthalmologist about whether or not to inject a given substance into the eye?

A. Yes.

Q. And you'd consult with an ophthalmologist about whether it's a good idea to inject benzyl alcohol into the vitreous, right?

A. I would defer to an ophthalmologist's opinion.

Q. You haven't spoken with an ophthalmologist to inform your opinions in this case, right?

A. I didn't have to because that's not what I'm using this information for. I'm not suggesting that this be injected in someone's eye.

Q. Doctor, you haven't spoken with an ophthalmologist to inform your opinions in this case, right?

A. That is correct.

Q. Okay.

I'd like to turn now to the doctor's Slide 47, please.

Doctor, you prepared this slide -- or -- with the

assistance of counsel?

A. Yes.

Q. When you presented this slide to the Court, I heard you say many of these are fusion proteins. Do you stand by that testimony?

A. There's a number of them that are fusion proteins, yes.

Q. Which ones of these are fusion proteins?

A. Lucentis, Avastin. I can't remember. I looked them up, and I saw that there was at least one other one. There's a number of these that are humanized mouse antibodies. So in that sense, they're fusion proteins that are man-made.

Q. Doctor, Lucentis is described on this slide as being an antibody. Do you see that under "Active Ingredient"?

A. Yes.

Q. Avastin is described on this slide as being an antibody. Do you see that?

A. Yes.

Q. Every single one of the drugs on this slide is described as being an antibody, right?

A. Yes.

Q. They're not described in this slide as being a fusion protein, are they?

A. An antibody is what the -- is how they are described in the prescribing information.

Q. Okay.

You can take that down.

Let's turn to Avery. This is Defendants' Exhibit 2264.

Can we put this up, please. Thank you.

Do you see the Avery reference, Doctor?

A. Yes.

Q. I want to ask you about the date of this reference. You see it's dated March 2006?

A. Yes.

Q. The paper doesn't indicate when in 2006 -- when in March of 2006 this reference was publicly available, right?

A. Not on this.

Q. You understand that Regeneron's position in this case is that the inventors of the '865 patent conceived of their invention no later than March 21, 2006?

A. I think I read that in Dr. Trout's report.

Q. If the Court accepts that March 21, 2006, date as the invention date for the '865 patent, then references can qualify as prior art only if they predate March 21, 2006, right?

A. There's no information in the evidence that was purported to demonstrate that Regeneron could swear behind the June 16th, 2006, date to get that earlier date. There was no information. There were empty protocols, and there was no data there. So that was a -- that was a red herring.

Q. Doctor, let me ask the question again.

If the Court accepts a March 21, 2006, invention date for the '865 patent, then references qualify as prior art to the '865 patent only if they were publicly available prior to March 21, 2006, right?

A. I'm not a patent attorney; so I can't answer that.

Q. You haven't seen any evidence in this case about when this Avery reference was published in March, right?

A. I looked up the -- I googled "ophthalmology journal" and looked and convinced myself that it was -- that Avery was listed in March of 2006, and that was adequate for me to feel comfortable with the publication date for this.

Q. You don't know when in March 2006 Avery was published, right, Doctor?

A. That is correct.

Q. Doctor, in your opinion, the ability to optimize a protein formulation was a skill possessed by the person of ordinary skill as of 2006, right?

A. Yes.

Q. And as of 2006, in your opinion, optimizing the stability of a protein formulation was routine for the POSA?

A. Yes.

Q. If a POSA were designing a suitable intravitreal formulation of a protein drug, it would be helpful to know a suitable concentration at which the protein has a low

aggregation tendency?

A. A POSA would determine that by routine experimentation. You can't know this ahead of time.

Q. If the POSA were informed of the concentration at which the protein had a low propensity for aggregation, then less experimentation would be required of the POSA, right?

A. Perhaps.

Q. You agree that pH has a strong influence on a protein's aggregation rate?

A. It could.

Q. It would be helpful for the POSA to know the pH range at which the protein drug has a low tendency to aggregate, right?

A. It would be nice but not essential because those experiments are relatively easy to run and would require on the order of several weeks. So I wouldn't say it's a major benefit to have that information because this is routinely done by the protein development chemist.

Q. By 2006, many analytical assays were known to the POSA for assessing the physical stability of protein formulations?

A. Yes.

Q. Size-exclusion chromatography was known to the POSA before 2006?

A. Yes.

Q. It was a routine technique at that time?
A. Yes.
Q. The POSA could develop a size-exclusion chromatography method without undue experimentation?
A. Yes.
Q. And size-exclusion chromatography was commonly used by the POSA to analyze the physical stability of protein formulations?
A. Yes.
Q. I want to run through several analytical techniques, and I'll try not to belabor this.

Reverse-phase liquid chromatography was a routine technique as of 2006?
A. Yes.
Q. The POSA could have developed one of those methods readily?
A. Yes.
Q. Hydrophobic interaction chromatography was a routine technique as of 2006?
A. Yes.

MR. HUNT: Your Honor, my apologies. Size-exclusion chromatography is set forth in the '865 patent. We're getting outside the scope of the direct here. We didn't have any direct testimony regarding the various analytical methods beyond what's disclosed and required by the claims of the '865

patent.

THE COURT: Understood.

Counsel?

MR. TRASK: If I may, Your Honor, there's one more that's directly discussed in the patent and certainly relevant to the data we've seen, and then I'll move on.

THE COURT: All right. Understood.

BY MR. TRASK:

Q. Laser light scattering analysis was a routine technique as of 2006?

A. Yes.

Q. And the POSA would have developed one of those techniques as of 2006 without undue experimentation?

A. Yes.

Q. Now, do you recall if any of the publications that we've discussed today set forth the order of addition of the formulation ingredients for making the formulation?

A. I don't recall that.

Q. Could the POSA have determined an appropriate order of addition to make the formulations falling within the scope of the '865 patent?

A. Yes.

Q. The work required to determine an appropriate order of addition would have been routine experimentation?

A. Yes.

Q. And it wouldn't require undue experimentation to make formulations falling within the scope of the asserted claims, right?

A. Correct.

Q. If a prior art reference disclosed the ingredients of a formulation but didn't provide the mixing rate to use when mixing those ingredients together to make a formulation, the POSA could have optimized the mixing rate?

A. Yes.

Q. And that work would not have involved undue experimentation?

A. No.

Q. Let's move to the topic of tonicity, Doctor.

The term "hypertonic" means that the formulation has a greater concentration of dissolved molecules than would be in equilibrium with living cells?

A. Yes.

Q. And the term "isotonic" means that the formulation has an equal concentration of dissolved molecules as compared to living cells?

A. Yes.

Q. Hypertonic and isotonic formulations are not the same, right?

A. Correct.

Q. And you agree that isotonic and iso-osmolar have

roughly the same meaning?

A. Yes.

Q. You agree that osmolality considerations would not motivate the POSA to develop an isotonic formulation for intravitreal injection?

A. Could you repeat that.

Q. You agree that osmolality considerations would not motivate the POSA, the person of ordinary skill in the art, to develop an isotonic formulation for intravitreal injection?

A. Well, I just testified here today that they would. I testified that iso-osmotic conditions were clearly indicated by two different references appropriate for intravitreal administration.

Q. Doctor, osmolality is a consideration but wouldn't motivate the POSA to develop an iso-osmotic formulation for intravitreal administration, right?

A. It's a strong consideration that he would take into consideration.

Q. But it wouldn't motivate the POSA to develop an iso-osmotic formulation, right?

A. I'm not sure I detect the thrust of what you're asking.

Q. Okay.

Let's go to the doctor's transcript at page 139, line 11 through line 16.

Doctor, I asked you the question, "Okay. I think the upshot of that is that osmolality is a consideration but wouldn't motivate the POSA to develop an iso-osmotic formulation for intravitreal administration" --

A. This was taken way out of context. You -- you had presented --

Q. Doctor --

THE COURT: Gentlemen -- gentlemen, one at a time.

Ask your question again, Counsel.

MR. TRASK: I was just reading from the transcript and the doctor cut me off. If I could finish.

THE COURT: That's why I said one at a time. Repeat, then we'll go from there.

MR. TRASK: Okay. Thank you, Your Honor.

BY MR. TRASK:

Q. I'll start from the beginning, Doctor. I want to read through this short snippet of testimony, and then I'd like you to confirm that I've read it correctly. Okay?

A. Yes.

"Q Okay. I think the upshot of that is that osmolality is a consideration but wouldn't motivate the POSA to develop an iso-osmotic formulation for intravitreal administration.

"A Apparently not."

Did I read that correctly?

A. Yes.

Q. We'll take that down.

The POSA would view a hypertonic formulation as suitable for intravitreal administration, right, based on the literature?

A. Would view a hypertonic solution? No. I wouldn't agree with that.

Q. Okay.

Can we put up the doctor's transcript at 136, line 19, through 137, line 2.

Doctor, at your deposition I asked:

"Q And when you say he wouldn't find it strange, you mean the POSA would view a hypertonic formulation as suitable for intravitreal administration, right, based on the literature?

"A Yes."

Did I read that correctly?

A. You read it correctly. This was taken out of context. You had shown me a document purportedly for an intravitreal dosage form that was at an extraordinarily high osmolarity. And I wasn't sure where this came from, and I was trying to think through the issues.

And I recall that it was said at some places that the eye is remarkably tolerant to hyperosmolar situations, but that

doesn't mean that one should take liberties to intentionally develop a hyperosmolar solution based upon that. One should always err on the side of being conservative.

Q. So your position, Doctor, is that you wouldn't administer a formulation that is too high in terms of its hypertonicity, right?

A. Certainly.

Q. So something over 850 milliosmoles would not be a good idea to inject intravitreally, right?

A. Right. And that doesn't mean that I would find it acceptable to administer something under that but well above what is normally considered iso-osmotic.

Q. So your testimony is that you could administer something that's hypertonic, not isotonic, but not something that's too high in terms of its hypertonicity, right?

A. The line of questions that you had put me through --

THE COURT: Doctor, that's what redirect examination is for. If you could just answer counsel's question.

THE WITNESS: Okay.

Repeat, please.

BY MR. TRASK:

Q. Your testimony is that it wouldn't be a good idea to inject a formulation that is too high in terms of its hypertonicity, but something that is somewhat hypertonic would be okay to administer?

A. No.

Q. Doctor, is it your position that something 850 milliosmoles or higher would be a good idea to administer intravitreally?

A. No.

Q. But you said remarkably -- that the eye is remarkably tolerant to hypertonic solutions, right?

A. Yes, but one should exercise a good degree of caution and not -- and be extremely conservative with designing a dosage form that is designed to go into the eye. Just because the eye may be tolerant in some individuals is no reason to try to seek approval for something that could very well be injurious to some fraction of the patient population.

Q. So you agree, then, Doctor, that something that is just slightly outside the range of isotonicity would be okay to administer intravitreally, but you wouldn't want to administer something as high as 850 milliosmoles, right?

A. I didn't say that.

Q. The eye is remarkably tolerant to hypertonic formulations, right?

A. There's a difference between asking the question -- what would happen if I injected something into somebody's eyeball that had a tonicity of 600 milliosmoles? What would happen to that person? That's one question.

Another question is should I go out and intentionally

develop a drug that is going to be administered to potentially millions of people with that degree of osmolarity? There's a difference there. There's a risk-benefit equation that your question does not recognize.

Q. Doctor, my question was simpler.

The eye is remarkably tolerant to hypertonic solutions, correct?

A. Yes. I said that.

Q. Let's turn to the Saishin reference. This is Defendants' Exhibit 2751. I believe this is one in both binders.

Can you put up 2751, please.

Doctor, you've relied on the Saishin reference during your direct testimony?

A. Yes.

Q. And you said it provided a motivation to administer VEGF Trap intravitreally, right?

A. Yes.

Q. Saishin was a study in mice, right?

A. Yes.

Q. And it involved administration of VEGF Trap?

A. Yes.

Q. And the authors were comparing two routes of administration for the VEGF Trap, subcutaneous and intravitreal, right?

A. Yes.

Q. Let's look at your Slide 58, please.

Now, you pointed to each one of these passages in support of your motivation to combine, right?

A. Yes.

Q. And your view is that these passages recommend to the POSA to administer VEGF Trap intravitreally?

A. Yes.

Q. Let's look at the broader context for these passages.

So the first passage, I want to show the full paragraph.

So you see the passage at the bottom in purple is the one you quoted on your slide, right?

A. Let me read this entire passage.

Yes.

Q. This is the full paragraph containing the passage that you included on your slide, correct?

A. I don't know. I forgot what it was, but I'll take your word for it.

Q. Have you not looked at this passage recently, Doctor?

A. I have not looked at it recently, correct.

Q. You see that the passage refers throughout to systemic administration of VEGF Trap, right?

I've highlighted in yellow the words "systemic," "circulating," and "subcutaneous." Do you see that?

A. I see that the statement "local administration of VEGF Trap R1R2 by intravitreous injection is a viable alternative. A single intravitreous injection of VEGF Trap R1R2 markedly suppressed the development of choroidal neovascularization over the course of two weeks."

That's what I see.

Q. Doctor, I'm asking you about the first passage on your slide. We'll get to the other one that you just read.

Do you see there's three passages on your slide on the right?

A. Yes.

Q. I'm asking you about the one at the top. Okay?

A. Okay.

Q. Do you see that that passage is part of the larger paragraph shown on the left side of this slide from Saishin, page 7?

A. Okay.

Q. Do you see that the broader paragraph refers to systemic, circulating, and subcutaneous injection?

A. Yes.

Q. And so when -- the passage you quoted that says "these data suggest" and goes on to discuss VEGF Trap, it's talking about systemic administration, correct?

A. It's recommending both.

Q. That passage right there is referring to systemic

administration. That's subcutaneous administration, right?

A. Well, authors typically will make a case for one route of administration. New paragraph. They will then make the case for the second route of administration. This is the first paragraph.

Q. It's your testimony, Doctor, that the concluding paragraph -- the concluding sentence of that paragraph is referring to intravitreal administration even though the entire paragraph is talking about subcutaneous administration?

A. I'm not sure what preceded this paragraph, and I'm not sure what was directly after this paragraph.

Q. Let's look at the second passage that you quoted, Doctor.

You see what I've done here is the same thing as I did on the last slide, but now we're looking at the second quoted passage from your slide? And I've shown the broader paragraph in which that passage appears from page 7 of Saishin.

Do you see that?

A. Yes.

Q. Do you see it says, "The effects of long-term systemic inhibition of VEGF are unknown. While there are theoretical reasons why it could be problematic, VEGF inhibitors have been tested as adjuncts to chemotherapy in cancer trials, and there have not been reports of severe problems clearly linked to blockade of VEGF. Should systemic

inhibition of VEGF prove problematic, there's an alternative."

And then it goes on to discuss intravitreal, right?

A. Yes.

Q. This passage, the passage you quoted, is described as an alternative to systemic subcutaneous administration should systemic inhibition of VEGF prove problematic, right?

A. And your point is?

THE COURT: Doctor?

THE WITNESS: Yes.

THE COURT: Please just answer the question.

THE WITNESS: I'm sorry.

THE COURT: Thank you.

BY MR. TRASK:

Q. Do you agree or disagree with that, Doctor?

A. I agree with what you said.

Q. Let's look at the third passage you quoted on your slide.

You see here this is discussing recommendations pertaining to subcutaneous administration and recommendations pertaining to local delivery. That's intravitreal administration, right?

A. Yes.

Q. And what the authors are recommending here in this paragraph is for subcutaneous administration to move into clinical trials. That's trials in humans, right?

A. Yes.
Q. That's a big step, right, from mice?
A. A big step from mice, yes.
Q. For intravitreal administration, the passage you quoted, the authors merely say that additional preclinical studies are recommended, right?
A. Yes.
Q. Preclinical studies are studies in animals?
A. Yes. Well, that makes sense.
Q. Okay.

We can take that down.

Let's look at the Ferrara 2006 publication, PTX -- Plaintiff's Exhibit 701.

You see the Ferrara paper, Doctor?

A. Yes.
Q. Now, this is a 2006 publication; is that right?
A. Yes.
Q. Now, we've referred today, and you've referred, to two other publications. The Saishin publication that we just looked at, right?
A. Yes.
Q. And Avery publication that you mentioned, right?
A. Yes.
Q. Do you know whether Ferrara was published before or after those publications?

A. I don't know.

Q. Let's look at --

Can I have Reference 114 in the Ferrara paper, please.

Do you see the Ferrara authors are citing the Avery paper, right?

This is page 12 of Exhibit 701.

A. Okay.

Q. And there's a citation to the Avery paper that you've mentioned several times today, right?

A. Okay.

Q. Ferrara came after Avery, right?

A. I guess, yes.

Q. It had to have because it cited the Avery paper, right?

A. Yes.

Q. Do you know if the Ferrara authors discussed the Avery paper?

A. I don't recall.

Q. Did you read the Ferrara paper in full, Doctor?

A. I did, but this was quite some time ago.

Q. Let's turn to the discussion in Ferrara of the Avery paper.

Now, do you see here I've highlighted a sentence that ends in Reference 114. You'll recall that Reference 114 is the

Avery paper, right?

A. Okay.

Q. We just looked at that.

And what Ferrara says about the Avery paper -- report, it says, "This case report attracted much interest and prompted a more recent, larger, uncontrolled open-label series of 79 subjects with neovascular AMD and 4- to 15-week follow-ups during which improvements in nonstandardized visual acuity measurements and in retinal anatomy, as assessed by optimal coherence tomography and fundus fluorescence angiography, were observed without associated inflammation or other significant safety issues."

Do you see that?

A. Yes.

Q. And then it goes on. That's the Avery paper, right, that you discussed?

A. Yes.

Q. And it goes on to say, "Although intriguing, these early findings are difficult to compare with data from rigorous double-masked controlled Phase III trials of verteporfin photodynamic therapy, pemigatinib, and more recently ranibizumab."

Do you see that?

A. Yes.

Q. It's saying that "The Avery results are preliminary

and difficult to compare with more rigorous studies," right?

A. That's what it says.

Q. And then it goes on at the bottom of this passage on page 6 to say, "It's also noteworthy that early clinical studies with" -- some of those other drugs -- "suggested a considerably greater benefit in AMD patients than that eventually demonstrated in Phase III studies, further emphasizing the difficulty of interpreting early clinical results."

Do you see that?

A. Yes.

Q. So Ferrara explained that the results from Avery were intriguing but difficult to compare with more rigorous studies, right?

A. That's what he said.

Q. And he said that earlier drugs suggested a considerably greater benefit than eventually panned out in later studies, right?

A. That's what he said.

Q. Now, you're aware that Ferrara cites Saishin as well?

A. Correct.

Q. Let's look at that passage.

Here's Ferrara's discussion of the Saishin paper on which you rely. Saishin is Reference 80 on page 11, and the discussion of Saishin is at page 4.

Do you see that on the screen?

A. Yes.

Q. Ferrara's understanding after reviewing the Saishin paper was different than yours, right?

A. Yes.

Q. Ferrara and the coauthors of that paper concluded that "Interestingly, these studies show that systemic administration" -- that's subcutaneous administration, right?

A. Yes.

Q. -- "of the VEGF Trap inhibits neovascularization by about 75 percent; however, intravitreal administration of the same agent resulted in about 25 percent inhibition."

Did I get that right?

A. You did, but he didn't mention anything about the difference in dosing.

Q. He also goes on to describe that "The limited efficacy observed in the intravitreal administration may be due at least in part to the existence of a barrier to the transretinal penetration of large molecules, such as the VEGF Trap."

Did I get that right?

A. You got that right.

Q. Now, the Ferrara paper that we're looking at was published in the journal *Retina*, correct?

A. Yes.

Q. That's a peer-reviewed scientific journal?
A. Yes.
Q. The Ferrara authors were all from the biotech company Genentech?
A. Yes.
Q. In 2006 Genentech was a large, well-established biotech company, right?
A. Yes.
Q. Perhaps the most successful biotech company in history at that time, correct?
A. Correct.
Q. As of 2006 Genentech itself had a VEGF antagonist on the mark, right?
A. Yes.
Q. And they had another one in clinical trials, right?
A. Yes.
Q. Dr. Ferrara, the author of this paper, is credited as the discoverer of VEGF, right?
A. Yes.
Q. He invented the molecules in both Avastin and Lucentis, right?
A. Yes.
Q. You don't know him personally, do you?
A. No.
Q. You've never met him?

A. No.

Q. Were you aware before I told you at your deposition that Dr. Ferrara is a member of the National Academy of Sciences?

A. No.

Q. You agree that the National Academy is considered one of the highest honors that can be accorded to a scientist?

A. Yes.

Q. Were you aware before I told you at your deposition that Dr. Ferrara is the winner of the Lasker Award?

A. Yes.

Q. You were aware of that?

A. No, I was not aware of that.

Q. Are you familiar with the Lasker Award?

A. I am aware that it is a prestigious honor.

Q. It's sometimes referred to as America's Nobel Prize, right?

A. I suppose.

Q. That's because 86 Lasker Award recipients have gone on to win the Nobel prize, right? Does that sound right to you?

A. I suppose. I haven't studied that statistically to see the correlation.

Q. Can we have PTX 3345, please.

Were you aware of this New York Times article

reporting on Dr. Ferrara's receipt of the Lasker Award?

A. No.

Q. You can take that down.

In your opinion, Doctor, Dr. Ferrara was really scared of the upstart company Regeneron, right?

A. I believe it is reasonable to expect that Dr. Ferrara reflected the strong concern of Genentech for VEGF Trap R1R2 and even for the use of their own bevacizumab in place of ranibizumab and, in fact, refused to even contribute to the development of bevacizumab trials with Rosenfeld's work.

So there is, obviously, a concern that any competitive threat to ranibizumab should be squashed based upon what we learned from how Genentech dealt with Rosenfeld's request for funds.

Q. Doctor, in your view, Dr. Ferrara, the discoverer of VEGF and the inventor of Avastin and Lucentis, was really scared of the upstart company Regeneron, correct?

A. I didn't say that. I said that very often --

Q. Can we look at your deposition transcript, Doctor?

THE COURT: Let's let the doctor finish his answer first.

BY MR. TRASK:

Q. I'm sorry. Go ahead, Doctor.

A. I'm sorry. Very often employees of a company will reflect the corporate stance. These people receive stock

options and, you know, continued employment and other perks as well. It's reasonable to expect that there would be a desire to reflect the corporate position. That's completely different from saying the man is a brilliant scientist.

Q. Page 317, line 12, through 318, line 1, of the doctor's transcript.

"Q And you think they" -- "they" meaning Ferrara -- "misinterpreted Saishin?

"A I think Ferrara had a completely understandable bias. He's working for Genentech, right? He's got a franchise to maintain. He's really scared of that upstart Regeneron company. He's coming in, and they're going to blow them away with a better dosage form. So, yeah, he's going to do what he needs to do to keep his management happy and publish articles that are disparaging the competition."

Did I read that right?

A. You did.

Q. You think it's reasonable to suspect that, because Dr. Ferrara and his coauthors were Genentech employees, they're rendering opinions in a peer-reviewed scientific article that might be contrary to the science, right?

A. Dr. Ferrara's articles have been critically evaluated by Avery, and there were numerous methodological issues that

were raised against his findings that large molecules could not penetrate the retina.

He used an extraordinarily small amount of VEGF -- of HER2, the antibody that he used that was the large molecular antibody in his competition trials. This is a more -- a study where the lead author was Mordente. It was in, I think, 1989.

And what they found there was that there was no penetration from the human epidermal growth factor protein, which was on the order of about 150,000 daltons, whereas the smaller molecules were able to migrate through.

It has been since shown that the amount that he used, 25 micrograms, was too small and that you can overcome the barrier to migration in the retina if you use a sufficiently high concentration of antibodies.

So it was shown in 2004 that, if you use on the order of 1 to two milligrams of immunoglobulin G, you are able to penetrate the -- to the retina.

It was also found that Ferrara, when he did his experiment, did not use the most permeable part of the retina, which was the fovea, and instead he used the peripheral parts of the retina, in which the internal limiting membrane, the ILM, was the thickest.

If he had gone to the fovea, he would have encountered a much thinner part that would have posed much less of a barrier to large molecules.

In addition, the inner plexiform layer is missing in the fovea as well. So the experiment was poorly designed.

MR. TRASK: Your Honor, I'd like to respectfully move to strike that testimony. It wasn't responsive at all to my question and discussed a number of references and concepts that were nowhere in his direct examination.

THE WITNESS: I -- I'm sorry, Your Honor.

THE COURT: That's a request for me.

Overruled.

MR. TRASK: Let's turn now -- getting towards the end, Your Honor -- to the Gaudreault reference. This is Plaintiff's Exhibit 1839. This one I believe is in both binders.

THE COURT: You said 1839, Counsel?

MR. TRASK: That's correct, Your Honor.

BY MR. TRASK:

Q. Doctor, do you see the Gaudreault reference on the screen?

A. I do.

Q. This too was published by Genentech scientists, right?

A. Yes.

Q. And it was published in the journal *Investigative Ophthalmology and Visual Science*?

A. Yes.

Q. That's a reputable peer-reviewed journal?
A. Yes.
Q. Gaudreault studied the effects of ranibizumab dosed both intravenously and intravitreally in monkeys, right?
A. Yes.
Q. And Gaudreault reported that penetration of ranibizumab into the retina following intravitreal administration is critical for its clinical use, right?
A. That's what he said.
Q. The authors also reported that retinal penetration suggests the availability of ranibizumab to inactivate VEGF at the site of AMD, right?
A. That's what he wrote.
Q. Now, you disagree with that statement, right?
A. Yes.
Q. You think the Gaudreault authors overinterpreted the data, right?
A. There were several schools of thought. This was unsettled science at the time that all these publications were out. There was a faction that you are referring to where it was believed or at least promulgated that large molecules have a problem in penetrating the barrier to the retina. There were others who had done studies with rabbits, other animals, and had found that, no, we are able to see that we do get penetration.

So it was very unsettled at the time.

Q. Doctor, I asked if you think Gaudreault overinterpreted the data. Yes or no.

A. He had a point of view. He may have overinterpreted the data, I suppose, yes.

Q. Let's turn to the Ghate reference. This is Plaintiff's Exhibit 1576. It's in plaintiff's binder.

You referenced this paper during your direct, Doctor?

A. Yes.

Q. These authors are not Genentech scientists, right?

A. Correct.

Q. They're from the Emery University Eye Center?

A. Yes.

Q. In Atlanta, right?

A. Yes.

Q. No connection to Genentech that you're aware of?

A. They may have consulted for them. I don't know.

Q. You do not know one way or the other, right?

A. No.

Q. Let's look at page 281.

THE COURT: Counsel, yes?

MR. HUNT: Apologies, Your Honor. I need to object to this. I don't recall going through the Ghate reference with the good doctor on direct.

MR. TRASK: I believe that the doctor addressed it.

But even if I'm wrong about that, Your Honor, this goes directly to the doctor's credibility in refuting well-established science from individuals with a high degree of expertise across the nation, both at Genentech and elsewhere.

THE COURT: Overruled. If it's a credibility question, let's get to it, then.

MR. TRASK: Sure.

BY MR. TRASK:

Q. Let's look at page 281. There we are.

Do you see the authors here are discussing intravitreal injection?

A. Yes.

Q. And they say it's the most invasive route with the most serious complications, right?

A. Yes.

Q. And then let's look a little further down the page.

The authors here say that "The internal limiting membrane" -- that's the membrane in the eye that separates the vitreous from the retina -- "is impermeable to linear molecules greater than 40 kilodalton and globular molecules greater than 70 kilodalton; thus larger macromolecules will have a larger retention time, possibly weeks, but their effect on the retina after an intravitreal injection is limited."

Do you see that?

A. That's what it says.

Q. You don't agree with that statement in this peer-reviewed literature, do you?

A. As I indicated, there were two schools of thought, one that large molecules cannot penetrate, and there was an alternative school that said they do penetrate. And it was also unambiguous at the time that humans with AMD were getting better after receiving intravitreal injections of bevacizumab as early as mid-2005.

So that would be the relevant consideration as opposed to theoretical discussions about mouse, monkey, rat, and rabbit studies, the fact that this was actually being administered, bevacizumab was actually administered to humans as early as mid-2005. And then others started taking this up and repeating it, and they too were finding excellent clinical results.

So proof of concept for large molecules, curing or certainly delaying and improving the status of AMD patients with neovascularization issues was undisputed at that time. So I'm not sure I see the relevance.

THE COURT: Doctor, you were asked whether or not you agreed with the statement. You've now described two camps. Please answer the question. Do you agree with it or not?

THE WITNESS: No.

THE COURT: Thank you. The determination of whether questions are relevant or not is up to me. I understand and

appreciate your thoughts, but I'll handle any objections. Thank you.

Next question, Counsel.

BY MR. TRASK:

Q. Yes. Doctor, in your opinion the person of ordinary skill in the art would believe it's not necessary for a large VEGF antagonist molecule to enter the retina in order to exert its therapeutic effect, right?

A. There is a school of thought that believed that, yes.

Q. That's your opinion, right, doctor?

A. That was my opinion, and I've subsequently found that there are others who also expressed that.

Q. Subsequently to your deposition?

A. Yes.

Q. Now, in your view, Doctor, the mechanism of action for aflibercept is that the VEGF molecules are reacting with the aflibercept in the vitreous so that the aflibercept molecules never enter the retina, right?

A. I stated in my deposition that that was one alternative explanation for what was going on, yes.

Q. Doctor, you said it's the mechanism of action, didn't you, in your report?

A. No. I said that there were two possibilities. I said that either aflibercept was, in fact, penetrating through because in view of the contrasting experimental results from

different animal studies; so that was possible. And if it was not the fact that they couldn't penetrate through, I could envision an alternative explanation, which I proceeded to give you.

Q. Can we put up the doctor's report at paragraph 105, please.

Doctor, do you see here's a copy of your reply report. And in the highlighted passage in paragraph 105, you said, "The mechanism of action being that the VEGF molecules are reacting with VEGF Trap R1R2 in the vitreous humor and the VEGF Trap R1R2 would never enter the retina."

Do you see that?

A. I did say that. That's true, yes.

Q. Take that down.

In your view, Doctor, the person of ordinary skill in the art would believe that the VEGF antagonist would remain in the vitreous and suck the VEGF out of the retinal compartment, right?

A. Yes.

Q. In your view, annihilation of the VEGF by the VEGF antagonist, you're essentially having a vacuum cleaner sucking all out of the VEGF out of the retinal compartment, right?

A. That's what I said in my deposition, correct.

Q. That's what you testified was the mechanism of action of aflibercept?

A. I said that was one of the two possibilities. I had said -- when you asked me that, I said that was an alternative explanation, but I said it was also possible that aflibercept, in fact, did penetrate the retina, which we now understand to be, in fact, the case.

Now -- no, I'm sorry. I'm going to stop because you didn't ask me anything else.

Q. Doctor, you don't know anything about the rate at which VEGF is secreted from the eye, do you?

A. No.

Q. You don't know whether the rate that VEGF is produced in the retina is faster or slower than the rate at which it diffuses into the vitreous, right?

A. No.

Q. You're not an expert in the anatomy or physiology of the human eye?

A. No.

Q. You're not an expert in the anatomy of the human retina, right?

A. Right.

Q. You're not an expert on retinal kinetics?

A. I think, as I explained during my deposition, I understand kinetics. I'm an expert in kinetics, and I applied it to the retina.

Q. You wouldn't say you're an expert in retinal

kinetics, right?

A. I am not sure how to answer that.

Q. You were hired for this case just a few months ago, right?

A. Correct.

Q. Earlier this year?

A. Yes.

Q. You'd never studied the anatomy or physiology of the eye outside of this case?

A. That's correct.

Q. Outside of this case, you'd never studied the transport of molecules across ocular membranes, right?

A. Correct.

Q. Outside of this case, you've never studied the transport of molecules across retinal membranes, have you?

A. Right.

Q. You're not an expert on the physical barriers between the vitreous and the retina, right?

A. Correct, only after having read about it in this case.

Q. You're an expert in this case now having read the literature in this case?

A. I wouldn't say I'm an expert. I see that what I had proposed is, in fact, advocated by other experts in the field that they had proposed that this was a viable explanation for

what was going on. So I essentially anticipated what other experts had said.

Q. You can't identify by name the tissues that separate the vitreous part of the eye from the retina part of the eye, can you?

A. You have the inner limiting membrane, which, as I indicated, was very thin over the fovea, and because -- and you also have the plexiform layers, and there are other layers as well. But those are the two layers that have been suggested as being the barriers to migration.

Q. Did you study up on this just prior to trial?

A. Yeah, of course.

Q. You didn't know the answer to that question when I asked you at your deposition, did you?

A. Of course not, no. If I had, I would have told you.

Q. Before you were hired as an expert by Mylan in this case, you hadn't studied any of the processes in the eye at issue in this case, right?

A. That's correct.

Q. And you can't explain with certainty the role of the inner limiting membrane that you just referenced, right?

A. I'm not alone in that. Many of the experts that have been cited here cannot say with certainty what is going on.

Q. Are any of the other experts in this case offering the opinion that the VEGF antagonist works by sucking the

VEGF --

A. Yes --

Q. -- out of the retina --

A. Yes.

Q. -- by a --

A. Yes.

THE COURT: Doctor, one at a time, gentlemen.

Counsel, please ask your question.

BY MR. TRASK:

Q. Are any of the other experts in this case, Doctor, offering the opinion that VEGF antagonists can work by sucking the VEGF out of the retina like a vacuum cleaner?

A. Yes.

Q. Before you were retained by Mylan in this case, you weren't even aware of the existence of the inner limiting membrane in the eye, right?

A. Yes.

Q. Prior to this case you had no experience with drugs for age-related macular degeneration?

A. Correct.

Q. You had no experience with diabetic macular edema or diabetic retinopathy either, right?

A. Right.

Q. Other than your work on this case, you have no experience studying the mechanism of inflammation of VEGF

antagonists?

A. Say that again.

Q. Other than your work in this case, you have no experience studying the mechanism of inflammation of VEGF antagonists?

A. Correct.

Q. You're not sure if there are any cells in the vitreous of the human eye, right?

A. There's no cells in the vitreous of the human eye.

Q. At the time of your deposition, you weren't sure whether there were cells in the vitreous of the human eye, right?

A. Correct.

Q. You've never previously served as an expert in a case involving ocular drug administration?

A. Correct.

Q. Now, with respect to that vacuum cleaner theory that you've mentioned, Doctor, you haven't seen any literature as of 2006 stating that VEGF antagonists can sequester VEGF molecules outside the retina in the vitreous, right?

A. I'm not sure what the date was. It was around. I can't say for sure that it was before.

Q. Doctor, you testified in your deposition that you weren't aware of any literature as of 2006 stating that VEGF antagonists can sequester VEGF molecules outside the retina in

the vitreous, right?

A. That's what I stated in the deposition, that's correct.

Q. And in your view of all the literature that's been cited in this case and in your report, the publication that you would say best supports your theory about the vacuum cleaner mechanism of action of aflibercept is your kinetics textbook from 1978, right?

A. That and the knowledge of a POSA, yes.

Q. And your kinetics textbook from 1978 isn't even of record in this case, is it, Doctor?

A. No.

MR. TRASK: Nothing further.

THE COURT: Thank you, Counsel.

We're going to take a five-minute break before we begin direct. It's my intention to complete the doctor's testimony today, just as a heads-up.

I offer that also in case anyone has flights to catch or travel arrangements, please feel free to duck out. You don't need my permission to do that, but feel free to do so. But it's my intention to complete the doctor's testimony here today.

We're going to take five so you-all can switch. Thank you.

(A recess was taken from 4:32 p.m. to

4:44 p.m.)

THE COURT: Thank you, everyone. Please be seated.

Redirect, Counsel.

MR. HUNT: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. HUNT:

Q. Dr. Rabinow, do you remember when counsel asked you about the Court's claim construction as it relates to your invalidity opinions?

A. Yes.

Q. And counsel suggested that you did not consider both proposed constructions in forming your reply to Dr. Trout's opinions; is that right?

A. Yes.

Q. I'd like to call up DTX 7090, your reply expert report, page 13, paragraph 30. Is this your reply expert report, Dr. Rabinow?

A. Yes.

Q. Did you, in fact, set forth here in paragraph 30 both parties' claim constructions; is that right?

A. Correct.

Q. And it's your testimony that you considered both claim constructions in forming your opinions in this case, correct?

A. Yes.

Q. That includes the opinions set forth in your reply report?

A. Yes.

Q. Okay.

Thank you, Mr. Gibson. You can take that down.

Now, Dr. Rabinow, do you remember when counsel asked you about polysorbate 20 and the cosolvent limitation of the '865 patent claims?

A. Yes.

Q. But you're not offering any opinions today about whether polysorbate 20 is, in fact, acting as a cosolvent; is that right?

A. That's correct.

Q. Instead, your understanding is that if polysorbate 20 is found to be a cosolvent under the Court's construction, then the organic cosolvent limitations in the asserted claims must be found invalid in view of the many polysorbate 20 disclosures in the prior art; is that right?

A. That is correct.

Q. And your opinions today are based on the construction that the Court -- that was ordered by the Court; is that right?

A. Yes.

Q. Now, do you recall counsel asked you some questions about the Dix '226 patent?

A. Yes.

Q. In fact, I think counsel asked you if the Dix '226 patent disclosed diabetic retinopathy. Do you recall that?

A. Yes.

Q. He also asked you if the Dix '226 patent disclosed AMD, right?

A. Yes.

Q. Now, it's the '865 patent claims that are at issue in this case, right?

A. That's correct.

Q. And do the '865 patent claims contain any limitations requiring the use of the claimed formulation in any particular disease state?

A. No.

Q. So is it relevant whether the Dix patent discloses diabetic retinopathy in your analysis?

A. No.

Q. Do you remember when counsel asked you about your deposition testimony concerning the likelihood of the Court entering Regeneron's claim construction?

A. Yes.

Q. Now, you weren't pulling your punches, though; you were just assuming that Regeneron's construction could apply, right?

A. Yes.

Q. And so that's why you prepared two reports in this

case?

A. Correct.

Q. And as you testified earlier, your opinions are unchanged under either party's construction, right?

A. Yes.

Q. Do you remember when counsel asked you about the amino acid sequence disclosed in the '865 patent?

A. Yes.

Q. And that's sequence ID4, right?

A. Yes.

Q. And it's your opinion that the person of ordinary skill in the art would understand, based on their knowledge as of June 16th, 2006, that the disclosure of VEGF Trap R1R2 would necessarily mean that the amino acid sequence ID Number 4 is present; is that right?

A. Yes.

THE COURT: Yes, Counsel?

MR. TRASK: Your Honor, we've been tolerating a lot of this, but these are all leading questions.

THE COURT: Understood. Sustained.

BY MR. HUNT:

Q. Did you consider sequence ID Number 4 from the Dix '226 patent in your analysis, Doctor?

A. Yes.

Q. Did you do any comparison of the sequence in the

Dix '226 patent to the claims at issue here?

A. Yes.

Q. And what was the relationship between the sequence ID4 disclosed in Dix '226 and sequence ID4 disclosed in the '865 patent?

A. They were identical.

Q. So is it your opinion that the Dix '226 patent discloses the sequence ID4 claim in the '865 patent?

A. Yes.

Q. Dr. Rabinow, do you recall counsel's questions regarding the priority date of the '865 patent?

A. Yes.

Q. Have you assumed for purposes of your analysis that the '865 priority date -- well, strike that.

Have you offered any opinions in this case regarding whether Regeneron is entitled to the June 16th, 2006, priority date I believe you previously testified applies?

A. In my expert report, I discuss that, yes.

Q. Have you seen any evidence suggesting that Regeneron is entitled to anything other than the June 16th, 2006, priority date?

A. No.

Q. Now, counsel asked you some questions regarding Rudge; is that right?

A. Yes.

Q. And I believe you testified that the Rudge article was published in 2005; is that right?

A. Yes.

Q. Did Dr. Trout dispute the priority date of the Rudge reference in his responsive report?

A. I don't recall that he did.

Q. Now, counsel asked you some questions regarding the Lam reference as well, right?

A. Yes.

Q. Now, by at least 2005 what is it that the Lam reference reported with regard to stable liquid formulations?

A. That antibodies were stable for two years at 5 degrees centigrade.

Q. Okay.

And if we could call up DTX 3556, the Lam reference, at page 31. Specifically on the left side, I'd like to go to Column 7, lines 53 through 58, paragraph starting "the term 'antibody.'"

Now, Dr. Rabinow, we're at DTX 3556, page 31. Does the Lam reference define the term "antibody"?

A. It says what it includes.

Q. Does it indicate that the term "antibody" in the Lam patent is being used in its broadest sense?

A. Pretty much so, I would guess, yeah.

Q. Now, are you also using the term "antibody" in its

broadest sense today?

A. Yes.

Q. And you've testified that antibodies are like fusion proteins, right?

A. Yes.

Q. Is it your testimony that the formulation disclosures in the prior art for antibodies are relevant to formulations of aflibercept?

A. Yes.

Q. Earlier today I think counsel asked you if you consulted with any ophthalmologists. Do you remember that?

A. Yes.

Q. Now, did -- the asserted claims of the '865 patent are formulation claims, right?

A. That's correct.

Q. Are there any specific ophthalmology limitations in the '865 patent?

A. No.

Q. So in your view was it necessary to consult an ophthalmologist?

A. No.

Q. And do you understand with regard to isotonicity that iso-osmotic has the same meaning as isotonicity?

A. Yes.

Q. I'd like to briefly look at the Saishin reference,

which we can pull up on DDX 4, Slide 58.

Dr. Rabinow, these are a few passages from Saishin that you relied upon in your direct examination, correct?

A. Yes.

Q. And counsel asked them about you on cross -- or asked you about them on cross?

A. Yes.

Q. And this is DTX 2751, page 7, right?

A. Yes.

Q. Now, you relied on the phrase in the first box; is that correct?

A. Yes.

Q. Could you please read the -- read into the record the statement on the first box of DTX 2751, page 7.

A. "These data suggest that VEGF Trap R1R2 deserves consideration as a potential treatment for two complications of diabetic retinopathy, retinal neovascularization, and macular edema."

Q. Now, diabetic retinopathy, is that a disease of the eye?

A. Yes.

Q. What about retinal neovascularization?

A. Yes.

Q. And macular edema?

A. Yes.

Q. And Saishin discusses intravitreal administration, as I believe you testified, right?

A. Yes.

Q. So what would the person of ordinary skill in the art reading Saishin, and specifically the disclosures that we just discussed, understand regarding the use of an intravitreal injection with VEGF Trap R1R2?

A. Strong recommendation for continued development with a promise of success -- or an expectation of success, shall I say.

Q. Do you recall counsel's questions regarding Genentech, Dr. Rabinow?

A. There was a lot of discussion about Genentech. I'm not sure which ones you're referring to.

Q. Well, how about when counsel asked you if Genentech was perhaps the most successful biotech company in history?

A. Yes, I recall that.

Q. Have we looked at a number of disclosures from Genentech today?

A. Yes.

Q. And those -- what sort of scientific area were those disclosures in?

A. They were in the formulation development area.

Q. And there were a multitude of them, right?

A. Yes.

Q. And counsel on redirect even asked you about a Lasker Award winner that works at Genentech; is that right?

A. Yes.

Q. So the person of ordinary skill in the art in June 16th of 2006, is it your opinion that they would be interested in reviewing formulation disclosures from Genentech?

A. Yes.

Q. Now, the '865 patent claims, I believe we've discussed that they're formulation claims, right?

A. Yes.

Q. Do the '865 patent claims have anything to do with the anatomy of the human retina?

A. No.

Q. Do the '865 patent claims have anything to do with retinal kinetics?

A. No.

Q. Do the '865 patent claims have anything to do with transport of molecules across retinal membranes?

A. No.

Q. And does one need to be an expert in the physical barriers between the vitreous and retina to understand the '865 patent claims?

A. No.

Q. Now, Dr. Rabinow, on your direct examination do you recall discussing Dr. Trout's objective evidence opinions?

A. Yes.
Q. Specifically safety and efficacy?
A. I recall some things. I'm not sure exactly what things you're referring to.
Q. Okay.
Mr. Gibson, could we have Slide 119, please.
I will be very quick, Doctor. I think there may have been something unclear in the record. I'd like to clear it up.
MR. TRASK: For the record, Your Honor, outside the scope of the cross. I never covered this publication or this slide during the cross-examination.
THE COURT: Go ahead, Counsel.
MR. HUNT: I apologize, Your Honor. I do believe that the Thomas publication was covered during cross; but, regardless, this will be very short. I'm just trying to clarify --
THE COURT: I believe it was. Go ahead. Overruled.
MR. HUNT: Thank you.
BY MR. HUNT:
Q. Is it your opinion that Eylea's safety and efficacy is related to the aflibercept molecule?
A. Yes.
Q. And not to the formulation; is that right?
A. That's correct.
Q. And is it correct that the aflibercept molecule's

properties provide Eylea's safety and efficacy?

A. Yes.

Q. Now, I just have a couple more questions, Dr. Rabinow.

Do you recall counsel's questions regarding the Liu reference?

A. Yes.

Q. There's disclosure of stability data in Liu, right?

A. Yes.

Q. And Liu -- what company was Liu working for?

A. Genentech.

Q. And I believe we discussed the concentrations in Liu; is that right?

A. Yes.

Q. Is there a concentration range disclosed by the Liu reference?

A. It was 40 to 150 mg/mL.

Q. Do you consider those to be high concentration?

A. I do.

Q. So the Liu reference disclosed high-concentration protein formulations and stability data relating thereto, right?

A. That's correct.

MR. HUNT: With that, Your Honor, I have no further redirect questions. I do have some exhibits I'd like to move

in when we're done.

THE COURT: No. Understood. I know we've got a couple of exhibit issues to cover. We'll do that after any recross.

MR. TRASK: Very briefly, Your Honor. That's a promise.

THE COURT: One which shall be enforced.

MR. TRASK: Understood, Your Honor.

THE COURT: Just kidding. Go ahead.

RECROSS-EXAMINATION

BY MR. TRASK:

Q. Doctor, do you recall counsel just asked you whether there are any specific ophthalmology limitations in the '865 patent?

A. Yes.

Q. You answered no, correct?

A. Correct.

Q. You know that Claim 1 of the '865 patent refers to intravitreal administration, right?

A. Yes, yes. That's correct.

Q. You were mistaken when you answered that question?

A. I was mistaken.

MR. TRASK: No further questions, Your Honor.

THE COURT: Thank you.

Any reredirect?

MR. HUNT: No, Your Honor. Just the aforementioned exhibits.

THE COURT: Understood. Let me scratch off my list first. I -- I believe it was on cross there was a reference to PTX 1526 and it should actually be PTX 576.

MR. TRASK: You anticipated exactly the correction I was going to make, Your Honor.

THE COURT: Okay. All right. Well, we'll note that correction in the record. With that, Counsel, go right ahead. And I won't take credit for it. Madam Clerk and Madam Law Clerk of course get them all.

Counsel, go right ahead with the exhibit list, slowly, please.

MR. HUNT: Yes, Your Honor.

Defendants move into evidence DTX 0013, DTX 0726, DTX 0728, DTX 0729, DTX 0730, DTX 2264, DTX 2265, DTX 2751, DTX 3040, DTX 3492, DTX 3506, DTX 3510, DTX 3549, DTX 3556, DTX 3588, DTX 3592, DTX 3610, DTX 3611, DTX 3619, DTX 4041, DTX 5036, DTX 5037, DTX 5038, and, finally, DTX 5040.

THE COURT: Thank you, Counsel.

Any objection to any of those?

MR. TRASK: Could I have just a brief moment to confer?

THE COURT: Certainly.

MR. TRASK: No objection, Your Honor.

THE COURT: Without objection, each of those exhibits are hereby deemed admitted.

(DTX 0013, DTX 0726, DTX 0728, DTX 0729, DTX 0730, DTX 2264, DTX 2265, DTX 2751, DTX 3040, DTX 3492, DTX 3506, DTX 3510, DTX 3549, DTX 3556, DTX 3588, DTX 3592, DTX 3610, DTX 3611, DTX 3619, DTX 4041, DTX 5036, DTX 5037, DTX 5038 and DTX 5040 were admitted.)

MR. HUNT: Thank you, Your Honor.

THE COURT: Thank you, Counsel.

MR. TRASK: Your Honor, I just have two cross exhibits to admit, PTX 3344, PTX 3346.

THE COURT: Any objection to those?

MR. HUNT: Your Honor, these were not previously disclosed to us; so we certainly reserve the right to object to these as new exhibits not previously disclosed. And we will endeavor to do so in an expeditious fashion.

THE COURT: Understood. Those were used as impeachment, correct, Counsel?

MR. TRASK: That's right, Your Honor.

THE COURT: Consistent with this Court's prior rulings, objection noted but overruled. Those exhibits will be deemed admitted.

(PTX 3344 and PTX 3346 were was admitted.)

THE COURT: And then we fixed the numbering on the --

is it Ghate? Am I pronouncing that correctly?

Any other exhibits that require the good doctor to remain in that chair?

MR. HUNT: No, Your Honor.

THE COURT: All right.

Doctor, thank you so much, sir. You can step down. Thank you.

How long is Ms. Chu's deposition?

MS. MAZZOCHI: Sadly, Your Honor, it is more than an hour.

THE COURT: All right, then. That feels like a week to me. My fingers crossed for a different number, Counsel, but I understand.

MS. MAZZOCHI: Your Honor, maybe if we take the weekend we'll go back and look at it with a fine-tooth comb and see if we can shave a few minutes off.

THE COURT: Always appreciated. We'll call it a day in terms of evidence presentation in a week.

Let me ask this question: With a slight change in the Court's children's summer camp and activities schedule, any objections if we start at 9:00 a.m. next week as opposed to 9:30?

MS. MAZZOCHI: None from us.

MR. BERL: None, Your Honor.

THE COURT: Okay. We'll start at 9:00, then, next

week. My youngest has volleyball camp up the road that starts early; so I'll be here certainly by then. So we'll start at 9:00. Monday, of course, is a federal holiday; so we begin on Tuesday.

Let me ask this question, just as sort of a planning and preview. Where do we stand in terms of remaining witnesses from Mylan during this phase?

MS. MAZZOCHI: Yes, Your Honor. Our next two live witnesses will be Dr. Jay Stewart as well as Dr. MacMichael. We do not have any reason today to doubt why they can't be both up and down, I would hope, on Tuesday. I will say we have been hoping that we could get Dr. Stewart on the stand today. We did not anticipate so much time on -- from Regeneron on their cross today. But that would be our goal, and then we have the Chu deposition.

THE COURT: Would that be the last witness in this phase from the defense?

MS. MAZZOCHI: Right. Then, again, our last live witness in terms of rebutting their commercial success witness will be Mr. Hofmann. Then the only issue is going to be -- I don't think we'll have to bring anybody back; but, again, if they bring in something new that one of our experts didn't have the ability to rebut, but that would be something we would think quick, like, 10, 15 minutes, I would hope.

THE COURT: Understood. Okay.

MS. MAZZOCHI: But I will say this, though, Your Honor. I am very concerned because we've been trying to be pretty judicious with the use of our time. So while we believe we are on track in terms of what we've planned out for our case in chief and response and planning for crosses with Regeneron, we're very concerned that Regeneron is over their time. So I just wanted to make sure we're clear we're going to continue to get an even split of the anticipated time.

THE COURT: Y'all are keeping your own clock. So y'all keep track of that. You came to an agreement. Surely someone here is charged with keeping track.

MS. MAZZOCHI: Oh, yes. More than one.

THE COURT: I assumed that someone here had that responsibility. You may turn out to be the MVP. Congratulations.

MS. MAZZOCHI: Thank you, Your Honor.

THE COURT: Thank you.

In terms of remaining lineup that plaintiff would anticipate calling at this juncture.

MR. BERL: Yes. After defendants rest, Your Honor, we'll then call one fact witness with respect to the method of treatment family. That's Ms. Chu. One expert witness on that, Dr. Csaky, as well as, on the formulation side, we have one inventor, Dr. Graham, as well as Dr. Trout to come back and address invalidity of the '865 patent. And we have one

commercial success expert, Dr. Manning.

THE COURT: I'm sorry. Doctor who?

MR. BERL: Manning.

THE COURT: Understood.

MR. BERL: We anticipate that we should be able to finish. I think we're obviously a little behind of where we thought we would be, but we think we should be able to finish next week perfectly fine just as planned.

THE COURT: Any time sooner than Friday would be --

MR. BERL: That, I won't promise.

THE COURT: Okay. All right. And then witness Hofmann might be the backstop after; is that correct?

MS. MAZZOCHI: That's correct, Your Honor. I suspect that after Dr. Manning goes, then it will be Dr. Hofmann's turn. Thank you.

THE COURT: All right. Okay. Anything else we need to take up at this juncture from plaintiff's perspective?

MR. BERL: Not from Regeneron, Your Honor.

THE COURT: Defense?

MR. HUNT: No, Your Honor.

THE COURT: All right. Great. Feel free to leave whatever you'd like in the courtroom. No one will be in here in the interim. So I'll leave it at that.

We'll be ready to roll on Tuesday morning at 9:00.

Happy Father's Day, all those who observe and

celebrate. Have a wonderful weekend. We'll see everybody Tuesday morning.

(Proceedings concluded at 5:08 p.m.)

CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 16, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 16th day of June 2023.

/s/Cindy L. Knecht

_____

Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 6

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 20, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

APPEARANCES:

On behalf of the Plaintiff:

David I. Berl
Ellen E. Oberwetter
Arthur J. Argall, III
Kathryn S. Kayali
Andrew V. Trask
Williams & Connolly, LLP
680 Maine Avenue, SW
Washington, D.C. 20024
202.434.5000

Andrew E. Goldsmith
Kellogg, Hansen, Todd, Figel & Frederick, PLLC
1615 M. Street NW, Suite 400
Washington, DC 20036
202.326.7945

APPEARANCES CONTINUED ON NEXT PAGE

On behalf of the Plaintiff, continued:

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

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

On behalf of the Defendant:

Deanne M. Mazzochi
William A. Rakoczy
Heinz J. Salmen
Eric R. Hunt
Lauren M. Lesko
Neil B. McLaughlin
Lawrence Scott Beall
Katie A. Boda
Rakoczy, Molino, Mazzochi & Siwik, LLP
6 W. Hubbard Street, Suite 500
Chicago, IL 60654
312.527.2157

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

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

(Video deposition of Karen Chu)

Tuesday Morning Session,

June 20, 2023, 9:00 a.m.

- - -

THE COURT: We convene for day one, week two, of trial. Good morning, Counsel. Happy West Virginia Day to everybody.

Mylan may call its next witness.

MS. BODA: Good morning, Your Honor. Katie Boda.

Defendants' next witness will be Karen Chu by video deposition. Regeneron identified Ms. Chu in response to our 30(b)(6) topics identified in DTX 202, including conception and reduction to practice, the patent examples, and several issues relating to aflibercept development and associated clinical trials.

THE COURT: I'll note again Regeneron's objection to playing of the video in its entirety. Objection noted.

(Video deposition of Karen Chu.)

Q. Thank you. Good morning, Ms. Chu. My name is Deanne Mazzochi. Can you please state your full name and address for the record.

A. Yes. Karen Chu, and my home address is 73 Richbell Road, White Plains, New York 10605.

Q. And then what was your initial role and responsibilities at Regeneron?

A. So when I joined the company, I joined as a senior

clinical trial manager. And then as is true, I think, for a lot of small companies in that role, wore several different hats and had a broad range of responsibilities as it related to clinical development. And over the years moved into more of a clinical project management role, and then finally into my current role.

Q. Okay. And what -- was your initial title -- I think it was -- what was it? -- director of therapeutic area project management?

A. So that was not my first title at Regeneron.

Q. Okay. What was your first title?

A. I believe -- my recollection is that my first title was senior clinical trial manager. But the director of therapeutic area project management was promotion into a broader clinical project management role.

Q. And then did you ever have any individuals who reported to you in those roles?

A. At the time that I was a clinical trial manager I had a group of people that reported to me who -- who were more junior clinical trial managers and involved in the operations of the clinical trials.

Q. Okay. How do you differentiate what your role was versus what you call the operation of the clinical trials?

A. So within clinical research, there are several people that contribute to any aspect of conducting a clinical trial.

So the actual operations of the clinical trial, which includes everything from ensuring that clinical study sites are identified and trained appropriately to providing supplies for the clinical study sites to deciding which laboratories to use or how labs will be collected, that typically is considered part of the operations role. So they're -- really, that -- you know, they really oversee the actual execution of the clinical trials.

Q. Let's focus on VEGF Trap. And if I call VEGF Trap aflibercept, is that all right as well?

A. That is all right. I understand it to be the same molecule.

So I can confirm that the document says "Plaintiff's Rule 26(a) Initial Disclosures."

Q. Again, I'm trying to just get at what are identified as alleged inventions in Defendants' Exhibit 4, the '601 patent. You said that in your role you participated in the design of the studies, for example.

Can you tell me anything that you recall about anything inventive or unique or new or different about those particular trials that relate to the inventions set forth in the '601 patent?

A. Certainly with every new molecule, the properties of the molecule as well as considerations around its clinical use go into the design of any trial. And Eylea represented a new

anti-VEGF treatment that we felt had real potential advantages and designed the trials in a way that we felt we could demonstrate those unique properties to the best extent possible.

Q. And is it fair to say that your clinical trials were designed to try to optimize or maximize the chance of success?

A. So I think it's true that in clinical development you're always trying to maximize your chances of success.

Q. Would Regeneron have followed or pursued a clinical trial that it thought was going to fail?

A. So there's always a risk of failure. Clearly, you know, the -- especially for Phase III trials, there is a statistical threshold that you must meet. And there's always a chance that you would not meet that for various reasons.

So I don't think it's true that Regeneron would not have pursued a trial that had a chance of failure.

Q. Yeah. Maybe we can phrase it this way: Is it fair to say that, in your time at Regeneron, if Regeneron was going to pursue a clinical trial, they believed they would be able to meet that -- the clinical end points they put in place? They wouldn't have spent the money on a clinical trial if they didn't?

A. So, again, every clinical trial, you know, we try to design it for success. But there's always a risk that a clinical trial would fail for one reason or another, whether

that's safety or efficacy.

Q. When it comes to aflibercept, were there any clinical trials you designed that led to failure as opposed to success with regard to the ophthalmology category?

A. Can I ask for some limitations on the extent of my answer? Is there a time frame that we're referring to?

Q. Sure. Let's say 2006 forward.

A. So, actually, most recently Regeneron has reported two clinical trials with aflibercept that did not meet their primary end point.

Q. And which were those?

A. Those are trials in the treatment of retinopathy of prematurity.

Q. And what was the dosing regimen for those?

A. It's .4 milligrams either unilaterally or bilaterally for up to three monthly doses.

Q. When you say "for up to three monthly doses," you mean with three monthly doses or doses separated by three months between them?

A. Sorry. In retinopathy of prematurity, physicians treat initially with a single dose. If that does not regress the retinopathy of prematurity sufficiently, they can give a second dose a month later and a third dose a month later with similar considerations.

Q. So besides this particular study that Regeneron

conducted for the -- at the request of the FDA for pediatric patients, are there any other studies that Regeneron has pursued for aflibercept in the eye that have failed to meet their clinical end points?

A. Not that I am aware of.

Q. All right. Ms. Chu, can you just confirm you have a document before you marked DX 202 that is marked "Karen Chu 30(b)(6) Deposition Topics"?

A. Yes, the title of the document is "Karen Chu 30(b)(6) Deposition Topics."

Q. Right. But who was the individual who ultimately came up with the idea of dosing 2 milligrams approximately every four weeks for the first three months and then the 2-milligram dose approximately once every eight weeks, or once every two months, thereafter?

A. So, again, Regeneron operates in a -- you know, cross-functional team environment; so there was input given by many different functions and many different people. But George Yancopoulos and Len Schleifer were definitely heavily involved in these discussions, and any approval would have needed to have been given by George to move ahead with the study design.

Q. Right. I understand they had to give approval, but who actually came up with the idea of this particular regimen, in Regeneron's view?

A. I don't recall.

Q. All right. So, Ms. Chu, when it comes to Regeneron's position with regard to the '601 patent, does Regeneron have a position as to who was responsible for the conception of the full claims set forth in Claim 1 of the '601 patent?

A. George Yancopoulos is the named inventor on the '601 patent.

Q. And why does Regeneron believe that George Yancopoulos is the person who conceived of the methods set forth in Claim 1 of the '601 patent?

A. George has always and continues to play a very hands-on role in all research and development, including the development of aflibercept. And he was personally involved in many, many discussions related to the development of aflibercept across all phases of clinical trials, including the design of the Phase III studies.

Q. Okay. So is it Regeneron's position that the reason -- that the reason for George Yancopoulos being the named inventor is because he's the one who did the sign-off on the Phase III clinical design study -- sorry -- Phase III clinical study design?

A. So my knowledge is that George had tremendous input. And ultimately it was his decision to move forward with the final study design for the VIEW 1 and the VIEW 2 studies.

Q. Are there any documents that showed that it was George Yancopoulos, as opposed to someone else, who

specifically put together the 2-milligrams every four weeks for the first six months followed by 2 milligrams once every eight weeks, or every two months thereafter?

A. Off the top of my head, I don't recall specific documents.

Q. Did you try to reach out to Dr. Cedarbaum to prepare as a 30(b)(6) witness?

A. I did not reach out to Dr. Cedarbaum in preparation for this deposition.

Q. What about Mr. Ingerman, Avner Ingerman?

A. Right. Avner Ingerman.

Q. Avner Ingerman, right. Wasn't he also one of the individuals who was in favor of the eight-week interval?

A. My recollection of Dr. Ingerman's position at that time is that he was lobbying for an as-needed or prn dosing regimen, although he was part of many discussions about alternative dosing regimens that could be employed.

Q. Such as?

A. Such as every eight weeks or other potential dosing regimens.

Q. And what within the visual acuity data prompted shortening the interval from 12 weeks to eight?

A. So within the visual acuity data, even though visual acuity is a highly variable measure and this was a relatively small study in that there were about 30 patients per group, we

looked for trends to inform us of what's happening. And my recollection is that the most important aspect of the visual acuity was that the groups that were dosed with monthly injections first overall had a greater gain in visual acuity.

Secondly, that when those patients were allowed to go longer than four weeks without a dose, we saw some decline in visual acuity over that period.

Q. Okay. And was the period a 12-week period, an eight-week period, or was it a prn period?

A. So in this study, after Week 12, patients were dosed prn. So the duration between that Week 12 dose and subsequent doses was variable.

Q. Okay. Well, why go with eight weeks as opposed to six weeks or just sticking with monthly?

A. So we did include two monthly dosing groups in the VIEW 1 and the VIEW 2 study. We tested two separate doses, .5 milligrams and 2 milligrams. As I mentioned before, there were many considerations that went into the study design. And some of those considerations have to do with the constraints of a study conduct.

So one aspect of these studies is we must conduct them as what we call double-masked studies. And we perform sham injections at visits where patients are not receiving an active injection. And it was impractical to include a group where we had a six-week dosing interval because it would have

necessitated visits essentially every two weeks for all patients.

Q. Okay. So the every eight weeks just made the clinical trial design easier in terms of maintaining the mask?

A. It was both a dosing interval that we felt was supported by the data and also created a more practical way to conduct the study.

Q. Now, in the '601 patent, Claim 10, we have the same dosing regimen, but this time it's for a method of treating diabetic macular edema in a patient in need thereof.

Who was the one -- what is Regeneron's position as to who was the person who actually came up with the idea of applying this regimen to the DME indication?

A. So this regimen is different in that it is for 2 milligrams given every four weeks for the first five injections followed by approximately once every eight weeks, or every two months.

And my recollection is that, again, there were several discussions about the optimal study design for treating diabetic macular edema. And those conversations would have included both people from the clinical team as well as senior management.

Q. Right. Who decided that the dosing was going to be for the first five injections as opposed to three or four?

A. My recollection is that George Yancopoulos made that

decision.

Q. Is that documented anywhere?

A. I don't recall if there is specific documentation of that.

Q. If you can take a look at the '601 patent, is the clinical trial protocol for the Phase III VIVID or VISTA studies set forth in any of the patent examples?

A. To answer that question, I would have to go through the entire patent. Is that something I should do?

Q. Sure. You can start with Example 1, which begins at Column 8.

A. So in my review of the Patent '601, I do not see a description -- or the VIVID and VISTA trials given as an example, but I do see the Phase II clinical trial in diabetic macular edema described as Example 5.

Q. And if I understand you, it was the data from this Phase II study that justified the dosing regimen for the VIVID and VISTA studies for diabetic retinopathy?

A. So data from this Phase II study did inform decisions regarding the VIVID and VISTA study designs.

Q. And why is it that Regeneron believed that the DME data could be transferred over to the diabetic retinopathy indication?

A. So as I mentioned, data from the VIVID and VISTA studies included a secondary end point of a proportion of

patients with two or more step improvement in diabetic retinopathy. Patients with diabetic macular edema do have underlying diabetic retinopathy at various severities. And we did see a statistically significant outcome of improvement in patients that were treated with aflibercept in the VIVID and VISTA studies -- oh, I'm sorry -- in the -- yes, in the VIVID and VISTA studies. Sorry.

Q. Let me know when you have that exhibit before you.

A. I have Exhibit 204 in front of me.

Q. Okay. I'd like to take a look at Claim 6 of the '601 patent.

A. Okay. I see that.

Q. And -- yeah. So here again, I just have a question. What can be done to the dosing regimen in Claim 1 to ensure that a patient is going to be able to meet these requirements of Claim 5 and Claim 6 and -- specifically using this measurement technique that's set forth in Claim 6?

A. So I would respond the same way, that the response to treatment is highly variable with individual patients.

Q. Okay. So how are we going to know, then, if an individual patient actually meets the standard?

A. So in the treatment and monitoring of an individual patient with neovascular age-related macular degeneration, visual acuity would be assessed prior to treatment initiation and at an interval deemed appropriate by the treating physician

during the course of treatment.

Q. Ms. Chu, can you take a look at DX 205 and confirm that it is the FDA-approved Eylea labeling?

A. So I have Exhibit 205 in front of me, and it appears -- this appears to be the Eylea USPI revised as of May 2019.

Q. Well, are you aware of any change to the formulation description that appears here as compared to when the Eylea product was first approved in 2011?

A. In my experience and knowledge, I am not aware of any changes to the formulation as described here in the USPI.

Q. And then we've got George Yancopoulos, who is listed, at least on this org chart, as the CSO. Is he still the CSO today or does he have a better title?

A. My understanding is he still has the title chief scientific officer.

Q. Okay. Anything, though, that would justify having the longer dosing interval that you recall?

A. So I can't remember if this was specifically in Neil's purview, but we did know that, based on the aflibercept molecule comparing to Lucentis, that it did have a longer half-life in the eye of animals. And so that gave us an indication that potentially a longer dosing interval might be possible. But certainly animal studies are only somewhat translatable to human studies.

Q. Okay. And then from Regeneron's perspective, which clinical trial was it that allowed you to conclude that aflibercept might have a longer half-life in the human eye that might justify a longer dosing interval?

A. So we -- during the course of Eylea clinical development, we did not measure half-life in the human eye. That would have required sampling from ocular fluids, which, to do serially in patients, is very difficult and causes additional safety risk for patients. So the data from the 0508, or CLEAR-IT 2, study was really the clinical data that we looked at in order to decide which dosing regimens to test in Phase III.

Q. Okay. Can you confirm that Exhibit 207 is a Friday, January 30th, 2004, email from Jesse Cedarbaum to you and others involving what was described as draft VEGF Trap AMD press and some thoughts for release on the start of an AMD trial?

A. I see that the email is dated Friday, January 30th, 2004, and that I am one of the recipients of the email.

Q. Was it common for Regeneron to prepare press releases when they were about to start clinical trials?

A. Regeneron was a small company back then; so the initiation of a clinical development program would have been something that we would have disclosed.

Q. Do you have Exhibit 209 in front of you?

A. Yes, I have Exhibit 209 in front of me.

Q. All right. Can you confirm that the top email was copied to you and others on Tuesday, August 31st, 2004?

A. Yes. I am on the cc line of this email dated -- just to say dated August 31st, 2004.

Q. Macugen was dosing its product intravitreally, correct?

A. That is correct.

Q. Did these results cause Regeneron to start thinking more closely about doing an intravitreal injection?

A. I believe that the results from the Macugen trials gave us more information about the safety and feasibility of intravitreal injections given regularly to these -- to the -- to AMD patients over the course of a year of treatment.

Q. Did the Macugen results give you any sense that there might be more willingness in the marketplace to accept an intravitreal injection?

A. The Macugen results from these Phase III studies definitely supported that intravitreal administration of a product in wet AMD patients was possible.

Q. All right. And at this time it was known to Regeneron that ranibizumab was also out there in Phase III trials, right?

A. Yes. The Lucentis trials were being conducted concurrently at this time.

Q. And it also mentions at the end of the paragraph that Regeneron's VEGF Trap was also currently in clinical and preclinical trials, right?

A. Yes. The last sentence is "Other antiangiogenic agents currently in clinical and preclinical trials are Angstrom's A6, OXiGENE's CA4P, and Regeneron's VEGF Trap."

Q. At this point in time, were you looking at the Lucentis dosing regimen as one that you might want to copy or emulate?

A. I would say at this time we were monitoring the Lucentis clinical development program closely from a competitive intelligence perspective.

Q. Right. And certainly by the time we got to the 2010 time frame, at the time when you had submitted your Phase III clinical trials, ranibizumab had been shown to produce some consistent vision gain, right, when injected intravitreally?

A. So the pivotal Lucentis trials in neovascular AMD were the ANCHOR and MARINA trials. And they demonstrated vision gain with ranibizumab dosed every four weeks, or monthly, for the -- for a year. So Week 52 was their primary end point.

Q. Do you have that exhibit before you?

A. Yes, I have Exhibit 210.

Q. Okay. Can you confirm that Exhibit 210 contains an email string including an email from Ilham Zoughi, Z-O-U-G-H-I,

to you and others dated March 3rd, 2005?

A. Yes, I see that I am a recipient of this email from Ilham Zoughi.

Q. If you look at the bottom line, the author there said -- "We've been" -- the study clinician was quoted as saying, "We've been injecting anti-VEGF drugs into the eye for the past three years with very encouraging results."

Do you see that?

A. I do see that as part of the quote here.

Q. Right. And that quote is attributed to Philip J. Rosenfeld, MD, PhD?

A. So this email just said Rosenfeld, which I assume to mean Phil Rosenfeld.

Q. Right. Now, did Regeneron also reach out to get input from Phil Rosenfeld in the context of this clinical trial work?

A. Dr. Rosenfeld was a respected key opinion leader in the retina community, and he is someone that we interacted with occasionally to discuss aspects of the clinical development program.

Q. Do you recall there being any impact within Regeneron when it was reported that Avastin, a VEGF inhibitor, was producing positive results in the eye?

A. I don't remember this study or the data from this study having a specific impact at Regeneron.

Q. All right. But what about Avastin generally, the experience that clinicians were having with Avastin injecting it into the eye to get -- to stop vision loss?

A. So this press release is referring to systemic administration of Avastin.

Q. Right.

A. But Dr. Rosenfeld was involved in running his own investigator-initiated studies with intravitreal Avastin.

Q. Right. Right. And he indicates, in this document at least, that he had been doing that for at least three years?

A. That is what the document says.

Q. Right. So did the fact that someone like Dr. Rosenfeld and others were injecting Avastin directly into the eye, did that influence their thinking as to whether it would be useful to dose VEGF Trap into the eye?

A. Dr. Rosenfeld, as well as other retina specialists in the community, provided information that gave Regeneron more confidence regarding the feasibility of moving forward with an intravitreally delivered product.

Q. Okay.

A. So the study in Example 1 was referred to as the CLEAR-IT 1 study; the study in Example 2 was the CLEAR-IT 2 study.

Q. Okay. Perfect. Thank you.

And then if we go on to the next column, Example 4,

the Phase III clinical trials, was that the VIEW 1 study or VIEW 2?

A. So this section under Example 4 refers to two parallel Phase III clinical trials carried out to investigate the use of VEGF-T to treat patients with neovascular -- with the neovascular form of age-related macular degeneration. So this section appears to be referring to both the VIEW 1 and the VIEW 2 studies.

Q. Okay. And then if you can jump forward to Column 14, there is an Example 5 provided there. Did that clinical study also have a name?

A. Example 5 is the Phase II clinical trial of VEGF-T in subjects with diabetic macular edema. This study was referred to as the DA VINCI trial.

Q. Okay. And then Example 6, did that clinical trial have a name?

A. So in Example 6, it's referring to a randomized multicenter double-masked trial in treatment-naive patients with macular edema secondary to CRVO. And I believe this is referring to a study that we called the COPERNICUS study, although there was a second CRVO trial conducted called the GALILEO study.

Q. Can you confirm that this is a document, an email string with the first one dated Sunday, January 8th, 2006, regarding an AMD expert meeting, from Neil Stahl to Jesse

Cedarbaum, you, and others?

A. I can confirm that the date of this email is Sunday, January 8th, 2006, the subject is regarding AMD expert meeting, it's from Neil Stahl, and I am one of the recipients of this email.

Q. One of the other questions to ask these experts was do they think that the PIER regimen of Lucentis will work?

Do you see that?

A. I do see that question.

Q. What was your understanding of PIER regimen for Lucentis?

A. So the PIER study was an investigator-initiated study conducted by Dr. Phil Rosenfeld that -- my understanding of that regimen is that it was three initial monthly doses of .5 milligrams of Lucentis followed by quarterly dosing; so every-three-month dosing.

Q. Let me know when you have that.

Are you identified as one of the individuals who participated in this advisory panel meeting?

A. Just give me a second to review this.

Okay. So I am listed as one of the Regeneron attendees for this meeting.

Q. And one of the items listed here that Regeneron wanted to get the consultant's impressions of was how will Lucentis be used in practice: Monthly as in ANCHOR and MARINA,

induction followed by quarterly maintenance as in PIER, or induction followed by PIER and criteria-based dosing as in SAILOR.

Do you see that?

A. I do see that under 3A.

Q. Now, the title of this was "CLEAR-IT 3 Advisory Panel Meeting."

What was CLEAR-IT 3?

A. My recollection is that CLEAR-IT 3 was the initial name that Dr. Cedarbaum wanted to give the Phase III AMD studies.

Q. Okay. So CLEAR-IT 3 eventually became known as the VIEW 1 and VIEW 2 studies?

A. The Phase III studies were eventually named VIEW 1 and VIEW 2, yes.

Q. Can you confirm it's dated Friday, February 10th, 2006, from Srilatha Vuthoori to you and many others at Regeneron?

A. This email is dated Friday, February 10th, 2006. The subject is "Actions and decisions VGT team meeting." And it's from Sri Vuthoori, and I'm one of the recipients.

Q. Okay. Let me give you a document that has production numbers NYLAFL8703 through 8711, which I will mark as DX215.

A. Okay. I have Exhibit 215 in front of me.

Q. Okay. And do you see it says citation in the upper

left-hand corner it says, "WHO drug information Volume 20, Number 2, 2006"?

A. I see that the document is labeled in the upper right-hand corner "WHO Drug Information Volume 20, Number 2, 2006."

Q. And then this was titled "International Nonproprietary Names for Pharmaceutical Substances."

A. I see the document is titled "International Nonproprietary Names for Pharmaceutical Substances."

Q. All right. Can you go ahead and turn to page 8706 as the Bates number. It's page 118 within this volume. And do you see a reference on this page to aflibercept?

A. Yes, I see on the second half of the page there is a reference to aflibercept.

Q. In the context of your clinical work, did you ever use the term "aflibercept" to refer to any chemical structure other than VEGF Trap-Eye?

A. So the terms VEGF Trap, VGFT, VEGF Trap-Eye, and aflibercept, depending on the time period, were used somewhat synonymously. VEGF Trap-Eye was almost always used to distinguish between the systemic formulation of aflibercept versus the intravitreal formulation.

Q. Right. But the underlying structure of aflibercept, the molecule, didn't change whether it was VEGF Trap-Eye or VEGF Trap or aflibercept; is that fair?

A. It is my understanding that the active ingredient was the same in VEGF Trap-Eye and aflibercept whether that was referring to the oncology product or the intravitreally delivered product.

Q. I would like to mark as Defendant's Exhibit 218 a document with production numbers RGN-EYLEA-MYLAN-553211 through 212.

And can you confirm this is a May 9th, 2006, email from Jesse Cedarbaum to you and others discussing Rosenfeld's Lucentis PrONTO press release?

A. This is an email dated Tuesday, May 9th, 2006, with the subject "Rosenfeld's Lucentis PrONTO press release" from Jesse Cedarbaum, and I am listed as one of the recipients.

Q. Okay. Now, according to this press release, it says, "Open label on controlled study of Lucentis showed improvement in vision with five to six doses at one year."

Do you see that?

A. I see that the title is "Open label on controlled study of Lucentis showed improvement in vision with five to six doses at one year."

Q. Do you recall whether anybody ever talked about a dosing regimen that you thought might be superior to the FDA-approved regimen for Lucentis?

A. We had -- we thought it was possible that aflibercept could be superior to ranibizumab. And the design of the

Phase III clinical trials was such that we did include a 2-milligram every-four-week dosing group as well as a .5-milligram every-four-week dosing group with the ability, if we met noninferiority in those groups, to then be able to test for superiority.

I should just clarify that that would have been true for all of the groups, including the third treatment group, which was three initial monthly doses followed by a dosing every eight weeks.

Q. During your time at Regeneron, has Regeneron identified any head-to-head dosing regimen where it believes aflibercept can demonstrate superiority to Lucentis in a manner that the FDA or clinicians would accept?

A. In the protocol T study, which was a study conducted by the Diabetic Retinopathy Clinical Research Network, with aflibercept, ranibizumab, and bevacizumab dosed in the same paradigm, which was a different paradigm than Regeneron has tested in our trials, aflibercept was superior to both ranibizumab and bevacizumab.

Q. Okay. And that particular dosing regimen of aflibercept you just mentioned that was shown to be superior to Lucentis, is that an FDA-approved dosing regimen or not?

A. That dosing regimen is not specifically reflected in our labeling.

Q. Do you remember generally what was -- what they were

doing in that one in terms of did it deviate from monthly dosing? was it number of injections?

A. My recollection is that it was monthly dosing for a certain number of doses and then criteria-based dosing based on the protocol --

Q. Okay.

A. -- which allowed for a longer treatment interval.

Q. And can you confirm this is an email from Michael Roosevelt to you, among others, dated Tuesday, May 9th, 2006?

A. Okay. I have Exhibit 219, and the date of the email is Tuesday, May 9th, 2006, with the subject "Action Items - May 9th, 2006," from Michael Roosevelt, and I am one of the recipients of this email.

Q. Then we've got the 0508 study, and that was one of the DME studies?

A. 0508 was the Phase II study in wet AMD with intravitreal aflibercept.

Q. And what was the name of that trial?

A. We referred to that as the CLEAR-IT 2 trial.

Q. Do you recall any concerns expressed internally at Regeneron about aflibercept's ability to achieve any efficacy end points by the 12-week -- with a 12 weeks' high dosing interval?

A. Are you referring to during the ongoing study?

Q. Yeah, either while the study was conducted or

afterwards.

A. So once we had -- so this email is referring to a time when the studies were ongoing. Once we received data from the studies and analyzed it, we did have some concerns that, based on the OCT data and an assessment of the visual acuity data, that the 12-week interval was one where we were seeing some loss of efficacy over that duration.

Q. And how were you defining loss of efficacy?

A. So, primarily, we were looking at the central retinal lesion thickness measured by optical coherence tomography, which was a very quantitative measure of the fluid in the retina. And one aspect of that data is that we would see a rapid reduction in retinal fluid after dosing with aflibercept, and over the longer time period without treatment, we would see some of that fluid begin to reaccumulate.

Q. And on this one I'd like to start with the email at the end of the chain from George Yancopoulos to you and others dated Tuesday, May 16th, 2006. So let me know when you're there.

A. Yes, I have Exhibit 220 in front of me, and I see the email from -- in the string from George Yancopoulos dated Wednesday, May 17th, 2006, and I am one of the recipients.

Q. Okay. And they're also talking about the PrONTO data, which was Dr. Rosenfeld's Lucentis study, right?

A. Yes, this email is referring to the PrONTO study.

Q. It looks like Dr. Yancopoulos is saying, about the PrONTO data, that Lucentis was not lasting for two months, which could provide a major opportunity for VEGF Trap interval advantage. Do you see that?

A. Yeah. So this is an email from the string dated Tuesday, May 16th, 2006, subject, "PrONTO data."

Q. Okay. So was that -- was Dr. Yancopoulos's assessment of the Lucentis PrONTO data something that caused everybody to start saying, okay, we know Lucentis can't go for more than two months?

A. So we were -- I don't recall specifically if this data in any way translated to further discussions about the dosing regimens planned for the VIEW 1 and VIEW 2 studies.

Q. Well, he says, "This indeed may provide us a major opportunity for VEGF Trap interval advantage."

Did you look at that and get excited and say, yeah, it will, or was it just more, like, whatever, you just continued on your merry way?

A. We were excited about the possibility of aflibercept having a longer treatment interval based on the properties of the molecule itself as well as the emerging data from the clinical development program.

I believe that Lucentis was approved in 2006 and was, because of their clinical trial results, slated to become standard of care. So I think that, you know, it wasn't

specifically any outcome from Lucentis trials that made us excited, but we were certainly monitoring the competitive landscape closely.

Q. What was your -- to your recollection, what was Regeneron's rationale for why the VEGF Trap aflibercept molecule would be able to last longer as compared to Lucentis ranibizumab?

A. So my understanding of Regeneron's rationale is that, first, aflibercept is a larger molecule and, as a result, has a longer half-life than Lucentis does, as well as the fact that we have a much, much higher binding affinity and other kinetic properties of binding to VEGF that we felt would be advantageous for aflibercept and contribute to potentially a longer duration of action.

Q. And to date, as far as you're aware, has Regeneron ever validated that those two things, having a longer half-life and increased binding affinity, actually is what's allowing aflibercept to be dosed at these longer intervals as compared to ranibizumab?

A. So the evidence we have of the longer duration of action is from the clinical trial results based on outcome in the clinical studies.

Q. Now, if we can go to the front page of Defendant's Exhibit 220, you were also cc'd again on the email string, this time on May 17th, 2006, from George Yancopoulos, about the

PrONTO data, and he was responding to an email from Avner Ingerman.

Do you see that?

A. I do see the email dated 17 May 2006 from George to Avner and others where Avner is responding to an email from -- or sorry -- George is responding to an email from Avner.

Q. Now, Avner was discussing not just PrONTO but also the MARINA and ANCHOR trials. Those were also -- those were official Lucentis trials run by Genentech, right?

A. The MARINA and ANCHOR trials were the Phase III studies sponsored by Genentech for Lucentis in neovascular AMD.

Q. Okay. In discussing those trials, he said, "It may suggest that the so-called 'clinician prn practice' following 'induction dose' is as good as monthly injections for at least the first year, and that is probably the take-home message that the market will follow."

Do you see that?

A. I do see that sentence in the email.

Q. Do you know whether anybody agreed or disagreed with Avner's assessment that that's how clinicians would likely respond to this data?

A. Sorry. Can you just restate the question?

Q. Sure.

Do you recall within Regeneron whether people agreed or disagreed with Dr. Ingerman's view that clinicians would

probably perceive the clinician prn practice following induction dose was as good as monthly injections for at least the first year when it came to ranibizumab?

A. My recollection is that Dr. Yancopoulos strongly disagreed with the concept that prn dosing was as good as monthly dosing as studied in the ANCHOR and MARINA trials.

Q. So why did Dr. Yancopoulos agree to any type of prn-type dosing in the later part of the VIEW studies if he was adamant it wasn't going to work?

A. My recollection is that the most critical portion of the study and the portion of the studies that defined our initial dosing regimen in our application to the FDA was the one-year data from the VIEW 1 and the VIEW 2 studies.

Q. Let me know when you have that.

A. Okay. I have Exhibit 222 in front of me.

Q. All right. And can you confirm that there's -- that you were forwarded by Jesse Cedarbaum on or around September 5th, 2006, a message -- an email message involving Jesse Cedarbaum and Phil Rosenfeld, dated September 1st, 2006?

A. So I see the second sort of message in this string as a forwarded message from Jesse Cedarbaum, dated the 5th of September 2006. It was primarily to Len Schleifer, but I am copied.

Q. Well, one of the things that Dr. Rosenfeld told Jesse Cedarbaum which was passed on to you is he said, "You have a

chance of use a 4-milligram dose, which is a fourfold molar excess over Lucentis, with a good chance of better durability. The more I thought about your dilemma, I would go with the 2-milligram and 4-milligram dose every two weeks or four weeks for a fixed number of doses, then see the patients back every four weeks and dose as needed. With the competition closing in on you, I think your only choice is to go for the gold and design a Phase III now."

Do you see that?

A. I do see where the email states that phrasing.

Q. Do you remember internally ever discussing the possibility of using a 2-milligram dose in your Phase III clinical trials before Jesse Cedarbaum got this feedback from Dr. Rosenfeld?

A. I don't recall specifically the timing of the discussions regarding dose selection for Phase III.

Q. All right. If you look at the top email, this is Len Schleifer saying, "This is Phil Rosenfeld's view of our diabetes opportunity." And then he says in the second line, "Jesse showed him the four-week, five-patient DME data which showed a nice response at four weeks and then a small loss by six weeks."

Do you see that?

A. I do see where that sentence is.

Q. All right. Do you know which clinical trial data

that was that was the four-week five-patient DME?

A. My assessment is that that is referring to the 0512 study, which was the Phase I study with intravitreal aflibercept in DME.

Q. Is it possible that -- well, do you recall who was responsible for designing the Phase II DME study that's referred to here in Example 5 of the '601 patent?

A. So, again, I don't recall specifically who was involved at that time, but it would have included members of the clinical development group, including myself and Dr. Vitti. Alyson Berliner, I believe was the study director. We consulted with our regulatory colleagues as well as senior management and others regarding the study design.

Q. I would like to mark as DX224 a document with production numbers RGN-EYLEA-MYLAN-65438 through 449.

What was the purpose of the global project team?

A. The global project team was a cross-functional team established as part of the Bayer collaboration to oversee development for aflibercept with our codevelopment partner.

Q. And did the Bayer people have input into what your Phase III clinical trial would look like in terms of dosing regimens?

A. As part of the Bayer collaboration, they had input into aspects of the clinical development planning, including study designs, but the ultimate scientific decision-making

remained with Regeneron.

Q. Can you confirm on the first page of DX226, there's an email from you dated March 29th, 2007, to Jesse Cedarbaum where you were forwarding the conversation on VEGF Trap executive summary of scientific advice meeting with Swedish MPA?

A. Yes. So I have Exhibit 226 in front of me, and I see the second email in the string is a forwarded email from me to Jesse Cedarbaum on the 29th of March 2007 with the subject "VEGF Trap - Executive Summary of Scientific Advice meeting with Swedish MPA on 28 March '07."

Q. If we take a look at Jesse Cedarbaum's responsive email, can you confirm that that's dated March 29th, 2007, and went to individuals such as Avner Ingerman and George Yancopoulos?

A. Yes. So the first email in the string here is dated Thursday, March 29th, 2007, forwarded VEGF Trap executive summary of scientific advice meeting with Swedish MPA from Jesse Cedarbaum to Peter Powchik, Avner Ingerman, and others.

Q. Sure. Is Regeneron aware of anyone who put together for the Phase III VIEW 1-VIEW 2 clinical trial design a 2-milligram dose at an eight-week dosing interval before Dr. Cedarbaum's email we're looking at here of March 29th, 2007?

A. I don't recall exactly the discussions around the

eight-week interval or whether Dr. Cedarbaum, by virtue of this email, was the first person to suggest the eight-week interval.

Q. Can Regeneron identify anybody who did it -- who put those two pieces together -- 2-milligram dose, eight-week interval -- before Dr. Cedarbaum did?

A. I can't speak on behalf of Regeneron. I can only speak for myself, and I do not recall a person who specifically put that together in this time frame.

Q. And, Ms. Chu, if you can confirm this is an email from Kathleen Lawrence to you and others, dated Monday, April 2nd, 2007?

A. So I have Exhibit 227 in front of me with a date of April 2nd, 2007, subject, "Decisions & Actions: AMD Phase III Program Meeting, April 2, '07," from Kathleen Lawrence, and I am a recipient of this email.

Q. Do you recall if you were a participant in this AMD Phase III program meeting on April 2nd, 2007?

A. I don't recall this specific meeting, but in my role I would have attended such meetings.

Q. Now, the third bullet point down says -- this is for the first time we see this, "2 milligrams q8 weeks with PIER lead-in (dose monthly for first three months)."

Do you see that?

A. I do see that the third bullet states, "2-milligram q8 weeks with PIER lead-in (dose monthly for first three

months)."

Q. All right. Who actually assembled that particular regimen as one of the arms to consider for the VIEW 1 Phase III clinical trial?

A. I don't recall specifically who proposed that dosing regimen.

Q. Sure. In your capacity as Regeneron's 30(b)(6) witness, what's the significance of this April 4, 2007, email from George Yancopoulos to Darlene Jody?

A. So this email from George to Darlene Jody, who was a senior executive responsible for the Bayer collaboration with us, is communicating the Regeneron proposal and decisions around the optimal designs for the VIEW 1 and the VIEW 2 trials.

Q. Is there anywhere in here where Dr. Yancopoulos is advocating for starting off the regimen with three monthly 2-milligram doses and then going to the eight-week interval?

A. In my review of this email, I do not see that it includes mention of the three initial monthly doses for the q8-week group.

Q. And did you review this email in connection with preparing for your deposition in this case?

A. I have Exhibit 229, date Tuesday, April 10th, 2007, subject, "Forward: VEGF Trap-Eye GDP for REGN/Bayer" from George Yancopoulos to Darlene Jody. And, no, I did not review

this email in preparation for today's deposition.

Q. Right. And just to be clear, that dosing regimen of VEGF Trap 2 milligrams every -- dosed every four weeks times three, then q8 thereafter, that was a dosing regimen drafted by Bob Terifay, right, in this email string?

A. My recollection of how decisions were made at Regeneron at the time was that this proposal would not have been discussed at the joint development committee meeting unless George had had input and agreed that this was the proposal for the Phase III studies.

Q. Well, if George Yancopoulos had signed off on that as the dosing regimen, why is he actually arguing against that, then, on April 10th, 2007, to Darlene Jody?

A. My read of the email didn't give me the impression that George was arguing against it. If you can point to what specifically you're referring to, I'd be happy to review it again.

Q. Nowhere in this April 10th, 2007, email to Darlene Jody is George Yancopoulos advocating for the dosing regimen that Bob Terifay identified of an aflibercept dose of 2 milligrams dosed every four weeks three times followed by a dosing every-eight-week regimen, true?

A. I can't speak to George's intent.

Q. It's not a question of intent. It's a question of what's written here in the email.

A. It is correct that that is what -- what is written in this email is the sentence, "That is based on both U.S. and EU regulatory interactions. Such a study will definitively fulfill their requirements as one of the studies. While final dose/interval for the fourth arm of the study are a bit unsettled, we can use 2q8 for now as the most likely dose/interval."

Q. I'd like you to take a look at the email from Robert Terifay that is dated April 17th, 2007, to George Yancopoulos, Len Schleifer, Peter Powchik, Avner Ingerman, and Neil Stahl, subject, "U.S. commercial concerns regarding the Bayer compromise."

Let me know when you're there.

A. I see that email beginning on page -- the second page of this email -- the last three numbers are 333 -- from Robert Terifay, dated 17th of April 2007, to George Yancopoulos with others copied.

Q. Do you have an understanding as to why Robert Terifay would have been involved in these discussions over selecting the Phase III clinical trial regimen?

A. Bob Terifay was the head of our commercial group at that time and, as such, would have had input on the clinical development program as it related to commercial viability and commercial considerations.

Q. Again, if we look in DX230, the top email, dated

Wednesday, April 8th, 2007, from Robert Terifay to Peter Powchik, Len Schleifer, and George Yancopoulos, Avner Ingerman, Neil Stahl, and Laura Pologe, the second paragraph, he says, "From an 0508 perspective, it appears that 2q8 (especially if initiated as a 2q4 loading dose for the first three months) can offer similar improvement in visual acuity and maintain that level similarly to 2q4 and Lucentis q4. This would be a major win for VT" -- referring to aflibercept -- "versus Ran" -- referring to ranibizumab -- "in Phase III," right?

A. I see the email dated Wednesday, April 18th, 2007, from Bob Terifay to Peter Powchik and others with the first bullet stating that "From an 0508 perspective, it appears that 2q8 (especially if initiated as a 2q4 loading dose for the first three months) can offer similar improvement in visual acuity and maintain that level similarly to 2q4 and Lucentis q4."

Q. '601 patent, Claim 1.

A. So in patent '601, Claim 1, it's stated that a method for treating age-related macular degeneration in a patient in need thereof comprising intravitreally administering an effective amount of aflibercept, which is 2 milligrams approximately every four weeks for the first three months, followed by 2 milligrams approximately once every eight weeks or once every two months.

Q. Right. And that dosing regimen matches the one that

Robert Terifay is advocating for in DX230, his April 8, 2007, email, of 2q8 initiated as a 2q4 loading dose for the first three months, right?

A. My interpretation of the email from Bob Terifay is that he is describing the same dosing regimen.

Q. Ms. Chu, can you confirm that this document, DX231 is an email to you and others from Avner Ingerman, dated Thursday, August 2nd, 2007?

A. So I have Exhibit 231, which is an email dated August 2nd, 2007. The subject is "Emailing: NCT00509795.htm" from Avner Ingerman, and I am copied on this email.

Q. Okay. And in the text of this email, is he providing the information that was published at ClinicalTrials.gov in connection with ClinicalTrials.gov identifier NCT00509795?

A. So my review of this email this minute indicates that this is Dr. Ingerman forwarding the ClinicalTrials.gov posting of the VIEW 1 Phase III study.

Q. To your prior point, can you take a look at the last page of Defendants' Exhibit 231. Can you confirm that, above the last three lines, it says, "ClinicalTrials.gov processed this record on August 1st, 2007."

A. I do see where it says, "ClinicalTrials.gov processed this record on August 1st, 2007."

Q. And under the inclusion criteria, the signed informed consent, were patients obligated to keep secret their

participation in Regeneron's clinical trials?

A. No, patients were not obligated in any way to keep their participation in the study secret.

Q. Do you have it now?

A. I have Exhibit 232 in front of me.

Q. Okay. And are you identified as a coauthor on this presentation?

A. So this appears to be a poster, and I am listed as an author.

Q. And why did Regeneron want to present its data involving aflibercept and its clinical trial data at these scientific conferences?

A. So it's scientific practice that we share our results in the context of scientific congresses and publications, and thus this was part of this scientific exchange that we were contributing to.

Q. Could you try to find in your stack what they labeled as Defense Exhibit 232.

A. Okay. I have Exhibit 232.

Q. Ms. Mazzochi had some questions for you about Defense Exhibit 232. Do you know if this is a draft or final document?

A. I don't know if Exhibit 232 is draft or final.

Q. Okay. You can put that document aside.

If you could find in your stack Defense Exhibit 234.

A. Okay. I have 234.

Q. On Defendants' Exhibit 234, do you have a habit of letting people put your name on documents or scientific presentations that you don't review and approve?

A. No. If I am an author, I definitely would have reviewed and provided input into the content of the document.

Q. Right. And you would have made sure that any statements, at least to the extent they were within your area of operation, were truthful and accurate, right?

A. Yes. Part of my review would be for accuracy.

Q. And when you were assembling that information, that was done with an understanding that the data would become public, right?

A. Sure. So in assembling data for the purpose of a presentation at a scientific congress, it was understood that that data would become public.

(Video ends.)

MS. BODA: And for administrative purposes, defendants move into evidence the following exhibits, which I believe are all agreed to: DTX 200, DTX 202, DTX 204, DTX 205, DTX 207, DTX 209, DTX 210, DTX 211, DTX 212, DTX 213, DTX 214, DTX 215, DTX 218, DTX 219, DTX 220, DTX 222, DTX 224, DTX 226, DTX 227, DTX 228, DTX 229, DTX 230, DTX 231, DTX 232, and DTX 234.

MR. GREGORY: No objection.

THE COURT: No objection to those? Okay.

That list, Counsel, is hereby deemed admitted.

Any exhibits from the plaintiff's perspective from that deposition?

(DTX 200, DTX 202, DTX 204, DTX 205, DTX 207, DTX 209, DTX 210, DTX 211, DTX 212, DTX 213, DTX 214, DTX 215, DTX 218, DTX 219, DTX 220, DTX 222, DTX 224, DTX 226, DTX 227, DTX 228, DTX 229, DTX 230, DTX 231, DTX 232, and DTX 234 were admitted.)

MR. GREGORY: None from the plaintiff's perspective.

THE COURT: Understood. Why don't we go ahead and take our morning break at this point. We'll take ten minutes, then we'll proceed with Mylan's next witness.

(A recess was taken from 10:19 a.m. to 10:33 a.m.)

THE COURT: Mylan may call its next witness.

MS. MAZZOCHI: Thank you, Your Honor. The defendants call Dr. Jay Stewart as part of their invalidity case in chief. And Dr. Stewart's opinions specifically involve the issues relating to the dosing patent claims in compliance with 35 U.S.C. Section 112.

Your Honor, during the break, I believe we made efficient use of the binder distribution process; so hopefully you have copies up there.

THE COURT: Outstanding. Thank you all. You may proceed whenever you're ready, Counsel.

MS. MAZZOCHI: Thank you, Your Honor.

JAY M. STEWART, MD, DEFENDANTS' WITNESS, SWORN

DIRECT EXAMINATION

BY MS. MAZZOCHI:

Q. Good morning, Dr. Stewart. Will you please state your full name for the record.

A. Jay Stewart.

Q. Are you testifying on behalf of the defendants today?

A. Yes.

Q. Did you prepare demonstrative slides to assist the Court with your testimony today?

A. Yes.

Q. All right. Let's go ahead and turn to those. Can you briefly describe your educational background.

A. Yes. I received my undergraduate degree in biochemical sciences at Harvard College, my medical degree at Harvard Medical School. And I completed an internship at Brigham and Women's hospital and then a residency in ophthalmology at the University of California San Francisco, which we call UCSF. After that I did a fellowship training in vitreoretinal diseases and surgery at Doheny Retina Institute at the University of Southern California.

Q. When did you begin your own full-time practice?

A. In 2005.

Q. And can you describe some of your clinical and

academic positions, please.

A. Yes. So since 2005 I've been seeing patients at UCSF Medical Center. And this is a practice where we have many patients with age-related macular degeneration, or AMD, as well as other retinal conditions.

From 2009 to 2014 I was the medical director of that practice, in which capacity I oversaw decisions for the clinical practice. And since 2020 I've been the subspecialty medical director for the retina service.

Also since 2005 I've been seeing patients at San Francisco General Hospital, which is a facility where we have many patients with diabetes and diabetic retinopathy. I've been the director of the vitreoretina service at that site since 2006. And since 2014 I've been the chief of ophthalmology at that site, where I am responsible for overseeing all aspects of our department.

Q. Have you held any academic positions?

A. Yes. From 2005 to 2010 I was the assistant professor of clinical ophthalmology. From 2010 to 2016 I was the associate professor. And since 2016 I've been the professor of clinical ophthalmology.

Q. Have you received any grants to support your research?

A. Yes. I've had several grants from the National Institutes of Health to support research, one of which was a

study evaluating ultrasound for drug delivery into the eye.

Q. Do you currently serve as the editor of any medical journals?

A. Yes. I'm the editor in chief of the *American Journal of Ophthalmology Case Reports* and the associate editor in chief of *Annals of Eye Science*.

Q. For how many years have you been working in the field of ophthalmology?

A. Over 20 years.

Q. Approximately how many patients do you see each week?

A. About 75.

Q. And have you treated patients with age-related macular degeneration, diabetic macular edema, and diabetic retinopathy?

A. Yes.

Q. Prior to 2010 have you used any VEGF drugs to treat AMD, DME, or diabetic retinopathy?

A. Yes. I was using Lucentis as well as Avastin off-label.

Q. After Eylea came on the market, did you use that as well?

A. Yes. I've been using Eylea since it came on the market. And then more recently have also been using a new drug called Vabysmo, which is spelled V-A-B-Y-S-M-O, which is also approved for some of these indications.

Q. What do you consider to be some of your areas of expertise?

A. The diagnosis and treatment of vitreoretinal and other ophthalmologic conditions.

Q. I'd like you to take a look at DTX 7100.

And we'll put that up on the screen as well.

What is this document?

A. It's a copy of my CV.

MS. MAZZOCHI: Your Honor, at this time Mylan and Biocon proffer Dr. Stewart as an expert in the medical and surgical treatment of vitreoretinal and ophthalmic diseases.

THE COURT: Any voir dire or objection?

MR. GREGORY: No objection, Your Honor.

THE COURT: Without objection, the witness is deemed so qualified.

You may proceed, Counsel.

MS. MAZZOCHI: Thank you very much, Your Honor.

BY MS. MAZZOCHI:

Q. Dr. Stewart, have you heard the phrase "a person of ordinary skill in the art"?

A. Yes.

Q. Does the next slide, DDX 7.5, have both parties' definitions of a person of ordinary skill in the art displayed on them?

A. Yes.

Q. Do you qualify as a person of ordinary skill in the art at least as early as of January 2011 under either definition?

A. Yes.

Q. And have you applied that perspective of a person of ordinary skill in the art here?

A. Yes.

Q. Do your opinions change whether Regeneron or defendants' person of ordinary skill in the art definition applies?

A. No.

Q. You have these in your binder. It's PTX 3, the '572 patent, and PTX 1, the '601 patent. Did you review both of these patents in this case?

A. Yes.

Q. Can you summarize some of the issues that you considered with regard to Claim 6 of the '572 patent?

A. Yes. So Claim 6 depends upon Claim 1, which describes the method for treating an angiogenic eye disorder. And I had concerns about the definition of angiogenic eye disorder. It also describes a dosing regimen which I felt lacked written description and enablement.

Q. And when it comes to the term "angiogenic eye disorder," what are some of your concerns with the term "angiogenic eye disorder"?

A. I felt that the term was too broad and, therefore, was not enabled and also lacked written description support.

Q. Do you have specific concerns with the dosing information that's found in the patent?

A. Yes, that there is no limitation on the number of doses given and, therefore, it's not enabled and also lacks written description support.

Q. Thank you very much.

Can you summarize the issues that you looked at that were specific for Claim 25 of the '572 patent as well as Claims 11 and 19 of the '601 patent.

A. Yes. So Claim 25 depends upon Claim 15. Claim 11 depends upon Claim 10. And Claim 19 depends upon Claim 18. And all of these refer to a regimen of dosing that involves five loading doses. And I believe that there is no written description support for this and that it lacks enablement.

Q. And are your enablement positions with regard to these claims tied at least in part to some of the positions that Regeneron and Dr. Csaky have taken in this case for invalidity?

A. Yes.

Q. Have you also assessed the question of indefiniteness?

A. Yes.

Q. Can you explain that, please.

A. Yes. The term "approximately" is used at multiple points throughout the claims, and I feel that terminology is indefinite.

Q. Can you summarize some of the issues that you looked at with regard to the disclosures and the specification's related applications that may bear on the question of priority.

A. Yes. There were a series of applications that were filed in which new information was added to the subsequent filing.

Q. And did you consider whether that new matter supported or enabled the claims as well?

A. Yes.

Q. All right. Let's start with some of your enablement topics. And let's focus first on angiogenic eye disorder that appears in Claim 6 of the '572 patent.

So, Dr. Stewart, in connection with your review of the '572 patent's Claim 6, did you assess whether a person of ordinary skill in the art at the time the patent applications were filed would have been able to fully make and use the claimed method to treat the full scope of angiogenic eye disorders without undue experimentation?

A. Yes, I did.

Q. Did you also consider whether a person of ordinary skill in the art at the time the various patent applications were originally filed as well as amended, whether that person

would believe the inventor actually invented and possessed the particular dosing methods to treat the full scope of angiogenic eye disorder conditions listed?

A. Yes.

Q. All right. Now, does the '572 patent specification discuss eye disorders associated with angiogenesis?

A. Yes, it does.

Q. And is that in the '572 patent at Column 1, lines 40 to 65, and Column 5, lines 30 to 48?

A. Yes.

Q. In connection with your opinions in this case, have you reviewed Dr. Yancopoulos's trial testimony, including page 155, about what he called the common mechanism, that is, VEGF driving abnormal blood vessel growth and leak, including a statement that all these disorders shared a common mechanism?

A. Yes.

Q. In your opinion, can VEGF inhibitors driving normal -- I'm sorry -- can VEGF inhibitors driving abnormal blood vessel growth and leak be used today to treat some of the diseases listed as angiogenic eye disorders in the patent?

A. Yes. And we do use them to treat some of these disorders.

Q. Can you give a few examples of what those disorders are.

A. Wet AMD, CRVO, DME, diabetic retinopathy.

Q. Are there any other diseases on the '572 patent specification list at Column 5 that the '572 patent calls an angiogenic eye disorder where there is not so?

A. Yes. Several, including proliferative vitreoretinopathy, also known as PVR; pannus; and pterygium.

Q. Dr. Stewart, in connection with your opinions, I'd like you to assume that angiogenic eye disorders are associated with the growth and proliferation of blood vessels, that aflibercept is a VEGF inhibitor, and that a person of ordinary skill in the art has all of the teachings and examples given in the '572 patent.

With that understanding, would a person of ordinary skill in the art believe that the inventor had invented a method where the Claim 6 drug dose and schedule would apply for intravitreal aflibercept to treat proliferative vitreoretinopathy, pannus, and pterygium?

A. No.

Q. Can you explain why, please.

A. Because aflibercept, being a VEGF blocking agent, would work to block VEGF, but these conditions have more complex mechanisms of disease of which VEGF is only one component.

Q. And how about today? Have those in the field found a way to make intravitreal aflibercept work to treat proliferative vitreoretinopathy -- PVR -- pannus, or pterygium

using the dosing regimen set forth in Claim 6?

A. No.

Q. Can you explain why that is.

A. Well, I think through an understanding, again, of the mechanism of -- action of the drug and the complex mechanism of these diseases and clinical experience in the field.

Q. To support your opinions that the term "angiogenic eye disorders" lacks written description and enablement across the full scope of the term, did you find any support in the medical literature?

A. Yes.

Q. Can you give the Court an example from the medical literature that you believe supports your opinions that the method of Claim 6 of the '572 patent does not work to treat the full scope of conditions the specification lists as an angiogenic eye disorder?

A. Yes. This publication from Shahlaee, et al.

Q. And is a copy of the Shahlaee publication in your binder at DTX 5430?

A. Yes.

Q. Can you explain why you cited this Shahlaee paper.

A. This is a paper that reviewed several methods of trying to treat proliferative vitreoretinopathy, and one of the methods that they discussed was the use of anti-VEGF treatment. And they presented the fact that several studies that looked at

this method of treatment found no success.

Q. Do you have any other examples from the medical literature?

A. Yes. This manuscript from Shahraki, et al.

Q. And is a copy of that publication in your binder at DTX 5431?

A. Yes.

Q. Can you explain why you cited Shahraki?

A. Well, this was a --

MR. GREGORY: Your Honor, I'm sorry. I have to object. This level of disclosures is not in his expert report anywhere.

MS. MAZZOCHI: Your Honor, it's in his opening expert report at paragraphs 76, 81, as well as --

THE COURT: Could I have the report?

MS. MAZZOCHI: It should be in your binder, Your Honor.

THE COURT: There's a lot in here, Counsel. What tab am I looking for?

MS. MAZZOCHI: Sure. DTX 7099, which is his opening report.

THE COURT: Paragraphs for that again, Counsel? I'm sorry.

MS. MAZZOCHI: Let's start at paragraph 81, where he specifically cites these three references we've been reviewing

for this very purpose, that a person of ordinary skill in the art would not think they could be treated and are currently not treated with aflibercept.

MR. GREGORY: I'm sorry. I think 7099 is his reply report.

MS. MAZZOCHI: Oh, I apologize. 7098.

THE COURT: What paragraphs, then?

MS. MAZZOCHI: Paragraph 81. Oh, no. I'm sorry. My apologies, Your Honor. Let me start that over.

In his reply report, paragraph 81 is -- Dr. Stewart specifically cited these three references I've been reviewing for this premise.

THE COURT: What's the objection, then, Counsel?

MR. GREGORY: The objection -- yes, Your Honor. My objection is that -- I'm trying to find this here. In paragraph 81 there is a very terse description -- or citation, a string cite, "see e.g.," these three references, and no description of the source that Dr. Stewart is offering now from the discovery.

THE COURT: Was Dr. Stewart deposed?

MR. GREGORY: Dr. Stewart was deposed.

THE COURT: All right. Objection overruled.

You may continue, Counsel.

MS. MAZZOCHI: Thank you, Your Honor.

BY MS. MAZZOCHI:

Q. So, Dr. Stewart, let's just circle back. Can you just explain why you cited this publication, the Shahraki publication.

A. Yes. This was a publication that reviewed treatment approaches for the condition of pterygium.

Q. And did injecting the anti-VEGF drug improve the outcomes for pterygium patients?

A. No. They described that one of the treatment options that they were reviewing, which was the use of anti-VEGF treatment, yielded inconclusive results.

Q. Now, I believe these two publications used bevacizumab as the anti-VEGF inhibitor. Why did you choose to rely on them to opine they wouldn't work with aflibercept?

A. Because they share a common mechanism of action, which is to counteract VEGF. And so if we don't see efficacy with bevacizumab, we also wouldn't expect that with aflibercept.

Q. Do you have an example from the medical literature that is specific to aflibercept that supports your opinions that the method of Claim 6 of the '572 patent will not work to treat one or more conditions the specification lists as an angiogenic eye disorder?

A. Yes. This manuscript from Sella, et al.

Q. And is a copy of the Sella publication in your binder

at DTX 5429?

A. Yes.

Q. Can you explain why you cited Sella in your report.

A. They used aflibercept for treatment of formed corneal neovascularization and reported that it was ineffective.

Q. And is formed corneal neovascularization a subtype of the more general description corneal neovascularization?

A. Yes.

Q. Are there any diseases in which formed corneal neovascularization also plays a role?

A. Yes. One of the conditions we mentioned earlier, which is pannus.

Q. Than what is pannus?

A. Pannus is a growth on the ocular surface that contains corneal neovascularization as well as fibrotic tissue.

Q. And did the '572 patent offer any data beyond the prior art pertaining to these specific diseases that you've just identified: formed corneal neovascularization, proliferative vitreoretinopathy, pannus, and pterygium?

A. No.

Q. How about a mechanism-of-action theory beyond anti-VEGF?

A. No.

Q. Does the specification give any hint or suggestion towards the appropriate dosing schedule that would be needed to

treat diseases such as formed corneal neovascularization, proliferative vitreoretinopathy, pannus, or pterygium?

A. No.

Q. And in response to your expert reports in this case, did Dr. Csaky identify any data or test results, either in the specification or the medical literature, showing that intravitreal aflibercept actually will work using the Claim 6 method to treat each angiogenic eye disorder we see in the '572 patent?

A. No.

Q. In response to your expert report, did Dr. Csaky identify any specific rationale in the specification or medical literature beyond mere anti-VEGF behavior as to why a person of ordinary skill in the art could expect aflibercept to work to treat those diseases I just listed?

A. No.

Q. And to reach your conclusion that intravitreal aflibercept does not work to treat these diseases at all, did you rely on just the medical literature, or did you rely on other things?

A. I relied on an understanding of the mechanism of action of the drug as well as the complex mechanisms at issue in these particular conditions and familiarity with the field.

Q. In terms of your own personal experience, have you had to treat patients that have all four of these conditions?

A. Yes, I have.

Q. And have you ever used aflibercept as part of their care?

A. No.

Q. In your opinion, based on what we just discussed, would a person of ordinary skill in the art reading the '572 patent specification believe that the inventor actually possessed a method of treating the full scope of these angiogenic eye disorders with aflibercept?

A. No.

Q. In your opinion, based on what we just discussed, would a person of ordinary skill in the art reading the '572 patent specification in the relevant time frame believe that the dosing method of aflibercept set forth in Claim 6 was enabled to actually work to treat the full scope of angiogenic eye disorders?

A. No.

Q. Now, for your nonenablement opinion, did you also consider factors that are used to assess the question of whether a person of ordinary skill in the art can practice the full scope of the claims without undue experimentation?

A. Yes.

Q. All right. And on your Slide Number DDX 7.29, are these eight factors listed here the undue experimentation factors that you considered?

A. Yes.

Q. Okay. Let's start with the first three of these factors: quantity of experimentation, direction or guidance, and presence or absence of working examples.

In your opinion, if a person of ordinary skill in the art had the Claim 6 dosing regimen and a patient who presented with formed corneal neovascularization, proliferative vitreoretinopathy, pannus, or pterygium, would they find enough in the specification to give treatment direction, guidance, or working examples relevant to those disease states?

A. No.

Q. And can you explain why.

A. Because we don't receive any guidance or examples or rationale shown in those specifications regarding those conditions. And so they would need to perform an entirely new research project to figure out whether it could be used.

Q. Now, in his pretrial opinions in this case, Dr. Csaky suggested that, as long as you have the list of diseases, the steps, and understanding of the VEGF mechanism and knowledge that aflibercept worked well to treat wet AMD and other diseases we see in the examples, that would be sufficient to treat all of these other angiogenic eye disorders.

Do you agree?

A. No.

Q. Can you explain why.

A. I think the issue is that some of these conditions involve more than just VEGF as their mechanism of causing pathogenesis in the eye. So that's one aspect which is the complexity of the disease mechanism.

Another aspect is shown in this figure, which is a picture of the eye where we see the ocular surface highlighted in yellow where several of the conditions that we were just discussing are located. And that's not proximal to the site of intravitreal injections; so we wouldn't necessarily think that administering intravitreally would be the most effective way to treat those conditions.

Q. Let's talk about the next undue experimentation factor, the predictability or unpredictability of the art.

Is there anything that a person of ordinary skill in the art could use from the specification to predict that aflibercept will perform well using the Claim 6 regimen in PVR, pterygium, formed corneal neovascularization, or pannus in a way that would let them achieve success?

A. No.

Q. And why is that?

A. Because there isn't any such guidance or examples shown that would allow us to predict that it would work for those conditions.

Q. And, also, if Regeneron argues that this art generally is unpredictable for diseases such as DME or DR, even

if you progressed to the Phase II clinical study phase, would that increase or decrease the experimental burden on the person of ordinary skill in the art for the specifications here in your opinion?

A. That would increase the burden.

Q. And on this factor pertaining to the breadth of the claims, what would a person of ordinary skill in the art perceive about the breadth of the term "angiogenic eye disorder"?

A. I think they would perceive that term to be excessively broad.

Q. Now let's take a look at the factor relating to the nature of the invention. Directing your attention to the '572 patent abstract, what does it describe as the nature of the invention?

A. A method for treating angiogenic eye disorders by administering VEGF antagonist.

Q. So in your opinion, is any failure of the claimed methods to work to treat diseases such as pannus, pterygium, formed corneal neovascularization, or PVR something that is merely peripheral or more central to the invention?

A. It's central.

Q. For the factors involving the state of the art and the level of ordinary skill in the art, will the state of the art and high skill set of that person reduce the experimental

burden?

A. No, because even knowing the state of the art and even if they have a high level of skill, they would still, I think, understand that there isn't information within the specifications to guide them to be able to use this treatment for those particular conditions.

Q. And we've had an issued patent out there for quite some time. Since the patent has issued, to your knowledge, has this become -- has aflibercept become the standard of care at all or otherwise used for proliferative vitreoretinopathy, pannus, or pterygium?

A. No.

Q. Let's turn, then, to your ultimate opinions when it come to the angiogenic eye disorder for Claim 6.

Do you understand that, to satisfy the written description requirement, the patent must describe an invention understandable to a skilled artisan and show that the inventor actually invented and possessed the invention claimed?

A. Yes.

Q. And in your opinion, based on what we've just reviewed, would a person of ordinary skill in the art believe that the inventor actually invented or possessed a working intravitreal dosing regimen, as we see in Claim 6, to treat the full scope of angiogenic eye disorders, including, for example, proliferative vitreoretinopathy, pannus, and pterygium?

A. No.

Q. In your opinion, based on what we just discussed, would a person of ordinary skill in the art believe that the specification enabled a person of ordinary skill in the art to practice the full scope of angiogenic eye disorders covered by Claim 6 without undue experimentation?

A. No.

Q. All right. Let's talk next about some of your opinions relating to dosing.

MS. MAZZOCHI: And, Your Honor, I'm happy to have Dr. Stewart go through and discuss the loading dose concept, but if you're good with that, I don't need to repeat it.

THE COURT: I think I've got a good grasp of it at this point.

MS. MAZZOCHI: I thought so, but I didn't want to assume.

BY MS. MAZZOCHI:

Q. Dr. Stewart, directing your attention to the summary of invention section of the '572 and '601 patents, did you find anywhere in the specification that placed any emphasis on the number of doses that should proceed the eight-week dosing interval?

A. Yes. They referred to three doses.

Q. Did the specification illustrate what this type of dosing regimen, the three doses at the start, would look like?

A. Yes, in Figure 1.

Q. And in Figure 1 of the '572 and '601 patents, how many total loading doses, spaced four weeks apart, are illustrated before beginning the eight-week dosing regimen?

A. Three.

Q. Was there any figure that showed five?

A. No.

Q. Did you review the specification statements about loading dose or secondary dose frequency?

A. Yes.

Q. And did you also review Dr. Yancopoulos's trial testimony, including at transcript pages 235 to 236?

A. Yes.

Q. In your opinion, do the specifications for the '572 and '601 patents place any upper limit on the term "secondary" or "tertiary" doses that we see in the claims?

A. No.

Q. Did the specification provide any rationale for why you should stop with secondary dosing and switch to tertiary dosing that was not already known in the prior art?

A. No.

Q. And can you explain why a little bit.

A. Well, because the language that's used here refers to one or more secondary doses and then one or more -- so the -- there's no upper limit basically shown as to how many doses

that you would use.

Q. And then when it comes to any adjustments that should be made to the course of treatment by the physician as we see in the -- in Column 4, does that column talk about or give any guidance or recommendations to physicians for performing those adjustments up or down or beyond what was known in the art?

A. No. It just says according to the needs of the patient following clinical examination.

Q. And where would a person of ordinary skill in the art have to go, then, for guidance or reasoning as to why they should change their loading dose regimen?

A. I think it would be difficult, not having that information provided here, to know when to do so.

Q. Separate and apart from what was known in the art?

A. Right.

Q. Does the specification provide any reason to expand or limit the number of secondary or tertiary doses to use beyond what the person of ordinary skill in the art had already thought about and used for indications, such as DME or diabetic retinopathy?

A. No.

Q. Did you see anything in the specification that explains to a person of ordinary skill in the art that they should not be concerned about risks or side effects of more loading doses for the DME or DR regimen?

A. No.

Q. Did the specification for the '572 and '601 patents articulate for the person of ordinary skill in the art any reason to choose or select four secondary doses or a total of five monthly loading doses as opposed to the many other options found in the specification, particularly in the context of a DME or diabetic retinopathy indication?

A. No.

Q. All right. I'd like to direct your attention back to Column 4, specifically lines 22 to 31 of the '572 patent, because this is some text that Dr. Csaky pointed to to suggest that the number four on this list is enough to pick or support a dosing method with five monthly loading doses versus others.

In your opinion, is that enough?

A. No, it's not.

Q. And can you explain why.

A. Because it refers to two or more doses being shown. And if we could go back to that slide, it -- in fact, it says, for example, two, three, four, five, six, seven, eight, or more secondary doses. And so there's no indication that four is being differentiated or called out as compared to all the other numbers that are there.

Q. And so then can you summarize some of the problems that you identified regarding the specification when it comes to the dosing regimens?

A. Yes. Several. One was the fact that there were -- there was a preference for three doses, as we saw earlier, as opposed to five, and there was no particular justification or data as to why we would pull out five from the number of loading doses that was presented.

There was also no guidance across the entire scope of all the angiogenic eye disorders as to why we would choose a particular secondary or tertiary dosing regimen for each of the conditions.

There also wasn't any express guidance for DME and diabetic retinopathy on, again, choosing the five loading doses. And, in fact, there wasn't any clinical data at all regarding diabetic retinopathy shown in the specification.

So just in general, I think that the fact that there was no theory or rationale setting aside a lack of examples as to why you would transition between dosing regimens.

Q. Okay. And let's take a look at Dr. Yancopoulos's trial testimony at page 205. Does that testimony support or refute your opinions here?

A. It supports it.

Q. Can you explain why?

A. Because it refers to the fact that there are -- there wasn't any particular reasoning or rationale behind why you would go between the loading doses and the eight-week dosing.

Q. Dr. Stewart, did you find any data or rationale in

the '572 or '601 patent specification as a whole that was identified or called out in a way that would provide a blaze mark to a person of ordinary skill in the art to guide them towards selecting a particular dosing regimen of five loading doses followed by every-eight-week dosing for the specific indications of DME or DR?

A. No.

Q. I'd also like to spend a little bit of time to discuss Example 7 because that's another one of the things that Dr. Csaky pointed to in support for the five loading doses in response to your testimony.

Now, as a preliminary matter, did you also review, as part of your opinions in this case, DTX 5330, Patent Application Number 13/940,370 filed on July 12, 2013, as a continuation-in-part application?

A. Yes.

Q. And did DTX 5330, this July 12, 2013, continuation-in-part patent application, add anything new to the existing specification?

A. Yes. Example 7.

Q. So focusing on Example 7, then, which was added to the specification in July 12, 2013, did Example 7 contain any new clinical data?

A. No.

Q. What did Example 7 contain?

A. It contained, essentially, a laundry list of dosing regimens that could be used for this treatment.

Q. Can you explain generally what this laundry list of dosing regimens in Example 7 did include?

A. Yes. There were a variety of scenarios that were presented. One of them was treating every four weeks with the injection.

Another scenario involved treating every four weeks for the first eight weeks, followed by several different options, one of which was to give an injection every eight weeks.

Another scenario was to give an injection on a less frequent basis according to the physician's determination. And another scenario was to give injections on an as-needed or pro re nata, or prn, process.

There was another scenario in which injections were given every four weeks for, essentially, a series of durations -- 12, 16, 20, 24, et cetera, weeks -- followed by injections every eight weeks.

And then finally there was one scenario where a single injection was given in which all subsequent injections would be given on an as-needed basis.

Q. And if we look, for example, at the one you have in the upper right-hand corner where it says "once every four weeks for the first 12 weeks followed," did that also include

options for every eight weeks, physician assessments, prn dosing as well?

A. Yes.

Q. Okay. And -- sorry -- then what was the last regimen that we found in Example 7?

A. This is the single injection followed by an as-needed schedule.

Q. And that was called prn dosing?

A. Yes.

Q. Have you reviewed Dr. Yancopoulos's trial testimony at page 232?

A. Yes.

Q. Is Dr. Yancopoulos's testimony relevant to your opinion that Example 7 does not have any statements of preference?

A. Yes, it supports that.

Q. Okay. And why is that?

A. Because he said that we don't know which of these regimens would be able to produce the best visual outcomes.

Q. What did Dr. Yancopoulos identify in trial testimony you reviewed as needed to generate that guidance towards a regimen that would produce the best visual outcomes?

A. Phase III clinical trial data.

Q. Is any Phase III clinical trial data in the specification for DME?

A. No.

Q. Is there any clinical data at all, whether Phase I, II, or III, in the specification that is specific to a diabetic retinopathy indication alone?

A. No.

Q. In your opinion, does Example 7 give the person of ordinary skill in the art any added insight as to why or when to stop monthly dosing or every-four-week dosing and switch to a longer dosing interval?

A. No, it doesn't.

Q. In your opinion, does Example 7 give the person of ordinary skill in the art any added insight as to why they should select one of these particular regimens for any particular disease without the need for more experimentation or insight?

A. No.

Q. Did Example 7 include, though, a dosing regimen that could be characterized as having five doses separated by four weeks before transitioning to eight-week dosing?

A. Yes.

Q. Now, are there any blaze marks in either Example 7 or the specification generally that, in your opinion, would explicitly guide a person of ordinary skill in the art towards that regimen with five monthly loading doses followed by eight-week dosing?

A. No.

Q. And directing your attention to Column 16, lines 35 to 51, of the '572 patent, is that section where there are instances where you could have one loading dose followed by four monthly doses for a total of five monthly loading doses?

A. Yes.

Q. And did the specification express, in your opinion, any preference amongst these five loading dose different regimens we see in Example 7, eight-week dosing versus the other two listed, such as prn?

A. No.

Q. Now let's turn to some of the clinical indications that follow Example 7.

Does the specification express any preference for using one of these Example 7 regimens with five loading doses or the one followed by the fixed eight-week dosing interval for any particular clinical indication?

A. No, it doesn't.

Q. In your opinion, does Example 7 as a whole or Example 7 in conjunction with the description of potential diseases provide sufficient blaze marks to a person of ordinary skill in the art to know which of these disease states might be preferred or the best for a physician to use with a given dosing regimen separate and apart from what was known in the prior art?

A. No.

Q. What diseases does the specification state these Example 7 dosing methods can be used for?

A. It lists a variety of eye conditions.

Q. Is DME singled out in the list anywhere or listed as preferred?

A. It does appear on the list, but it's not differentiated or called out as being preferred.

Q. Is diabetic retinopathy provided as a standalone indication?

A. No, it's not listed on this list.

Q. So if a person of ordinary skill in the art wanted to make decisions about concluding secondary to move to tertiary dosing or to select a fixed number of loading doses, in your opinion, does the specification point to any test, measurement, performance criteria they should use to make that decision that is separate and apart from what was already known in the prior art?

A. No, it doesn't.

Q. In your opinion, does the addition of Example 7 to the continuation-in-part specification that was filed in July 2013, does that help convince a person of ordinary skill in the art that the inventor possessed a method for treating all angiogenic eye disorders with any number of secondary and tertiary doses for all the diseases listed in the

specification?

A. No, it doesn't.

Q. Now, based on what we've just discussed, is there sufficient guidance in the specification to the person of ordinary skill in the art to establish that the inventor possessed the specific regimen of the method of Claim 19 of the '601 patent that has five loading doses followed by eight-week dosing specific to the diabetic retinopathy indication?

A. No.

Q. And can you give a brief explanation as to why.

A. Well, first of all, as I mentioned, diabetic retinopathy, there was no clinical information or evidence presented at all in the specification. And, again, there would be no reason shown as to why we would choose a particular regimen for that condition over any of the other regimens that were also mentioned in the example.

Q. Now, one of the things that Dr. Csaky did point to is that the original specification had Example 5 in it.

But what was the loading dose regimen and clinical indication that was specified in Example 5 as the required number of loading doses?

A. Three.

Q. Would a person of ordinary skill in the art accept, then, that the inventor possessed the specific regimen of the method of Claim 11 of the '601 patent that requires five

loading doses followed by an eight-week dosing regimen for DME if we accept Regeneron's view that the prior art taught away from increasing the number of loading doses?

A. No.

Q. And can you explain why?

A. Well, again, because if the prior art was telling us that we needed to not increase the number of doses out of the concerns that were mentioned, that wouldn't naturally lead you toward using five loading doses. And so that would be the reason.

Q. And would your answer be the same for the '572 patent, Claim 25, which also requires DME and five loading doses followed by an eight-week dosing regimen?

A. Yes.

Q. If the named inventor had discovered something special or distinct about this species using a method with five loading doses, what would you expect to see in the specification?

A. I would expect to see examples or rationale explaining that finding that would guide us to choose that regimen.

Q. And Dr. Csaky has also alleged that the success of the five loading doses for the treatment of DME and diabetic retinopathy was unexpected.

Have you seen that opinion from him?

A. Yes.

Q. And I believe Dr. Csaky said that it was subsequently found after the VIEW 1 and VIEW 2 trials that the five loading dose regimen for DME or DR worked, citing to publications from Brown 2015 about the VISTA and VIVID studies and Brown 2021 for the PANORAMA study.

Did you review those?

A. Yes.

Q. Did those change your opinions?

A. Well, no, because they came out in 2015 and 2021, which was after the patent at issue here.

Q. And do the Brown 2015 and Brown 2021 articles support the premise that the named inventor was in possession of a five loading dose regimen back in 2011 or 2013?

A. No.

Q. In any event, did any of this Phase III data that Dr. Csaky is relying on specific to DME and diabetic retinopathy make it into the specification of the '572 or '601 patents?

A. No.

Q. All right. So based on what you had just discussed, what did you ultimately conclude about the specification disclosures and whether there is written description support for choosing five loading doses followed by an eight-week dosing regimen in the context of the DME or DR regimens within

the specification?

A. I think, again, for diabetic retinopathy as its diagnosis, there wasn't any data shown as to the treatment of that condition. And when it comes to DME, the data that was presented used three loading doses. And so there wasn't any information -- there wasn't any guidance on why to expressly choose the five loading dose regimen over any others.

Q. So when it comes to Claim 25 of the '572 patent and Claims 11 and 19 of the '601 patent, in your ultimate opinion based on what we've discussed today, is there sufficient guidance in the specification to establish that the inventor had possession of the claims to these specific dosing regimens particularly with regard to the five monthly loading doses at the time the applications were filed in 2011?

A. No.

Q. How about for 2013?

A. No.

Q. All right. Let's focus now again on enablement and go back through those In Re: *Wands* factors. And let's start again with the first three factors relating to quantity of experimentation, direction or guidance, or the presence or absence of working examples when it comes to the dosing.

So for Claim 6, does the '572 patent specification give the person of ordinary skill in the art any guidance or reason as to why he should stop secondary dosing and move to

tertiary dosing beyond what was already known in the prior art?

A. No, it doesn't.

Q. And what kind of experimentation would a person of ordinary skill in the art have to do to decide from the specification the number of secondary doses that are needed when treating the full scope of angiogenic disorders in Claim 6, such as the ones we discussed earlier for PVR, pannus, and pterygium?

A. They would need to conduct an entirely new research project for each of those conditions to decide how and if the treatment could be effective for it and what the dosing regimen should be.

Q. Let's talk about one of the next factors, predictability in the art. Would you be able to predict whether or not any one of the numerous dosing regimens or numerous secondary dosing options that the specification permits would work for all of the disclosed angiogenic eye disorders covered by Claim 6 of the '572 patent, including PVR, pannus, and pterygium?

A. No.

Q. Let's take a look at the rest of the factors on your chart.

Can you explain how you weighed the remaining factors -- the breadth of the claims, nature of the invention, state of the prior art, and relative skill -- for the full

scope of the Claim 6 dosing regimens?

A. Yes. As I mentioned earlier, I think that the claim is excessively broad and its inclusion of a variety of diagnoses under the category of angiogenic eye disorders. There wasn't any information presented in the prior art as to why that particular treatment regimen should be used. And I think that, even with a high level of skill, a person of ordinary skill in the art would have a difficult time knowing how they should proceed with that without conducting research and experimentation.

Q. And in that context, you're referring to the pannus, PVR, and pterygium, for example?

A. Correct.

Q. Now let's talk about the five loading dose claims.

If, as Dr. Yancopoulos suggested in his testimony, and if Dr. Csaky testifies consistently with his opinions put here on your slide that the Phase II DME data was not enough for a person of ordinary skill in the art to reasonably expect success in clinical practice that phase proof was needed, if we accept those things, what would be the experimental burden on the person of ordinary skill in the art when it comes to clinical practice of the DME and DR claims with five loading doses that we see in Claim 25 of the '572 patent and Claims 11 and 19 of the '601 patent?

A. They would be high if they have to conduct Phase III

trials for each of those.

Q. And is there a working example or guidance or reasoning why in the specification that expressly calls out any benefit to having five doses for DME or DR beyond what was already known in the prior art?

A. No.

Q. Again, does the specification give any working examples specific to addressing diabetic retinopathy as a standalone indication?

A. No.

Q. So for these five loading dose claims, if, as we expect, Dr. Csaky is going to opine that the art taught away from and discouraged the use of five loading doses for safety reasons, in your opinion, does the specification resolve those allegedly discouraging safety concerns when it comes to using five loading doses in DME or DR patients?

A. No, it doesn't.

Q. And how do you know that?

A. Because we don't see any guidance about the safety being assured that we should use a five-loading-dose regimen.

Q. On this question of examples and guidance and direction, Dr. Csaky did point to Example 7 as containing a dosing regimen with five monthly loading doses followed by eight-week dosing, among others.

In your opinion, is that helpful here?

A. It's not.

Q. And can you explain why.

A. I think the issue is simply that the five-loading-dose regimen was one of many regimens that were presented, and there was no differentiation of that regimen over all the others. So we wouldn't know that that should be the best one to use.

Q. And was there at least any attempt to tie increased loading doses to a particular disease state such as DME or DR?

A. No.

Q. Now, in the relevant time period, did those of ordinary skill in the art change their dosing strategies if diabetic retinopathy was presented without DME?

A. Yes. I think diabetic retinopathy without DME has different clinical end points, and the clinical decision-making for injections is different. In fact, one might think that the number of loading doses might be fewer or the frequency of injections might be fewer if you're not trying to treat macular edema but rather trying to treat other biomarkers and end points in diabetic retinopathy.

Q. And either way, does the specification suggest to the person of ordinary skill in the art that they should be varying the number of loading doses depending on the type of diabetic retinopathy that the patient has?

A. No.

Q. So then in your opinion, and particularly if, as Dr. Yancopoulos and Dr. Csaky have suggested, getting workable dosing regimens are not routine and involve years of costly and difficult advanced human Phase III clinical trial data before someone can reasonably expect a regimen to work in their clinical practice, will the person of ordinary skill in the art have a high or low experimental burden when it comes to the DME and DR claims with five loading doses we see in Claim 25 of the '572 patent and Claims 11 and 19 of the '601 patent?

A. It would be high.

Q. And can you explain why.

A. Simply because, in order to carry out these studies, it would be essentially a Phase III clinical trial for each of these indications. And to be able to arrive at that conclusion, it would be a high burden of experimentation.

Q. Now, again, in your opinion -- and, again, this is qualified by if -- as Dr. Csaky suggests here, the art suggested reducing loading doses to three or four or even less, does the specification give a person of ordinary skill in the art any type of express reason to buck that trend and pick five loading doses instead for DME or DR with a belief that it would work?

A. No.

Q. And that's true even if they have the specification in hand?

A. Correct.

Q. Can you explain how you weighed the remaining factors, the breadth of the claims, the nature of the invention, the state of the prior art, and the relative skill for the '572 patent's Claim 25 and '601 patent Claims 11 and 19 pertaining to the five-loading-dose regimens?

A. I thought that these were more neutral with regard to those claims.

Q. Okay. And can you explain why.

A. So why I felt they were more neutral? Is that what you mean?

Q. Yes.

Actually, if we could go back one slide.

Yes, if you can explain briefly why.

A. Simply because these claims were narrower, and they were not relying upon as broad of a terminology as was present in the other claims. And that's primarily my thought process here.

Q. So in view of the testimony that you've given, what is your ultimate opinion regarding enablement for Claim 6 of the '572 patent?

A. So my concern there is that, again, because there was essentially an unlimited number of dosing regimens -- doses that could be given and dosing regimens for -- even for diseases that we wouldn't think it would be effective for, that

that would cause problems for enablement. And, again, there was no guidance or teaching to suggest why it should do so. So this would lead to a need for excessive experimentation.

Q. In view of testimony that you've given, what is your opinion regarding whether the five loading doses for the DME claims found in Claim 25 of the '572 patent, Claim 11 of the '601 patent, are enabled by the specification, again, with the qualification if this Court were to accept Regeneron and Dr. Csaky's opinions about the art?

A. Again, because there was no specific teaching or guidance as to why that particular regimen should be chosen for DME, that would, for me, cause concerns around enablement and leading us to have to do experimentation to find that out.

Q. And likewise in view of the testimony that you've given, what is your opinion regarding whether Claim 19 of the '601 patent is enabled if -- and, again, this is if with a qualification -- this Court were to accept Dr. Csaky and Regeneron's view of the art?

A. I think similarly, because we don't see any guidance or teaching regarding diabetic retinopathy and, in fact, no clinical data at all about that condition save for the form that has DME, we again would consider this to require experimentation to determine if it could be effective or not.

Q. And, Dr. Stewart, in view of -- for all of those -- again, with the qualifications relating to what Regeneron's

position has been and Dr. Csaky's opinions have been -- would that experimentation be undue for a person of ordinary skill in the art?

A. Yes.

Q. Dr. Stewart, in view of the testimony that you have given, do you also have any opinions regarding the priority date that should be given to Claim 25 of the '572 patent, Claim 11 of the '601 patent, and Claim 19 of the '601 patent?

A. Yes.

Q. And can you summarize that for us briefly, please.

A. Essentially that the only scenario in which five loading doses followed by an eight-week dosing regimen was shown within the specification was in Example 7. And so that was in July of 2013. So it wouldn't -- I wouldn't think that it could go to a date earlier than that for that particular regimen.

The previous submissions didn't include support for that regimen. And none of the regimens that were -- there wasn't express callout for why that regimen should be chosen, and so there wasn't anything, I think, beyond what we already knew as to why you would treat a patient in that fashion.

Q. But even though there was no dosing regimen with five loading doses until the continuation-in-part application where they added Example 7 in July 12th, 2013, even with Example 7, is it still your opinion that the -- that there is no written

description support or enablement for those claims?

A. Yes, it is.

Q. All right. Now, do you also understand that Dr. Csaky has made some allegation that Regeneron may deserve an earlier priority date perhaps based on some internal documents from Regeneron?

A. Yes, I do.

Q. Did Dr. Csaky explain why he thought this was so?

A. No.

Q. Did you review these internal Regeneron documents?

A. Yes.

Q. And did your opinion regarding the priority date change after your review?

A. No.

Q. And can you explain why.

A. Because, again, I didn't see any justification for why those regimens should be called out for those particular conditions even from review of those documents.

Q. All right. If you take a look at DTX 5329 in your binder, can you confirm that this is U.S. Provisional Patent Application Number 61/432,245 filed January 13, 2011?

A. Yes.

Q. And if you could take a look at DTX 5332 in your binder, can you confirm that this is U.S. Provisional Patent Application Number 61/561,957, filed November 21st, 2011.

A. Yes.

Q. And are both of these applications in the chain of applications that eventually issued as the '572 and '601 patents?

A. Yes.

Q. If you could take a look at DDX 572 in your binder.

And I think that's one of the spiral-bound ones that's in the pocket, Your Honor. Did you prepare or have prepared this demonstrative exhibit?

A. Yes.

Q. Can you explain what it shows?

A. It shows the information presented and the different submissions being highlighted in different fashion. The information from the January 2011 submission is in plain text. The information added in the November 2011 submission is highlighted in blue, and the information added in the July 2013 submission is highlighted in yellow.

Q. If you could take a look at DDX 601 in your binder. Did you similarly prepare this demonstrative exhibit for the same reasons and using the same color-coding?

A. Yes, I did.

MS. MAZZOCHI: So just to sum up for the record, Your Honor --

BY MS. MAZZOCHI:

Q. And, Dr. Stewart, if you could confirm this.

The highlighted copies of the patents DDX 572 and 601 put new material not found in the original provisional application, DTX 5329, but found in DTX 5332 in the November 2011 application, Dr. Stewart, those are in blue highlights in your DDX exhibits?

A. Yes.

Q. And the highlighted copies of the patents, DDX 572 and 601, included new material not found in the original provisional application but which we do see in the July -- in DTX 5330, the July 2013 continuation-in-part application in yellow highlights?

A. Yes.

Q. Dr. Stewart, now let's move to our next major category, which is indefiniteness. Do you understand that patent claims are indefinite if they fail to inform a skilled artisan with reasonable certainty about the scope of the invention at the time the patent application was filed?

A. Yes.

Q. And do you understand that part of that analysis is whether a person of ordinary skill in the art would be able to determine with reasonable certainty what the claims do and do not cover?

A. Yes.

Q. Did you identify claim terms that, in your opinion, are indefinite?

A. Yes. The use of the word "approximately" that appears in multiple locations throughout the claims.

Q. And why, in your opinion, is the use of the word "approximately" a problem in the context of these claims?

A. Because it creates uncertainty around what the dosing regimen should be that would fall inside the scope of the claims.

Q. Okay. Well, to illustrate this, let's focus on Claims 10 and 11 of the '601 patent. What terms does approximately modify in Claim 10?

A. In Claim 10 it modifies every four weeks and every eight weeks.

Q. What terms does approximately modify in Claim 11?

A. In Claim 11 it modifies every four weeks, every 28 days, or monthly.

Q. Now, in the context of the '572 and '601 patent claims, why can't we say that approximately every four weeks means the same thing as approximately every 28 days or approximately monthly?

A. Because each of those has a different unit of time measure, and so it creates uncertainty around whether they mean the same thing or not.

Q. Turning to your next slide, 77, can you explain what you've shown on this slide.

A. This is a figure showing a calendar with a schedule

of injections, with the first injection being given on February 1st. The next injection four weeks later is on March 1st. And four weeks after that would be March 29th. But when we use the term "approximately every four weeks," it creates some range of error on either side of those particular injection dates.

Q. Okay. If we can turn to your next slide, 78. Can you explain what you've shown on this slide.

A. Yes. This is also a schedule showing an initial injection given on February 1st, 28 days later on March 1st, and again 28 days later on March 29th. But when we have the term "approximately every 28 days," this also creates uncertainty with a range of error on either side of those particular dates.

Q. Turning to your next slide, 79, can you explain what you've shown on this slide.

A. Yes. Again, a schedule of injection, with the first injection on February 1st, another injection four weeks later on March 1st, and four weeks after that on March 29th. But here if we think of this in the context of approximately monthly, exactly monthly would be March 1st, but with approximately monthly it creates a larger range of error around when exactly that injection would fall.

And so we can see that even the injection on March 29th, which is actually the eight-week injection, conceivably

could fall within an approximately monthly description.

Q. Does the specification use the term "approximately" anywhere outside the claims?

A. It's used once to describe the number of subjects enrolled in a clinical trial.

Q. Does that help give you any guidance as to the appropriate range to be given the term "approximately" in the claims we've been looking at here?

A. No.

Q. Did you see the term "approximately" applied to any dosing interval in the specification where the dosing interval was allowed to have some variability?

A. No.

Q. What did Dr. Csaky say about the definition of the term "approximately"?

A. His response to provide clarification around this topic used the word "approximate." So it didn't actually clarify this further for me.

Q. Does Dr. Csaky's definition provide the person of ordinary skill in the art with any more clarity, in your opinion?

A. No.

Q. Did you also consider Dr. Csaky's comments that approximately should be used merely to accommodate scheduling issues?

A. Yes.

Q. And he explains that the standard could be based on scheduling issues involving both the physician or the patient. Does that, in your view, help give the person of ordinary skill in the art reasonable clarity --

A. No.

Q. -- as to the scope of the claims?

A. No.

Q. And why not?

A. Because the schedule of the physician and the schedule of the patient might be subject to different constraints. A patient might not be able to come on a particular day depending on various factors. And that might create a certain range of error as far as when the patient could come back versus a doctor's schedule that might entail only having appointments available on certain days of the week and causing perhaps even a greater range of error around when the schedule would resume.

Q. And do you understand that Regeneron has also proposed that approximately should also take into account not just the ability to return to the office but a whole new metric which is a standard of retaining remarkable efficacy?

A. Yes.

Q. And does that standard of retaining remarkable efficacy provide, in your opinion, more clarity regarding the

term "approximately"?

A. It doesn't.

Q. And why not?

A. Because that would -- could potentially determine -- depend upon how we determine efficacy. We might determine efficacy based upon vision or anatomic features of the eye, and that might lead you to different strategies such as treat and extend and other regimens that involve maintaining efficacy over a certain period of time with a lesser frequency of injection. And so having to retain efficacy doesn't actually help guide us to know what the schedule should be.

Q. And could retaining efficacy also include a prn regimen?

A. It could.

Q. All right. So if you're trying to perform the method of Claim 11 of the '601 patent and want to be sure you're inside the scope of the claims, what does the person of ordinary skill in the art need to do?

A. I think the only way to be sure you're inside the scope is to give the injection exactly every 28 days.

Q. And what if you wanted to dose aflibercept to a patient and make sure that you were outside the scope of Claim 11 of the '601 patent?

A. Well, I think that would be very challenging because of what I showed earlier with the range of error around each

scheduled injection. And so it would be hard to know whether a particular date falls inside or outside of the approximate schedule.

Q. And what if you were trying to apply the patient or doctor's scheduling metric that Dr. Csaky proposed or the efficacy metric that Regeneron has additionally proposed? Would that help?

A. No, because, again, it would be difficult to know whether a particular consideration would cause you to fall inside or outside of the scope.

Q. Okay. And are these concerns that you've raised for the term "approximately" equally applicable to the other asserted claims -- Claim 6 of the '572 patent, Claim 19 of the '601 patent, and Claim 25 of the '572 patent?

A. Yes.

Q. All right. So based on the testimony you've just provided here, what is your ultimate opinion regarding the indefiniteness of the term "approximately" that appears in Claim 6 and Claim 25 of the '572 patent and Claims 11 and 19 of the '601 patent?

A. That it creates uncertainty around what the treatment schedule should be that would fall within the scope of the claim, and so it's indefinite.

Q. And if a person of ordinary skill in the art has multiple metric standards to choose from -- whether it's number

of days, number of weeks, number of months, scheduling issues, or efficacy issues -- does that complicate matters further or does that clarify matters further?

A. It makes it more complicated.

Q. And, Dr. Stewart, let's go ahead and sum things up, then. Can you summarize your opinions, please, for Claim 6 of the '572 patent.

A. Yes. So in this claim my concern regarding the term "angiogenic eye disorder" that I feel is too broad and incorporates conditions for which this wouldn't be enabled and lacks written description support.

The number of doses that's given was also unlimited, as we discussed. And so I feel that this is also not enabled and lacks written description support. And the use of the term "approximately" is indefinite.

Q. All right. And, Dr. Stewart, can you sum up your opinions, please, for Claim 25 of the '572 patent.

THE COURT: Just a smidge slower this time, Doctor.

THE WITNESS: I wasn't warned about that, but I'll try.

Yes. For this claim, there were no blaze marks given linking this particular condition, which is diabetic macular edema, to this specific regimen of five loading doses. And, again, that this was not enabled under Dr. Csaky's assessment of the prior art teachings.

I also again believe that the term "approximately" is indefinite.

BY MS. MAZZOCHI:

Q. And, Dr. Stewart, can you also summarize your opinions, please, for Claim 11 of the '601 patent.

A. Yes. Similarly, the absence of any blaze marks guiding me to this -- link this particular disease with this particular five-loading-dose schedule, it was also not enabled under Dr. Csaky's assessment of the prior art. And, again, the use of the word "approximately," which is indefinite.

Q. And then let's turn to the last claim, Dr. Stewart, to wrap up. Can you summarize your opinions, please, for Claim 19 of the '601 patent.

A. Yes. And similar to the others, there again were no blaze marks linking this particular condition to the five-loading-dose regimen. In fact, there wasn't any clinical data at all in the specification about diabetic retinopathy, the fact that it wasn't enabled again under Dr. Csaky's assessment of the prior art, and the indefiniteness from the term "approximately" being included.

MS. MAZZOCHI: And with that, Your Honor, unless you have any questions, I'm happy to pass the witness.

And if you like, we can also move into evidence the exhibits that we just discussed as an administrative matter. Those would be DTX 7100, DTX 5430, DTX 5431, DTX 5429,

DTX 5329, DTX 5330, and DTX 5332.

And I believe those are all not objected to.

THE COURT: Let's confirm. Any objection to any of those?

MR. GREGORY: No objection, Your Honor.

THE COURT: Without objection, those exhibits are hereby admitted.

Thank you, Counsel.

(DTX 7100, DTX 5430, DTX 5431, DTX 5429, DTX 5329, DTX 5330, and DTX 5332 were admitted.)

MS. MAZZOCHI: Thank you, Your Honor.

THE COURT: You want to start and stop, Counsel, or do you just want to take a break and start --

MR. GREGORY: Let's just go ahead, Your Honor, if that's all right.

THE COURT: Go ahead. But you've probably got about -- I'm going to say ten minutes before I've got to take a break and meet a 7-year-old downstairs.

MR. GREGORY: In that case, Your Honor, I don't think I have much, but I can't promise I'm going to be under ten minutes. We could take a break.

THE COURT: Why don't we go ahead and do that. I don't want to interrupt by exiting stage left -- going out that door and from there.

Doctor, this is a little bit of a gift to you. You

get to have lunch by yourself in the quiet. And I apologize. I don't know if you've been here for any of the other days of trial. If you have, you've heard me offer this caution or the rules of this proceeding, of course, prevent anyone from talking to you while you're midstream on your testimony.

So you're a man without a country, for lack of a better term, over our lunch break. The lawyers are hereby ordered to feed you, but they're ordered to not speak to you. So you're welcome for this little break.

Why don't we go ahead and take 45 minutes at this juncture, and we'll pick back up at 12:30 if that works for everyone. We can proceed with cross at that point.

Thank you all. My apologies. It's a different Kleeh kid's schedule this week than we're used to; so we'll see everyone at 12:30.

Again, Doctor, no one is being rude or discourteous. You're just sort of on your own.

Thank you all very much.

(A recess was taken from 11:44 a.m. to 12:37 p.m.)

THE COURT: Counsel, if you're ready, you may proceed.

MR. GREGORY: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. GREGORY:

Q. Good afternoon, Dr. Stewart. Nice to see you again.

You've offered opinions today about the '601 and the '572 patent. Those are PTX 001 and 003 respectively, right?

A. Yes.

Q. And I think we may have a number of disagreements between you and I about the legal implications of some of the words in the patents, but I want to make sure that we can agree about what the words actually are.

First, let me just be clear. You understand that the specification of the '572 patent and the '601 patents, they're effectively identical, correct?

A. I would need to compare them word for word to confirm that, but I know they are largely similar.

Q. In your discussion with defense counsel earlier this morning, you used, I believe, the '572 patent as your example for the specification of both of them; is that right?

A. I believe so.

Q. So I'd like to do the same just to save a little bit of time, if that's okay with you.

A. Okay.

Q. All right. So with that established, let's take a look at the '572 patent. You can use defense counsel's binder that they used this morning with you. Again, it's PTX 003.

Please let me know when you have it in front of you.

A. I have it.
Q. So you studied this patent, right?
A. Yes.
Q. Closely?
A. Yes.
Q. Please take a look first at page 14, Column 2, lines 42 to 46, if you would.

So one thing we can agree on, Dr. Stewart, is that the specification does disclose that the methods of the present invention can be used to treat any angiogenic eye disorder.

We can agree on that, right?
A. Can you say which lines you're referring to?
Q. Lines 42 to 46 of Column 2 of page 14.
A. I see that that's what is stated, yes.
Q. And we also can agree that the specification describes more specifically that the methods of the present invention can be used to treat age-related macular degeneration, diabetic retinopathy, and diabetic macular edema.

You see those words, right?
A. I do.
Q. I want you now to turn to another document that I believe is in the binder that defense counsel used with you this morning. I believe it was DTX 5329. And that should be the '245 provisional application.

Do you have that in front of you?

A. Yes.

Q. I believe you testified this morning this is the provisional application, dated January 13, 2011.

Do you recall that?

A. Yes, I do.

Q. I want to look at paragraph 6 on page 5 of this provisional patent application.

Just let me know when you're there, and we'll put it up on the screen for you as well.

A. I'm sorry. It has number two at the bottom of the page. I see what you're referring to.

Q. You see paragraph 6?

A. Yes.

Q. Another thing we can agree on here is that the provisional application includes the same disclosure that we just saw from the '572 specification, right?

A. Yes.

Q. You'd agree that this provisional application here discloses that the methods of the present invention can be used to treat any angiogenic eye disorder.

We agree on that, right?

A. That's what it says.

Q. And just like the '572 specification, it discloses that the methods of the present invention can be used to treat age-related macular degeneration, diabetic retinopathy, and

diabetic macular edema, correct?

A. Yes.

Q. Okay. Look back at the '572 patent, the one you spent a lot of time on this morning. I specifically want to direct your attention to page 16, Column 5, lines 30 to 48. We're going to put it up on the screen for you as well.

Do you have that passage in front of you, Doctor?

A. Did you say Column 5? Oh, yes, I do. Yes, I do see it in the middle of the column.

Q. And here this portion of the specification contains a slightly longer list of angiogenic eye disorders, correct?

A. Yes.

Q. And you agree -- we can agree that the '572 patent here again discloses that the method of the invention can be used to treat angiogenic eye disorders, right?

A. It does say that.

Q. And we can again agree that here, the '572 patent discloses that the methods of the invention can be used to treat age-related macular degeneration, diabetic macular edema, and diabetic retinopathies, right?

A. Yes.

Q. I want to do a little bit of comparison now between the patent and the provisional. You're welcome to flip back and forth in the binder, and I'll also put it on the screen for you.

First I want to look at Column 2, line 57 to 60, at page 14 of the '572 patent. I want to compare it with paragraph 8 of the '245 provisional.

We can agree, Doctor, that these passages that I've just called out in both the '572 patent and the '245 provisional, they are identical, right?

A. Yes.

Q. We can agree that they both disclose topical or intraocular administration, correct?

A. Yes.

Q. We can agree that they both single out intravitreal administration, correct?

A. Yes, they cite that in the "for example" section.

Q. Okay. Another comparison.

Next, please let's look next at Column 3, line 66 over to Column 4, line 9, on page 15 of the '572 patent. I also want you to look at paragraph 16 of the '245 provisional. And, again, we'll put that on the screen for easy reference there.

Do you have that before you?

A. Yes, I do.

Q. Again, we can agree that both of these passages in the '572 patent and the '245 provisional, they're identical, right?

A. Yes.

Q. And we can agree that both of these passages disclose an exemplary embodiment in which each secondary dose is administered three to four weeks after the immediately preceding dose, correct?

A. Yes.

Q. And, likewise, we can agree that both these passages disclose an exemplary embodiment where each tertiary dose is administered at least eight weeks after the immediately preceding dose, right?

A. At least eight is listed as one of many choices up to 14 and a half or more.

Q. It reads, "Each tertiary dose is administered at least" -- and then there's a parenthetical, and then -- "weeks after the immediately preceding dose."

That's what it says, right?

A. Yes, it does.

Q. Eight is called out specifically, right?

A. Yes, it's the first in the series of numbers.

Q. Just a few more of these, Doctor.

Let's take a look next at Column 4, line 22, at page 15 of the '572 patent -- so I think you can stay right where you are -- and also paragraph 18 of the '245 provisional. And it's up on the screen as well for ease of reference, sir.

Please let me know when you have it before you.

A. I have it.

Q. We can again agree that these passages in the '572 patent and the '245 provisional, they're identical, right, sir?

A. Yes.

Q. And we can also agree that both the '572 patent and the '245 provisional in these passages disclose methods wherein two or more secondary doses are administered to a patient, right?

A. Yes.

Q. And we can also agree that both the '245 provisional and the '572 patent disclose methods wherein two secondary doses are administered, right?

A. That is one of the examples given.

Q. It's set out right there in black and white, right?

A. Yes. It's the first of the numbers that are listed in parentheses.

Q. And we can also agree that both the '572 patent and the '245 provisional disclose methods wherein four secondary doses are administered, correct?

A. Yes, it's also one of the many numbers that are listed there.

Q. Well, to be clear, sir, how many numbers are listed there? It's seven, right?

A. Well, it says "or more"; so that encompasses any number beyond that point.

Q. And how many numbers are specifically called out by

name?

A. Seven.

Q. And four is one of those seven that's listed, correct?

A. Yes, it is.

Q. Let's take a look -- one more at least. Let's take a look at Column 4, line 32, on page 15 of the '572 patent -- so you don't have to turn far there -- and then paragraph 19 of the '245 provisional.

Again, we can agree that these passages are identical, right, sir?

A. Yes.

Q. And we can also agree, can't we, that both the '572 patent and the '245 provisional disclose, again, in these passages administering secondary doses in four-week intervals, right?

A. Yes.

Q. And we can also agree that both the patent and the provisional application disclose in these passages administering tertiary doses in eight-week intervals, correct?

A. Yes.

Q. I want to skip all the way down now to Example 7 of the '572 patent, and that's going to be at page 21.

Would you take a look there?

A. Yes.

Q. And you see that the '572 patent Example 1 -- Example 7, it's titled "Dosing Regimens," correct?

A. Yes.

Q. And Example 7 does, in fact, set forth various dosing regimens?

A. Yes.

Q. I think on direct examination you referred to them as a laundry list. Is that right?

A. Yes.

Q. To be clear, we may call them -- there's a specific number there. There's 20; isn't that right?

A. There are 20 entries. I think that the reason that I view it as going beyond that level is because some of these encompass various permutations that can be considered.

Q. There are 20 entries, right, sir?

A. There are 20 entries on this example.

Q. And I want to look at Column 16, lines 35 to 38. Column 16, for reference, is page 21.

Do you have that before you?

A. Yes.

Q. I believe you highlighted this particular exemplary dosing regimen during your testimony this morning; is that correct, Doctor?

A. Yes.

Q. We can agree, can we not, that this particular

regimen includes the administration of 2 milligrams of aflibercept by intravitreal injection once every four weeks for the first 16 weeks followed by 2 milligrams of aflibercept via intravitreal injection once every eight weeks.

That's what it says, right?

A. Yes.

Q. And you understand that intravitreal injections once every four weeks for the first 16 weeks, that's five loading doses, correct, sir?

A. Yes.

Q. So this particular exemplary dosing regimen set out here in Column 16 includes monthly loading doses, right?

A. Yes.

Q. It includes fixed extended dosing -- or fixed extended interval doses of every eight weeks as well, right?

A. Yes.

Q. It recites only one interval, time interval, for the loading doses. That's four weeks, right?

A. Yes.

Q. It recites only one time interval for the fixed extended doses. That's eight weeks, right?

A. Yes.

Q. It identifies the precise number of loading doses be administered. That's five, right?

A. Yes.

Q. And take a look now, if you will, at the bottom of Column 15, which is right below -- at the bottom of Example 7. Actually, I'm sorry. Column 15 at the top of Example 7, right below the header.

Do you see that?

A. Yes.

Q. And it defines the exemplary dosing regimen we just looked at as exactly that, a example of a dosing regimen, quote, within the scope of the present invention, right?

A. Yes.

Q. Finally, let's take a look at the bottom of Example 7. So this is going to be Column 17, and then into Column 18 on page 22.

Do you have that before you?

A. Yes.

Q. And you agree with me, right, sir, that Example 7 discloses that that exemplary five loading dose method we just talked about may be used for the treatment of diabetic macular edema, right?

A. Yes. That is one of the conditions listed.

Q. And you agree with me, don't you, sir, that Example 7 discloses that this five loading dose exemplary regimen we just talked about could be used for the treatment of vascular retinopathy, right?

A. Yes. That's another of the conditions listed.

Q. Okay. Now that we've established, I think, a little bit more about what the patents actually say, let's talk about how you reached some of your opinions in this case.

I believe you offered several opinions that various patent claims at issue here lacked written description. Is that right?

A. Yes.

Q. You offered an opinion that Claim 6 of the '572 patent lacks sufficient written description because the specification of that patent does not disclose the inventor was in possession of a method of treating angiogenic eye disorders.

That's one of the bases for your opinions, right?

A. Yes.

Q. And your understanding is that for this claim -- that is, Claim 6 of the '572 patent -- to have written description support, the specification must provide clinical data for a substantial number of the exemplary angiogenic eye disorders listed in the specification of the '572 patent, right?

A. No.

Q. Doctor, did you have your deposition taken in this matter?

A. Yes, I did.

Q. And I actually took your deposition; is that right?

A. Yes.

Q. So we met a couple months ago, and we sat in a

conference room and I asked you a series of questions, correct?

A. Yes.

Q. And you understood you were under oath during that deposition?

A. Yes.

Q. You understood you had an obligation to tell the truth?

A. Yes.

Q. To be accurate?

A. Yes.

Q. You were, in fact, truthful and accurate in that deposition; is that right?

A. Yes.

Q. I want to put on the screen pages 111 to 112 of the doctor's testimony.

Doctor, I'm going to read this, and I want you to tell me if you were asked these questions and gave these answers at your deposition:

"Q Okay. So then to cycle back to my original question, is it your view that, to have adequate written description support for Claim 1 of the '572 patent, there would need to be disclosures in the relevant disclosure of clinical data for at least the majority of the listed angiogenic eye disorders?

"A I think that the person of skill in the art would need to believe that the inventor was in possession of that information for a substantial number of the listed disorders. And to me, in my opinion, having it for only three of the numerous is not sufficient.

"Q When you say that the person of ordinary skill in the art would need to believe that the inventor was in possession of that information for the substantial number of listed disorders, what do you mean by 'that information'? Do you mean clinical data?

"A Yes."

Doctor, did you hear those questions and give those answers at your deposition?

A. Yes, I did.

Q. You've also made various assumptions about the law to reach your written description opinions, right?

A. I'm not sure which assumptions we're referring to.

Q. Any assumptions. You made assumptions about the law to reach your written description opinions in this case, correct?

A. Perhaps. I'm not sure which assumptions we're referring to.

Q. Let me be more specific.

In performing your written description analyses in this case, one assumption you made was that the relevant disclosure being assessed for written description needed to include an example for every embodiment of the claimed invention; isn't that right?

A. I may have said that during deposition, but I'm pretty sure that I got some of my definitions mixed up when I was speaking about written description and enablement. So I'm not sure if that's what you're referring to in that moment.

Q. Let's take a look at the doctor's testimony from page 36, so between lines 8 and 13.

Doctor, I want to read this, and you can tell me if you were asked this question and gave this answer at your deposition.

"Q In performing a written description analyses in this case, you have assumed that the relevant disclosure must include examples for email embodiment, correct?

"A Yes."

Did you give that answer at your deposition, sir?

A. Yes.

MR. GREGORY: With the Court's permission, I'd like to pass out one exhibit here.

THE COURT: Understood. You may.

MS. MAZZOCHI: Your Honor, I'll just object to this

exhibit because it's outside the scope of the opinions that the witness testified to, not only on direct but also in his report.

MR. GREGORY: Your Honor, this is an expert ophthalmologist who's been offered by defendants in this case. He testified regarding this exhibit at his deposition. He's familiar with this exhibit. At the very least for the sake of efficiency, we'd rather do this now while he's currently on the stand than either get a subpoena and bring him back in that case or --

THE COURT: What is the relevance of DTX 3498?

MR. GREGORY: This is one of their core anticipation pieces of prior art from the DME claim, sir.

THE COURT: Understood. Overruled.

BY MR. GREGORY:

Q. Doctor, do you recognize DTX 3198 which I've just passed you?

A. Yes.

Q. And you saw this document actually before your deposition, correct, sir?

A. Yes.

Q. You saw it again at your deposition, correct, sir?

A. Yes.

Q. Let's put it up on the screen.

You understand -- why don't you also take out the

'601 patent while you're at it, and that is PTX 001.

THE COURT: Whereabouts in '601, Counsel?

MR. GREGORY: We're going to take a look at Claim 11 at the back of your packet.

THE COURT: For the record, that's on page 21 of Column 22.

MR. GREGORY: Thank you, Your Honor.

THE COURT: Thank you. Go ahead.

BY MR. GREGORY:

Q. You're familiar with Claim 11, correct, Doctor?

A. Yes.

Q. You understand that Claim 11 depends from Claim 10?

A. Yes.

Q. And thus includes all of the elements or limitations of Claim 10?

A. Yes.

Q. By the way, Doctor, I believe you testified earlier today, you have the qualifications of the person of ordinary skill in the art as to Claims 11 and 10 of the '601 patent, right?

A. Yes.

Q. Taking a look now at the press release before you -- let me back up for a second.

You understand that this is a Regeneron press release, DTX 3198, dated September 14th, 2009, right?

A. Yes.

Q. It's titled "Enrollment Completed in Regeneron Bayer Healthcare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)," right?

A. Yes.

Q. You agree with me, don't you, Doctor, that this press release, the September 14th, 2009, press release does not disclose all of the limitations of Claim 11 of the '601 patent, correct?

MS. MAZZOCHI: Again, Your Honor, here again I'd like to object because Dr. Albini already testified about this exhibit. The witness did not testify -- did not opine on this at all in his expert reports. And when they brought this up at his deposition, we likewise objected that it was outside the scope of his expert reports.

THE COURT: Understood. It's relevant to his methodology in reaching his opinions. Overruled.

BY MR. GREGORY:

Q. I'll repeat the question if you'd like, Doctor.

You agree that the September 14th, 2009, press release does not disclose all the limitations of Claim 11 of the '601 patent, correct?

A. When you say "all the limitations," where are you referring to?

Q. I'm referring to the elements or the limitations of

Claim 11 of the '601 patent.

Are you familiar with that claim?

A. Yes.

Q. Okay. And my question to you is whether the September 14th, 2009, press release discloses all the limitations of Claim 11 of the '601 patent.

A. The press release is about a study regarding wet age-related macular degeneration, and this claim relates to diabetic macular edema. So it's on a different topic.

Q. I'll direct your attention, sir, to the second page of the press release, the second paragraph on the second page.

Nowhere there or anywhere else in the September 14th, 2009, press release is there a disclosure of all the limitations of Claim 11 of the '601 patent, right?

A. It talks about diabetic macular edema and refers to several treatment regimens, including monthly injection every eight weeks after three monthly loading doses or as needed after three monthly loading doses, and the claim here refers to five loading doses.

Q. So is the answer to my question yes, sir?

A. Can you repeat the question?

Q. You agree with me, don't you, that nowhere in the September 14th, 2009, press release is there a disclosure of all the limitations of Claim 11 of the '601 patent?

A. The press release does not cite the specific dosing

regimen that's listed in the claim.

Q. We can take that down.

You'd agree with me, sir, that in 2011 people -- ophthalmologists were exploring when and how to deviate from monthly injection regimens, correct?

A. Yes.

Q. And the answer to that question was not as well as established as in subsequent years when treat and extend became more established, correct?

A. Correct.

Q. I want to shift gears one more time here.

You discussed your background a little bit earlier today, your CV and some of the journals that you contribute to, right?

A. Yes.

Q. You've published a number of papers, some of which you mentioned?

A. Yes.

Q. And a number of those papers are in peer-reviewed journals, correct?

A. That's correct.

Q. And the purpose of such publications is to present replicable research, correct?

A. Sometimes they may be review articles describing other people's research, or sometimes it might be primary

research that you're reporting on.

Q. Sometimes they may be case reports, right?

A. Yes.

Q. But regardless of the use, you strive to be accurate in your written submissions to medical journals, correct?

A. Yes.

Q. You strive to be clear in your written submissions to medical journals, correct?

A. Yes.

Q. Now, you've offered an opinion earlier today that the term "approximately" in the asserted claims of the '601 and the '572 patents is indefinite, right?

A. Yes.

Q. You opine that ophthalmologists wouldn't understand what that word meant, right?

A. No, I didn't opine that they wouldn't understand what it meant. I stated that it provided uncertainty around the specifics of a dosing schedule.

MR. GREGORY: Your Honor, with your permission, I'd like to approach and pass out a few more exhibits.

THE COURT: Okay.

BY MR. GREGORY:

Q. So, Dr. Stewart, we've passed around now a folder containing several exhibits. I'd like to talk about them each very briefly, and I do promise to be brief.

I want to first turn to PTX 626, which I believe should be the first document in the stack. Do you have that before you?

A. Yes, I do.

Q. And could you please take a look at the first page of that document.

A. Yes.

Q. This is a paper you authored in the journal called *Ophthalmology*, correct?

A. This was a journal *Ophthalmology Retina*, and I was a coauthor on this paper.

Q. And I want you to turn to page 1040 of this paper. I believe it's page 13 in the PDF or 13 in the printout.

Do you have that?

A. Yes.

Q. And in this paper in *Ophthalmology Retina* in a table detailing patient examination and management guidelines, you wrote, "Reattempting the refill exchange after approximately" -- you instructed -- I'm sorry -- "reattempting the refill exchange after approximately seven days."

Do you see those words?

A. Yes, I do.

Q. Let's look at the next paper in the stack. That's PTX 3352. Do you have 3352 before you?

A. Yes.

Q. This was another paper that you authored, correct?
A. Yes.
Q. It's in the journal *Investigative Ophthalmology & Visual Sciences*, right?
A. Yes.
Q. This is from 2011?
A. Correct.
Q. Okay. I want you to turn to pages 9276 and 9277.

We'll put them up on the screen for ease of reference.

Do you see that on those pages you wrote on the page first 9276, "In some instances approximately 20 minutes into the 30-minute measurement period, a single drop of bound salt solution was placed on the cornea if the investigators judged that the eye appeared dry." And then on the very next page, you wrote, "In this study, corneal permeability was quantified approximately three to six weeks after CXL."

Do you see that?
A. Yes.
Q. Those are your words?
A. Yes.
Q. There's a few more of these here, Doctor.

PTX 3350 should be the next one in the stack. Do you have that before you?
A. Yes.

Q. This is another paper that you wrote, right?
A. Yes.
Q. This time in the journal *Retinal Cases and Brief Reports*?
A. Yes.
Q. From a few years ago, 2017, right?
A. Yes.
Q. And on page 2 -- I believe it's page 2 of the document -- sorry -- page 1 of the document -- I believe actually the very first paragraph you write, "The patient had been diagnosed with uveitis and had been treated for approximately 18 months."
Those are your words, right, Doctor?
A. Yes.
Q. Turn to the next document in the stack. It's PTX 3351. This is an abstract for an ARVO meeting that you authored, correct?
A. Yes.
Q. ARVO stands for the Association for Research in Vision and Ophthalmology; is that right?
A. Yes.
Q. You're a member of that association?
A. Yes.
Q. You submitted this abstract at their annual meeting, correct?

A. Yes.

Q. Let's take a look at the second page of this two-page document. You write, "Postoperative intraocular pressures were reported with a pneumatonometer at approximately 4, 8, and 11 hours and twice a day thereafter for five days."

Do you see that?

A. Yes.

Q. Other than my mispronunciation, those were your words, correct, Doctor?

A. Yes.

THE COURT: Counsel, could we get a spelling of that effort of that word for the court reporter's benefit.

MR. GREGORY: Understood. The spelling is P-N-E-U-M-A-T-O-N-O-M-E-T-E-R.

THE COURT: Understood. Thank you.

BY MR. GREGORY:

Q. Look next at PTX 3348, if you would, Doctor. This is another paper that you authored, right?

A. Yes.

Q. And it's in the *International Journal of Retina and Vitreous*, right?

A. Yes.

Q. And this paper actually concerns, it looks like, anti-VEGF therapy, right?

A. Yes.

Q. Can you take a look at the third page of the document. Here, you don't use the word "approximately"; you use the word "about," correct?

You say, "Patients received aflibercept injections every six weeks on average and were then treated with ranibizumab or bevacizumab about six weeks after their last aflibercept injection."

Those are your words, right, Doctor?

A. Yes.

Q. One more of these. Take a look at PTX 3349.

Do you recognize this document, sir?

A. I do not. I recall being involved in this project when I was a resident, but I actually didn't realize it had gone forth to this level of submission.

Q. You don't have any reason to doubt that the Jay Stewart there in the inventor and applicant line is yourself?

A. That's me.

Q. This is an international patent application -- publication?

A. It looks to be so, yes.

Q. And if we can turn to, I believe, the second page of it, you'll see a heading called "Field of the Invention."

Do you see that?

A. Yes.

Q. And it recites that "The present invention generally

regards the field of medicine; more particularly, it regards the field of ophthalmology."

Do you see that?

A. Yes.

Q. And I want you to look at the claims in this patent application publication and in particular Claims 45, 48, and 54, which should be on pages 53 and 54 of the printout.

Do you see that?

A. Yes.

Q. And in each of these you used the modifier "about" before a measure of weeks or months. Do you see that?

A. I didn't use that modifier.

Q. This is your patent application publication, sir, isn't it?

A. As I said, I remember working on this project as a resident but didn't realize it had actually gone forward to this level. I wasn't involved in the composing of the language for this document.

Q. You didn't tell anybody that that word was too imprecise?

A. I just stated that I wasn't involved in choosing the language for this or writing it in any fashion.

Q. Okay. Shifting gears just a bit, Doctor, I want you to look at what should be the next document in the stack. That's PTX 628.

Do you recognize this document?

A. Yes.

Q. It's the label for Eylea or a label for Eylea, correct?

A. Yes.

Q. You've seen labels for Eylea before, right?

A. Yes, I have.

Q. In fact, you've reviewed them in your clinical practice, right?

A. Yes.

Q. I want you to look at the highlights of the prescribing information, the top part of the page that we have called out right now on the screen. I want you to make sure you have that in front of you as well.

Do you see that in the dosage and administration section of the highlights of prescribing information the Eylea label recites the recommended dose for Eylea is "2 milligrams administered by intravitreal injection every four weeks" -- and then there's a parenthetical -- "approximately every 28 days, monthly, for the first three months."

Do you see that?

A. Yes.

Q. Do you see that, similarly, at the very next bullet it says that "Although Eylea may be dosed as frequently as 2 milligrams every four weeks (approximately every 25 days),

monthly, additional efficacy was not demonstrated in most patients when Eylea was dosed every four weeks compared to every eight weeks"?

Do you see that?

A. Yes.

Q. Then do you see there are, I think, three more uses of the word "approximately" on this first page of the Eylea label modifying measures of time in either days or months.

Do you see that?

A. Yes.

Q. I want you to look at another document which I think you may be familiar with, PTX 0472. It should be the next one up in the stack.

Have you seen this document before, sir?

A. Yes.

Q. This is the Yesafili label, right, or a proposed Yesafili label?

A. Yes.

Q. You understand that Yesafili is Mylan and Biocon's proposed aflibercept biosimilar product, correct?

A. Yes.

Q. And you see the same uses of "approximately" to modify measures of time in either days or months as we just saw in the Eylea label here in the Yesafili label, correct?

A. It looks very similar.

Q. Have you told Mylan or Biocon that they should amend this language because it's unclear?

A. No.

Q. I want you to look at one more label for me. It's the last one, I believe, in the stack. It's PTX 1617.

This is a label for Lucentis, right?

A. Yes.

Q. The active ingredient is ranibizumab?

A. That's correct.

Q. And this is a label from June 2010, correct?

A. Yes, it is.

Q. This is before priority dates that you assessed in performing your various analyses in this case, right?

A. Yes.

Q. And you see again that the word "approximately" is used multiple times in the first page of the highlights of prescribing information to modify measures of time and days.

Do you see that?

A. Yes.

Q. You're familiar with Dr. Karl Csaky, right, sir?

A. I'm familiar with him as someone in the field. And as I mentioned at my deposition, I have seen him give one or more presentations at conferences in the past.

Q. You consider Dr. Csaky an expert in vitreoretinal diseases?

A. Yes.
Q. You consider him an expert in wet age-related macular degeneration?
A. Yes.
Q. You consider him an expert in diabetic macular edema?
A. Yes.
Q. And you consider him an expert in diabetic retinopathy, right?
A. Yes.
Q. And you would agree that Dr. Csaky is well respected in the fields of wet AMD, DME, DR, and vitreoretinal diseases generally, correct, sir?
A. I believe so.
MR. GREGORY: No further questions at this time.
THE COURT: Redirect, Counsel?
MS. MAZZOCHI: You knew there would be, Your Honor. I apologize.
THE COURT: It makes the record look cleaner when I ask.
MS. MAZZOCHI: I do appreciate that.

REDIRECT EXAMINATION

BY MS. MAZZOCHI:
Q. Dr. Stewart, for all of these references that Mr. Gregory took you through, did any of them use the term "approximately" in the same inconsistent manner that the claims

you discussed did from the '572 and '601 patents?

A. No, not that I could tell.

Q. Can you expand on that a little bit?

A. I think the issue in the patent claims that we were discussing earlier was that there were several different means of -- measures of time being modified. And in the case of a patent claim, my understanding is that we want to be able to determine if a particular schedule falls in or outside the scope of that claim; so having that uncertainty in so many units of time makes it hard to know if a particular dosing schedule does fall in or outside of that claim.

Q. And if you can pull from that stack of papers that Mr. Gregory gave you. Let's start, for example, at PTX 3348.

A. Yes.

THE COURT: Which article is that, Counsel? I'm sorry.

MS. MAZZOCHI: 3348. This one is one of Dr. Stewart's articles titled "Conversion back to bevacizumab or ranibizumab for recurrent neovascular activity with aflibercept in age-related macular degeneration: a case series."

THE COURT: Okay. A thrilling title.

Sorry. Sorry, Doctor. Couldn't resist.

BY MS. MAZZOCHI:

Q. Dr. Stewart, if you could turn to the third page of

the exhibit, Table 1, where it talks about patient characteristics. Did you actually put a specific range or standard deviation that was permitted for the approximate interval?

A. Yes. We included the mean and the standard deviation.

Q. Does the '572 or '601 patent have that same degree of specificity or definition?

A. No.

Q. If you could take a look at the -- let's start with the Eylea labeling. And I believe that one was PTX 628. And we can go ahead and look at the dosage and administration section on the first page.

In the context of the labeling, did they apply the term "approximately" to two different types of units, as in approximately every 28 days and approximately monthly, as we see in the '572 and '601 patent claims?

A. I think it's only modifying days in these instances.

Q. Sure.

Does the label apply the term "approximately monthly" in addition to "approximately every 28 days"?

A. No.

Q. Does that change the scope, in your opinion?

A. Yes.

Q. Can you explain why.

A. Because monthly is a much larger unit of measurement. And so if you're approximating that, then you're going to have a wider error bar on your side of that timeline.

Q. But if you're looking in the context of the labeling where it says "approximately every 28 days, monthly," without the term "approximately" modifying the term "monthly," is the term "monthly" narrow in your opinion, or is it broad?

A. It's narrow.

Q. If you -- and would your answer be the same, for example, for the Yesafili labeling that you were directed to?

A. Yes.

Q. And, likewise, do you know whether the Lucentis labeling has any of that same problem that you saw in the claims of the '572 or '601 patent?

A. I think the Lucentis label is only using approximately to modify 28 days.

Q. So no worry about the scope of range on units?

A. Only one type of unit is used here.

Q. All right. Let's go back to a couple of things that Mr. Gregory asked you.

Now, Dr. Stewart, when Mr. Gregory asked you if things were disclosed on a page or disclosed in the press release, were you using the term "disclosed" in an ordinary sense or in a legal sense?

A. To me, that would be an ordinary sense.

Q. As in just what's written on the page?

A. Yes, meaning do I see it on the page.

Q. Okay. Let's go back to Example 7, which I believe is in PTX 3, exhibit page 21.

And let's highlight that first set of language on the bottom of Column 15 that runs from around line 61 to 67.

Do you have that, sir?

A. Yes.

Q. Now, Mr. Gregory pointed you to only one little snippet of the first two lines under Example 7. Can you read the whole thing into the record.

A. "Example 7: Dosing Regimens. Specific, nonlimiting examples of dosing regimens within the scope of the present invention are as follows: VEGFT 2 milligrams (0.05 milliliters) administered by intravitreal injection once every four weeks (monthly)."

Q. Now, would the person of ordinary skill in the art read those first two lines that you read referring to specific nonlimiting examples, would the person of ordinary skill in the art view that language as limiting the number of regimens to 20 or not limiting the number of regimens to 20?

A. Not limiting because it says nonlimiting.

Q. And then, likewise, to the extent -- I think Mr. Gregory asked you if all of these regimens could be used. Is there anything that a person of ordinary skill in the art