months in a glass vial?

A. It shows that it was unchanged from the initial measurement; so it's good stability.

Q. Now, in the course of your stability study work on aflibercept formulations, did you also vary the amounts of polysorbate 20?

A. We did.

Q. Let's look at PTX 2265, page 1.

What is this document, Dr. Graham?

A. This is the 205th stability study protocol.

Q. And what amount of polysorbate did you test here?

A. 0.06 percent.

Q. And if we look at page 2, Table 1, of PTX 2265, was a glass vial tested in this study as well?

A. Yes, it was.

Q. Was that Device 7?

A. Yes, it is.

Q. Let's compare the formulation of the SS205 protocol that we just looked at with the formulation of Example 5 of the '865 patent, PTX 2, page 8, Column 10. How do these two formulations compare, Dr. Graham?

A. So they have the same components. The difference is that there is .03 percent polysorbate in Example 5 and .06 percent polysorbate in Study 205.

Q. Did you look at these -- this .06 percent

polysorbate 20 formulation by size-exclusion chromatography?

A. Yes, we did.

Q. Let's look at PTX 2266, page 15. Is this the SEC data for the glass vial at 5 degrees C?

A. Yes, it is.

Q. And what was the percent native conformation as measured by SEC following storage in a glass vial for two months at 5C for this formulation?

A. 99.0 percent.

Q. Did you run turbidity analysis here as well?

A. Yes, we did.

Q. Let's look at PTX 2267, page 17.

THE COURT: Counsel, once we go through this table, if we're at a spot to take our afternoon break.

MR. TRASK: Absolutely, Your Honor.

BY MR. TRASK:

Q. Is this the turbidity data for the SS205 study?

A. Yes, it is.

Q. And what was the turbidity at 5 degrees Celsius for two months in a glass vial?

A. It was unchanged from the initial measurement.

Q. Is that a good result?

A. Yes.

MR. TRASK: Okay. Happy to break at this point, Your Honor, if you'd like.

THE COURT: Why don't we go ahead and do that, then. We're going to take ten minutes. We'll resume at 3:00, a couple minutes after that.

Doctor, you haven't been in the courtroom; so this may be a new speech for you. Because you're midstream on your testimony, no one can speak with you in particular about your testimony. So everyone would run the other way as opposed to greeting you.

THE WITNESS: Sounds good.

THE COURT: You're welcome.

I just didn't want you to think that anyone was being rude or discourteous to you. But you can go ahead and step down, sir. But you're a man without a country for the next ten minutes or so.

We'll see everyone in a few. Thank you.

(A recess was taken from 2:54 p.m. to 3:15 p.m.)

THE COURT: Apologies. That break ran over. We had a cataclysmic user error with the Keurig coffee machine. That was my user error. Don't worry. We're getting new carpet as part of the great asbestos project. That's what we're telling ourselves.

Counsel, you may proceed.

MR. TRASK: It doesn't show on the black robe.

THE COURT: That's the beauty of the black robe.

Thank you, sir. Go right ahead.

MR. TRASK: Thank you.

BY MR. TRASK:

Q. If we could turn back to Stability Study 207 briefly, Dr. Graham.

A. Sure.

Q. And if we look at PTX 2275. And, actually, this one is not in your binder; so I'm going to hand up copies of this.

MR. TRASK: With the Court's permission?

THE COURT: You may.

BY MR. TRASK:

Q. Doctor, do you have PTX 2275 in front of you?

A. Yes.

Q. Okay.

And for the record, this is Bates-stamped RGN-EYLEA-MYLAN-00475679. And it's a native Excel file printed as a PDF.

Doctor, we previously discussed the two-month 5C-degree pull date in exhibit -- in Stability Study SS207. Does this exhibit, PTX 2275, show the same pull date at two months, 5 degrees C, that we discussed in connection with PTX 1825 for Stability Study 207?

A. Yes, I believe it does.

Q. And for the record, what is the pull date at two months, 5C, in Stability Study SS207?

A. 21 March 2006.

Q. Okay. I'd also -- we can put that aside for the moment.

I'd also like to discuss or revisit briefly in connection with SS207, PTX 2277, page 15. And this -- actually, this is -- if we could look at the bottom of this Excel spreadsheet.

So, Doctor, I think you testified about the date at the bottom of this Excel spreadsheet, SS207, indicating when the two months' SEC data was run?

A. Yes.

Q. Can you explain the date it was run and the connection to the date shown at the bottom of this spreadsheet.

A. Okay. So this is a sequence number. What we do is we start the sequence and we assign a date code to it. So 06 is 2006, 03 is March, 20 is the 20th of March. The F is the system number or system identifier that we used.

So this sequence actually was started the day before the samples were pulled. And we did that because we were running standards and systems suitability, and we wanted to ensure that we got all the standard system suitability, all that done, and then allowed -- had a system that's all set, ready to go, you walk in in the morning, you pull out your samples, you put them on, and you run them that day. We didn't want things drifting later and later. We just wanted to be set

and primed and ready to go.

Q. Okay. So what was the date that you were getting the size-exclusion chromatography analysis machine ready?

A. So the date we were getting it ready was the 20th, which was the date before the pull.

Q. And that's March 20th, 2006?

A. Yes.

Q. And then what's the date on which you actually ran the sample for 5 degrees C, two months?

A. They would have gone up on the 21st, the day they were pulled.

Q. And that's March 21, 2006?

A. Yes.

Q. Okay.

We can take that down.

Thank you, Doctor.

Doctor, did you sit for a deposition in this case?

A. Yes, I did.

Q. Do you recall during your deposition counsel for defendants showed you some internal Regeneron documents where polysorbate was referred to as a stabilizing agent?

A. Yes, I did.

Q. During your work involving formulations of aflibercept, did you sometimes call polysorbate 20 a stabilizer or a stabilizing agent?

A. Yes, I did.

Q. Did you also refer to polysorbate 20 as an organic cosolvent in connection with that work?

A. Yes, I did.

Q. And did you also call polysorbate 20 at times a surfactant?

A. Yes.

Q. Can you explain why you were using these different labels?

A. So surfactant is kind of self-explanatory. It's the chemical structure of the polysorbate.

Cosolvent is, you know, what we were using it for within the formulation. And a cosolvent stabilizes the formulation; so hence stabilizer or stabilizing agent.

Q. So would I be mistaken if I called polysorbate 20 a stabilizing agent?

A. No, you would not be.

MR. RAKOCZY: Your Honor, I'm going to object. Again, expert testimony. Also, he's offering opinions on construction of claims. He didn't offer any of that before. We're hearing this for the first time.

THE COURT: Counsel?

MR. TRASK: This is not in connection with the claim, Your Honor. I'm referring to the documents that he prepared in the course of his development of the invention.

THE COURT: Well, let's stick to those actual documents as opposed to what's his interpretation thereof.

Otherwise, sustained.

MR. TRASK: Thank you, Your Honor.

BY MR. TRASK:

Q. Let's look at PTX 672.

What is this document, Doctor?

A. So this is the pharmaceutical development section that I wrote for Eylea.

Q. Section of what?

A. The BLA.

Q. Is this the Eylea BLA?

A. Yes.

Q. Okay. And you're familiar with this document?

A. Yes.

Q. It's a long document, 483 pages. What was your specific involvement with this document?

A. I wrote it.

Q. The whole thing?

A. Yes.

Q. Okay. If we turn to page --

A. Sorry.

THE COURT: Understood, Doctor.

BY MR. TRASK:

Q. If we turn to page 26 of this document, Dr. Graham,

did you write this section of the document as well?

A. I did.

Q. And what is this section of the document?

A. It is describing the choice of organic cosolvent and the selection of the concentration for the formulation.

Q. If we look at the last paragraph on page 26 of Exhibit PTX 672, do you see where it says polysorbate 20 was selected as the organic cosolvent?

A. Yes. It says polysorbate 20 was selected as the organic cosolvent because a lower concentration was required to stabilize the VEGF Trap when subjected to agitation stress.

Q. Why did you call polysorbate 20 an organic cosolvent in this document?

A. Because that's what I was using it for in the formulation.

Q. And you understood, when you wrote this document, that it would be submitted to the FDA?

A. Yes.

Q. And was it, in fact, submitted to the FDA?

A. Yes, it was.

Q. And this is an accurate statement?

A. Yes, it is.

Q. Okay.

We can take that down.

Now, when you were working to develop more stable

intravitreal formulations of aflibercept, were you aware of public information about other existing protein formulations?

A. Some, yes.

Q. And in the course of your work, did you ever consider taking the aflibercept and just plugging it into a formulation that had been used to stabilize a different protein?

A. No.

Q. Why not?

A. All right. So proteins are individuals. No two proteins really behave exactly the same. They have different likes and dislikes. So a formulation that works well for one protein may not work well for another one. Things like pH are critical. Choice of stabilizer can be critical.

MR. RAKOCZY: Again, objection, Your Honor. Again, that's expert opinion testimony. He can testify about his personal experience with aflibercept, but now he's venturing into other proteins and what would and would not work.

THE COURT: That's sustained.

BY MR. TRASK:

Q. Moving on, when developing your invention, was tonicity a consideration for you, Doctor?

A. To a degree.

Q. Okay. Can you explain that?

A. So we knew that we -- or thought that we did not want to inject something that was 1,000 milliosmoles. We thought

that could potentially be bad. But we weren't necessarily concerned that we had to be exactly isotonic with the environment. We figured we had wiggle room.

Q. And you testified earlier that Example 5 of your '865 patent was not an isotonic formulation; is that right?

A. That is correct.

Q. Did you nonetheless consider the formulation of Example 5 to be a candidate formulation for intravitreal injection?

A. Yes.

Q. Now, does -- the '865 patent on which you're named as an inventor, does that identify which of the formulations it discloses is the one that corresponds to Regeneron's Eylea formulation?

A. No, it does not.

Q. Does it indicate anything about whether Regeneron preferred one of those formulations over another?

A. Not that I've seen in the document, no.

Q. Were you permitted as a Regeneron employee to publicly identify the formulation for Eylea before the Eylea product was released onto the market?

A. I was not.

Q. And to your knowledge, prior to Eylea's launch, was the formulation that you invented that eventually became the commercial Eylea formulation ever publicly identified as

Regeneron's commercial formulation?

A. Not to my knowledge, no.

Q. Now, you invented formulations of aflibercept that have greater than 98 percent native conformation following storage?

A. Yes.

Q. To your understanding at the time, did the FDA require some degree of stability in the products that it approves?

A. Yes.

Q. To your understanding at the time, did the FDA require at least 98 percent native conformation for an approved intravitreal product?

MR. RAKOCZY: Your Honor, I'm going to object to the extent he's asking what the FDA did or didn't think, did or didn't require.

MR. TRASK: He just testified that he wrote part of the BLA --

THE COURT: Understood, but let's focus on his understanding as to why or why not certain things might or might not be included in there.

Overruled with that caveat.

BY MR. TRASK:

Q. Okay. Dr. Graham, when you were developing your aflibercept formulations, did you understand that you needed to

achieve at least 98 percent native conformation in order for the product to be approved?

A. That would not have been an obligate requirement. We needed a stable formulation. A stable formulation is supported based on what your clinical experience is. We wanted the 98 percent or -- as pure as we could possibly get it because we wanted the best possible product, you know, for the patient. That was our goal.

Q. Now, is aflibercept a fusion protein, Doctor?

A. Yes, it is.

Q. Is aflibercept an antibody?

A. No.

Q. Are fusion proteins and antibodies the same thing?

A. No, they are not.

MR. RAKOCZY: Objection, Your Honor. Again, expert testimony.

THE COURT: Sustained.

BY MR. TRASK:

Q. Okay. So one brief point to wrap up, Doctor.

You've been working as a scientific researcher for about how long?

A. Well, 22 years at Regeneron, ten years at the City of Hope, and then -- god -- since probably -- what? -- '81 at Penn State. So what? 42 years, give or take.

Q. And of all the scientific work you've done over the

course of your career, where did the inventions of the '865 patent rank?

A. Well, that's probably at the top of the heap.

Q. Why is that?

A. Well, I have a very personal story with respect to Eylea. My mother suffered from wet AMD. I knew that my grandmother, her mom, had gone blind. I didn't know why. Now, my mom was a very, very private person. She never revealed what was going on with her. She had basically gone blind in one eye from the disease, and we didn't know this. And then she started complaining about her eyesight. And then we realized or learned, she finally fessed up, that she had the disease in the other eye.

You know, she was getting regular doses of Lucentis every month, but her vision was getting worse. My wife and I were, like, trying to find every opportunity so she could see my daughter, you know, get to see her at swim meets and get to see her and spend time with her while she still could see her.

And by the time or before -- shortly before Eylea was approved, her vision had gotten to 21/20, 21/40. She wasn't driving anymore. You know, she was somebody that always liked to do crossword puzzles and word things, couldn't see to do those. So it was kind of very dire.

Eylea got approved. I had seen the clinical data and thought, well, this looks better. I started having

conversations with her ophthalmologist, which she didn't like much, but I kind of was I'm not going to sit there and let you go blind; I want to see if there's something we can do. I suggested Eylea. I got back oh, these things are all the same.

I finally, in March of 2011, got to the point where I stood and looked at him and said, okay, why are you sentencing my mother to blindness? What we're doing right now is not working. It's just getting worse. Can we just try something better or different? If it doesn't work, we're no worse off.

And he agreed at that point to order the drug in. She did her three loading doses. Her vision improved. She got to the point where she was seeing 20/40. With eyeglasses, she was driving again. She got to see Kendra grow up. And it maintained her vision up until the last few months of her life.

You know, what can you do better than save your mother's sight?

MR. TRASK: Thanks so much, Doctor.

Nothing further at this time.

THE COURT: Understood.

Cross?

MR. RAKOCZY: May we approach with some binders, Your Honor.

THE COURT: You may.

MR. RAKOCZY: Good afternoon, Your Honor. William Rakoczy for Mylan and Biocon.

THE COURT: You may proceed, sir.

CROSS-EXAMINATION

BY MR. RAKOCZY:

Q. Good afternoon, Dr. Graham.

A. Good afternoon.

Q. Nice to meet you.

Dr. Graham, I'd like to start with DTX 722. And we'll pull it up on screen, and it's also in your binder that hopefully you were just handed.

A. Yes.

Q. I'd like you to look at page 1. You see this is an email dated March 21st, 2006, correct?

A. Yes, I do.

Q. And it's from Kathleen DeWald to you?

A. Yes.

Q. Is that right?

And I'd like to go to the attachment at page 2. And here you see a product composition, correct?

A. I do.

Q. It contains phosphate -- strike that.

And the formulation, under the "Product Composition" heading, contains phosphate, NaCl, polysorbate 20, sucrose, and 40 mg/mL VEGF Trap, correct?

A. I do.

Q. And I'd like to focus on the first sentence of the

paragraph above it. It states, "This is an unstable formulation for VEGF Trap since there are minimal excipients for intravitreal delivery and the formulation contains a high concentration of VEGF Trap."

Is that right?

A. That is correct.

Q. Now, below that it actually goes on to caution that the drug product should -- being held or stored at 25 degrees C should be kept to a minimum during the manufacturing process, correct?

A. Yes. I see those words on the page.

Q. And at temperatures above 25 degrees C -- strike that.

Temperatures above 25C must be avoided, correct?

A. That's correct.

Q. And that this drug product should be held or stored at less than minus 20 degrees C, correct?

A. I see that, yes.

Q. Now, I'd like to look at the table just below that. And in this table we see polysorbate 20 identified as a stabilizer as its function, correct?

A. Yes.

Q. It's not identified as a solvent, correct?

A. The description on the page says stabilizer.

Q. And the solvent in this formulation is the water or

the water for injection, correct?

A. That is the description for water for injection on the page.

Q. Now, let's take a look at one of your signed memos on your ITV formulation.

Let's pull up DTX 737.

And here we see a signed memo from you dated April 6th, 2006, correct?

A. Hang on. I'm trying to follow you.

Q. DTX 737. And I have it on the screen as well. We'll go to page 2.

A. Yes, I see page 2.

Q. And you see your signature dated April 6th, 2006, at the very top, correct?

A. Yes, I do.

Q. And this is entitled "40 mg/mL VEGF Trap for ITV in a sucrose- and polysorbate-containing formulation," correct?

A. That is correct.

Q. Now, we see just below that the same cautionary statements on storing the drug product.

Do you see that?

A. There are cautionary statements. They're not exactly the same, though, no.

Q. It says the drug substance, formulated drug substance, or drug product, the time it's held or stored at 25

degrees C should be kept to a minimum during the manufacturing process, correct?

A. That's the words on the page, that's correct.

Q. And, again, it cautions that temperatures above 25 degrees C must be avoided for this formulation, correct?

A. That is correct.

Q. And it says that this drug product formulation should be held or stored at 2 to 8 degrees C, correct?

A. Well, yes, it says 2 to 8 degrees C on this page, correct.

Q. Now, let's go down to the table below this as well. And here again, we see that water is identified as the function in the formulation -- or as the solvent in the formulation, correct?

A. Well, WFI is identified as the solvent, yes.

Q. And that's water for injection; is that right?

A. That is correct.

Q. And the polysorbate 20, its function is identified as stabilizer, correct?

A. Yes, it is.

Q. It's not the solvent, correct?

A. It's identified as stabilizer.

Q. And it's not the solvent in this formulation, correct?

A. It's identified as a stabilizer.

Q. My question is it is not the solvent in this formulation? Is that right or is that not right?

A. Water is identified as the solvent in the formulation.

Q. And water is the only solvent in this formulation; is that right?

A. Water is what is identified as the solvent in the formulation.

Q. Let's take a look at another one of your memos, DTX-- I believe the next one would be -- let me back up. I want to stay on this one.

This particular memo does not have any stability data for the formulation in it, correct?

A. If -- can you show me the whole screenshot of this.

Q. Yes. Can we pull up that whole page, DTX 737, page 2.

A. Okay. So this document does not have stability data associated with it. It's a recipe that was provided to the manufacturing group so that they could formulate the material. It's not -- it's not our common practice and has never been our common practice to include stability data with a recipe.

Q. My question is simple. In this document there's no stability data, no turbidity data, no native conformation data; is that right?

A. That's correct.

Q. Let's go to DTX 736. And we have another one of your memos. Can you confirm for me on page 3 that you, in fact, signed and dated this document April 21st, 2006; is that right?

A. Well, I see that on page 1 of 2 I signed it.

Q. And that is on page 3 of the exhibit; is that correct?

A. Oh. I'm sorry. I didn't understand what you were meaning by page 3.

Q. At the bottom you should see DTX 736.0003 of the exhibit.

A. Yes, I do.

Q. And under the heading "Formulation," you see this formulation contains phosphate, NaCl, polysorbate 20, and 40 mg/mL VEGF Trap, correct?

A. Yes.

Q. And we see similar cautionary statements in this memo as well for the formulation; is that correct?

A. That is correct.

Q. The time that the drug product is held or stored at 25 degrees C should be kept to a minimum, correct?

A. During the manufacturing process, yes.

Q. And temperatures above 25 degrees C must be avoided, correct?

A. Yes.

Q. And the drug product should be held or stored at 2 to

8 degrees C, correct?

A. That's correct.

Q. And like the prior memo, there's no stability, turbidity, or native conformation data in this particular memo; is that right?

A. No. It's a recipe.

Q. Can we go to the formulation table at the second half of this page. And here again, water for injection, or WFI, is identified as the solvent; is that right?

A. That is correct.

Q. And polysorbate 20 is identified as the stabilizer, correct?

A. Yes.

Q. Now, let's look at DTX 725 and look at the lead formulation. And I want to focus in this exhibit first on the email on page 1 which is dated May 8th, 2006, from Dr. Furfine to you.

Do you see that?

It's in the middle of the page.

A. Yes, I do.

Q. And you see Dr. Furfine addresses you. He says, "Ken, can you provide to Ellen the two formulations that we are moving into the tox study." Correct?

A. Yes.

Q. And then you then responded in the email above this

and you provided two formulations; is that right?

A. Yes, it is.

Q. And the formulation above is entitled the lead formulation; is that right?

A. It is.

Q. That formulation contains phosphate, NaCl, polysorbate 20, and sucrose, and 5 to 4 mg/mL VEGF Trap; is that right?

A. That is what's written on the page, yes.

Q. And then there's a backup formulation as well, correct?

A. Yes.

Q. Now, this email that you forwarded with the lead and the backup formulation, you didn't provide any tox study information in the email, correct?

A. No, I did not provide any tox study information.

Q. And that's because, as of the date of this email, May 8, 2006, these are the formulations, the lead and the backup, that were going to be moved into the tox study; is that right?

A. So as of May 2006, I'm not sure if -- which tox study this is referring to. There were a number of tox studies. Looking at this and knowing Ellen's function, she's pharmacokinetics; so she does PK studies. So she would be looking at a range of these things possibly for an ongoing tox

study. So I'm not sure what you're referring to.

Can you be more specific?

Q. Well, we can look at Dr. Furfine's email again in the middle of the page. Dr. Furfine asked you to send her the formulations --

A. Yeah.

Q. -- that you were moving into the tox study, correct?

A. Okay.

Q. All right. Let's look -- you mentioned the BLA. You worked on and drafted parts of that, right?

A. Yes.

Q. Excuse me. The Eylea BLA, correct?

A. Yes.

Q. Let's pull up PTX 1519 and go to page 5. And this is already in evidence. And here we see the description composition of the drug product from the Eylea BLA, correct?

A. That is correct.

Q. And at Table 1 again we see polysorbate 20 identified as a, quote, stabilizer agent, end quote, correct?

A. Yes. It's identified as a stabilizer agent in Table 1 and I think maybe another table or two in the document. But in the pharmaceutical development section, it was described as a cosolvent.

Q. We're going to get to the -- I promise you we'll get to the pharmaceutical development section next.

Very quickly, though, the function here on Table 1 in the Eylea BLA is identified as stabilizing agent, correct?

A. Yes.

Q. And the BLA does not identify polysorbate 20 here in PTX 1519 as a solvent, correct?

A. Could you say that again, please.

Q. The Table 1 of the Eylea BLA here in PTX 1519 does not identify polysorbate 20 as a solvent, correct?

A. That is correct. It's not identified as a solvent.

Q. And that's because polysorbate 20 has never been considered to be a solvent, correct?

A. For our purposes, we've always used it as a cosolvent or stabilizing agent.

Q. Let's pull up your deposition. You recall being deposed in this case, correct?

A. Yes, I do.

Q. And you understand you were under oath during that deposition, correct?

A. Yes, I was.

Q. And you swore to tell the truth?

A. I did.

Q. We're going to pull it up on screen, but it's also in your binder, Dr. Graham, DTX 5103. And the exhibit is page 46 of the transcript. We're going to look at transcript page 179, lines 19 to 25.

A. Can you give me the DTX number again, please.
Q. Yes. DTX 5103.
A. Okay.
Q. At page 46. And I also have it on screen for you.
Were you asked this question; did you give this answer?
"Q So I guess I'm not understanding why Regeneron listed here in its BLA document, Exhibit 738, that the function of polysorbate 20 is stabilizing agent and not solvent like water for injection. Can you explain this?
"A Well, polysorbate 20 has never been considered to be a solvent."
Was that the question you were asked and the answer you gave?
A. Yes, they are.
Q. And that's a true answer, correct?
A. Yes.
Q. Now, I think you mentioned -- and I don't need to go through it again, but there are other places in the BLA that identify polysorbate 20 as a stabilizing agent, correct?
A. Yes.
Q. Well, let's pull up the pharmaceutical development portion that you drafted, which I believe you testified was at PTX 672.

You recall that?

A. Yes.

Q. Now, you mentioned a portion of this document where you called polysorbate 20 a cosolvent. I'd like to look at a different portion of the same document you drafted. And let's go to page 108 of PTX 672. And I'm going to look at Table 63, I believe. You see Table 63, the document you drafted, is entitled "Role of excipients in the IVT2 VEGF Trap-Eye formulation," correct?

A. Yes.

Q. And we see polysorbate 20, excipient, the reason for addition is identified as "stabilizing agent," correct?

A. That's correct.

Q. And it goes on to describe it as "increases stability when agitated or subjected to freeze/thaw stress," correct?

A. That is correct, yes.

Q. I'd like to switch gears briefly and talk about one of the other excipients you mentioned, which are buffers. Your '865 patent only uses a phosphate buffer; is that right?

A. It describes a pH range. And the pH range tells anybody that works in this field that there are a series of compounds that you can use as a buffer.

Q. But it doesn't mention any other buffers by name beyond phosphate, correct?

A. The phosphate is mentioned as -- by name as an

example of a buffer.

Q. And matter of fact, you recall your counsel showed you all those examples on the screen from your patent.

You remember that?

A. Yes.

Q. And they all used a phosphate buffer, correct?

A. All the examples used a phosphate buffer, yes.

Q. Now, in fact, you don't recall using a histidine buffer to develop an intravitreal formulation of VEGF Trap prior to the filing of your '865 patent application in 2006, correct?

A. I don't believe that we did, no.

Q. In fact, your boss, who is Dr. Dan Dix; is that correct?

A. Yes, my boss was Dan Dix.

Q. I think you know where I'm going here. Dr. Dan Dix had Dr. Dan Dix nevers, right?

A. Yes, he did.

Q. And one his nevers was -- Dan Dix nevers, I believe you said, things that you would never do, according to Dr. Dix, is that you would never have a liquid formulation with a histidine buffer; is that correct?

A. So Dan is quite a character. Unfortunately, he's suffering from Parkinson's right now, but he had a list of nevers. And one of the list of nevers he had is you would

never use histidine in a liquid formulation. It was his preference. He had lots of preconceived notions around things.

You know, I personally have used histidine buffer in other formulations. And, actually, with one of the products I developed subsequent to Eylea actually completely got rid of all the Dan Dix nevers in one fell swoop with one approved product. So he has those.

Q. Let's talk about Dan Dix nevers for aflibercept, not other formulations.

A. Well, Dan Dix's nevers were for formulations, period. They were not specifically for aflibercept.

Q. And you never used histidine with aflibercept, correct?

A. I have used histidine with aflibercept.

Q. I believe you just told me that you never used histidine to develop an aflibercept formulation prior to the filing of your patent application.

A. Okay. You said prior to the filing of the patent application. You just said I never used.

Q. And that's correct?

A. So the question is what time frame are you talking about?

Q. Prior to your patent, you never used histidine to develop an aflibercept formulation, correct?

A. If you're going with prior to the patent validation,

no, I did not. After it, I did.

Q. And none of your patent examples, again, use a histidine buffer?

A. That's there in black and white. Yes, that's correct.

Q. All right. I'd like to talk about some of the stability study documents, or SS documents, that you testified. Do you recall that? We saw quite a few of them.

A. Yes.

Q. Before we do that, I'd like to pull up DTX 900, pages 36 and 37, and I want to look at and show you a Regeneron discovery response and ask you a couple questions about it if I could, sir.

A. All right. Hang on a second. Let me --

Q. And we're going to put this on screen to make it easy.

A. Well, the challenge is the screen is just a little bit too far for the glasses, and this is a little bit too close; so if I can get to the written document, I think I'll be a little bit better.

Q. At the bottom of page 36, you'll see Interrogatory 10. And in the middle of page 37, you'll see a response with respect to your '865 patent.

A. And you said bottom of which page?

Q. Bottom of page 36 is Interrogatory 10.

A. Okay.

Q. You see Interrogatory 10 asks, "For each claim of each of the initial patents, identify (a) the date that the claimed subject matter was first conceived and the date it was reduced to practice, and (b) the diligence leading to such reduction to practice, and for each such date and diligence, identify with particularity the documentary evidence supporting that date or diligence and at least three persons with any knowledge relating to that date or diligence."

You see that?

A. I see those words on the page, yes, I do.

Q. And the response in the middle of page 37 on your '865 patent says, "With respect to U.S. Patent Number 11,084,865" -- that's your patent, correct?

A. Yes.

Q. It goes on to say, "The inventors concede the inventions in the asserted claims of the '865 patent no later than March 21st, 2006, the date on which samples from Stability Study 207 were analyzed after two months' incubation."

Do you see that?

A. Yes, I do.

Q. It cites one page for the record, RGN-EYLEA-MYLAN-00475679. Do you see that?

A. Yes, I do.

Q. Have you seen this response before?

A. No, I have not.

Q. It doesn't identify you as a person to have any knowledge of the date of conception or reduction to practice, correct?

A. I don't see my name on the page, but this is getting into the realm of legal things. And if I'm not an expert on intravitreal injections after seeing my mother receive over 90 some-odd injections, I can't possibly be an expert on something that's a legal document without a law degree, I don't think.

Q. My question is much simpler.

You're not identified as a witness with knowledge in this response, correct?

A. I don't see my name there.

Q. It identifies one page in Stability Study 207, correct?

A. I see that it identifies the page. I'm not sure what's on the page, but --

Q. And it does not identify all the other stability studies you testified about, like the 065 study, the 203 study, the 205 study. Those aren't mentioned here, correct?

A. No, I don't see them.

Q. As a matter of fact, you testified about more than one page today, right? I saw dozens of documents you testified about.

A. Yeah.

Q. All right. Let's look at one of those. Let's start with PTX 1825. And you recall this document, right?

This is the 207 study document.

A. Yes.

Q. Are you okay for short if I just go by the number, the 207 study?

A. I think we can handle that.

Q. All right. So I want to start with the first page. For the 207 study, we see Amendment 7.0 dated November 8, 2010; is that right?

A. That is correct.

Q. Now, you know Michelle Looyenga, correct?

A. Michelle? What was the last name?

Q. Looyenga, L-O-O-Y-E-N-G-A.

A. Okay. It's Looyenga.

Q. Looyenga?

A. I'm sorry. The Loo threw me.

Q. My apologies. Looyenga. Did Michelle Looyenga help make the invention in your '865 patent?

A. So Michelle was one of the members of the technical staff that we had. She did help with study analysis. I think she probably helped label some of the samples and things that were put up.

Q. So did she help invent the formulation?

A. I would say no, she did not.

Q. Let's take a look at one of her lab notebooks. And then we'll jump back to 1825. But for a moment, let's jump to PTX 2304.

And you see this is a Michelle Looyenga lab notebook, correct?

THE COURT: Counsel, could I ask you to spell Ms. Looyenga's last name for our record, please.

MR. RAKOCZY: Michelle, last name L-O-O-Y-E-N-G-A, Looyenga.

THE COURT: Thank you. My apologies if I'm mispronouncing that.

MR. RAKOCZY: No worries.

BY MR. RAKOCZY:

Q. And you see this is a lab notebook from Ms. Looyenga dated March 9th, 2006, correct?

A. I do.

Q. Let's go to page 32 of PTX 2304. And here we see at the top this is the protocol for the 207 study, correct?

A. Okay. You're on page what number?

Q. 32.

A. Okay. I'm trying.

Okay. So 32.

Q. I just want to confirm this is the 207 stability protocol at the top, correct?

A. Okay. By page 32, you don't mean laboratory notebook

page 32.

Q. No. I'm sorry, sir. I will always try to refer to the exhibit number.

A. I'm sorry. I'm looking at the lab notebook, and I'm going why are we talking about IV mixtures?

Q. If you look at the bottom, you see PTX 2304.0032?

A. Yes. 0032. All right. I'm getting there.

Q. Are you with me?

A. I am working on it. If my fingers would work. I'm sorry.

Okay. I see 0032, yes.

Q. You see the protocol for the 207 study at the top on the left, correct?

A. I do.

Q. And let's go to the bottom and look at the signatures. And you see this was signed by Ms. Looyenga March 3rd, 2006, correct?

A. So the laboratory notebook was signed by Michelle on March 3rd, 2006. The protocol itself is not signed, however.

Q. And then it was witnessed August 22nd, 2006, correct?

A. Yeah, by Gareth Walsh, it looks like.

Q. Now, I want to jump back. And I'm sorry to put you through that. Let's toggle back to PTX 1825. That's the very large 207 document in your binder that you testified about. Let's go to page 85.

And you see here we have the purpose of the 207 study, correct?

A. And you said this is on page 85?

Q. Page 85 of PTX 1825, also on your screen.

A. Yes.

Q. And you see the purpose at the top is, "Determine the stability of 40 mg/mL VEGF Trap in the polysorbate 20-based intravitreal formulation when packaged in a prefilled syringe with six different component combinations," correct?

A. Yep.

Q. Now, the test article was the prefilled syringe, and the vial was the control in this study, correct?

A. So it goes on to say the stability of VEGF Trap, when filled in grass vials, will serve as a control for the study. So we were performing multiple pieces of work in one study. One, we had the formulations. We wanted to see how they perform in the vial.

The other thing is we were tasked with developing a prefilled syringe and had to contract to somebody to fill a prefilled syringe. Studies are a lot of work. So in one study we have six syringes, one vial. Yes, we called the vial as a control for the prefilled syringes because we expected, if anything, the prefilled syringes would perform worse than the vial.

Q. You understand the asserted claims in this case are

all to a vial, right?

A. Yes.

Q. And so in this test, the 207 test, just so the record's clear, the test article was the syringe and the control was the vial, correct?

A. Yeah. The control for the syringe was the vial, yes.

Q. All right. Let's go to page 92 of the same document. I just want to look at the signature at the bottom. It looks like your boss Dan Dix signed this February 3rd, 2006, correct?

A. He signed it for the second time, yes.

Q. And this protocol was amended numerous times; is that right?

A. Over the course of three years, yes, it was amended a number of times. This, I think, if I look back at it, we identified that there were a number of minor changes that needed to be -- or the lead technician on the study felt needed to be corrected.

One of them was we put up 39 vials instead of 42 that we planned. So she initialed and dated the corrections on the 17th of January when she realized she was short items, signed it. I signed it very shortly thereafter, and then Dan signed off on the changes as well.

Q. Let's go to page 103. I just want to get the dates of some of these amendments.

On page 103 we have Amendment 4.0 dated August 21st,

2008, correct?

A. Which page number are you on?

Q. We're on page 103, on your screen as well.

A. Okay.

Q. And that amendment is dated August 21st, 2008, correct?

A. That's the number in the upper left hand -- or right-hand corner, yes.

Q. And the first amendment -- I'm sorry -- the latest amendment, it's on the first page of the exhibit, page 1. And that was Amendment 7.0 all the way up to November 8, 2010, correct?

A. Yes.

Q. Now, let's go to page 137 and look at some of the data. On 137 at the top you see we have analysis of VEGF Trap by visual inspection, correct?

A. Hang on.

Yes.

Q. And if we look under vial under 5 degrees C, we can see at .5 months the technician wrote filamentous particle and one small particle, correct?

A. That is correct.

Q. Particles are not good, right?

A. Well -- so in this case, these were hand-filled vials in our lab. And we were used to getting extraneous particles

from filaments and fibers. And we had a scoring system that allowed a certain number of particles to be present.

This is totally different than GNP product, which is produced in a clean room in an environment that ensures no particles from dust and whatever else is floating around in your lab that's in there.

Q. I just asked if particles are bad. And I recall you testifying --

A. Particles are bad.

Q. Particles are "kind of a serious thing" and "very bad."

That's what you said, right?

A. That's true.

Q. And there are particles in this formulation, correct?

A. Yes.

Q. Let's look at another one. Let's go to page 142 of the same exhibit at the top. And we see some more visual inspection data. You see that?

A. Uh-huh.

Q. And for 5 degrees C. And here we see in several places the technician noted small particle, filamentous particle, small particles, particles, correct?

A. Yes.

Q. Particles all over the place. That's very bad, correct?

A. Well, so -- let's see. This is 2007. You're looking at Syringe Number 1, Syringe Number 2, Syringe Number 3, and Syringe Number 5, if I have the right page, 142. So this is syringes, and this isn't the vial.

Q. So this doesn't count? The syringe data doesn't count?

A. Well, you know, we're talking about a vial in the patent. One of the things that is a concern, when you move a formulation from a vial into a prefilled syringe, is you encounter a lot of different materials that are not in the vial. So syringes have silicone oil either sprayed or baked on the inside of them. Some syringes -- well, glass syringes have tungsten, and tungsten can cause proteins to precipitate. So it's kind of two different environments.

Q. I just want to get it straight.

You took us through a dozen studies showing us prefilled syringe data. And so I'm looking at prefilled syringe data that's got particles all over the place. And you're saying that's not relevant to the stability of the vial?

A. A vial is a very different environment.

Q. So all that syringe data we looked at would not be relevant to the stability of the vial, correct?

A. I would assess my stability with things in the vial. If it's unstable in a syringe, doesn't mean it's unstable in a vial. They're different beasts.

Q. All right. Let's go to page 14 of this same exhibit and look at some additional data.

And the first thing I want to note on this page, here we have the 207 study data for 5 degrees C. And it's dated -- can you tell me, what's that date at the top?

A. Which page are you on?

Q. We're on page 14 of PTX 1825.

A. Okay. So on the screen here, if I'm seeing it right, it looks like the 28th of August 2008.

Q. August 28th, 2008, at the top, correct?

A. Yes.

Q. Now, there are no dates in this table on when exactly the testing was conducted, correct? At least none that I can see.

A. So that would be captured at the end with the sequence information.

Q. We'll get there. But on this table right here, this doesn't say when this testing was conducted?

A. No. I don't see it on the table at all, no.

Q. And I see a syringe column but not a vial column, correct?

A. Yes. So the reason why you see a syringe column -- everything had a syringe column, but that's Device Number 1.

Q. I'm just asking do I see a syringe column and not a vial column. That's all I'm asking. Your counsel can ask away

whatever else he wants.

A. Okay. Well, you see a syringe column, and it's Device Number 1, which was a syringe.

Q. All right. Let's go to page 68 of the same document.

And here we see analysis of VEGF Trap by OD at 405 nanometers, correct?

A. That is correct.

Q. So I'll call this OD405 data for short. And at two months, you see the data that's been highlighted?

A. Uh-huh.

Q. And all this data, it ranges from .047 through about .0 -- 0.053, correct?

A. That is correct.

Q. And it's all been crossed out and rewritten, correct?

A. Yeah. It looks like there were two entries there.

Q. Now, let's jump to page 111 of this same document -- and let me back up.

You said that the way this document is compiled, this is the way that it was kept in the normal course of business?

A. So this is a file. It is called a study folder. It collected all the loose paper from the stability study. And things went in. Sometimes things went in in the middle; sometimes things went in the end.

Q. Because it kind of looks like a dog's breakfast, like someone threw everything in the air and then just recompiled

it?

A. Well, I wouldn't say that they threw it in the air. It was like, I'm stuffing it in, I've got it, I'm stuffing it in, I've got it. You know, that's kind of the way it was done.

Q. All right.

A. Is it a good way to do it? Well, we have better ways now, but --

Q. Let's jump to page 111 of the same exhibit, PTX 1825. And here we see Amendment 5.0 --

A. Yeah.

Q. -- to the 207 study dated August 19th, 2008, correct?

A. That is correct.

Q. And I'd like to look at the second paragraph. And you see it states that, "Variability between HPLC systems and HPLC column lots over time may cause variability in purity results between samples run at discrete points in time."

Do you see that?

A. Yes, I do.

Q. And the next sentence continues that "This may impact the ability to confidently identify trends in data which have been processed on different systems and across a wide spectrum of time," correct?

A. That is correct.

Q. All right. I'd like to switch gears if I could.

You testified about your provisional application. Do

you recall that?

A. Yes.

Q. I want to look at just a couple quick things hopefully. Let's go to PTX 3249. I believe it's already in evidence. And this is your provisional application you were looking at during your direct testimony. And I'd like to go to page 11.

THE COURT: I'm sorry, Counsel. What page was that again?

MR. RAKOCZY: PTX 3249 at page 11.

THE COURT: Thank you.

THE WITNESS: Looks like you're having trouble with this too.

BY MR. RAKOCZY:

Q. I'd like to focus on paragraph 8 starting the third line. You see it describes an ophthalmic formulation.

Do you see that?

A. You're on which page?

Q. I'm on page 11.

A. Yeah.

Q. Paragraph 8. And the third line down describes an ophthalmic formulation comprises about 40 to 50 mg/mL of the VEGF antagonist Sequence ID Number 4.

Do you see that?

A. Yes, I do.

Q. So that's disclosing a range of concentrations, 40 to 50 mg/mL, correct?

A. It lists a range of 40 to 50 mg/mL, yes.

Q. It's not describing 40 mg/mL, correct?

A. It's listing a range. What that plays out in the patent, I'm not an attorney; so I'm not going to try and interpret that one.

Q. Well, my question is simple. This formulation is describing a range, 40 to 50 mg/mL?

A. Yes.

Q. Not 40 mg/mL, correct?

A. That is what I see on the page. There's a range of 40 to 50 mg/mL.

Q. Now, let's look down on the same page, the next line. You see it describes a range of "0.01 to 3 percent polysorbate."

Do you see that?

A. Yes, I do.

Q. So that is not 0.03 percent polysorbate 20, correct?

A. It is a range that encompasses 0.03 percent polysorbate.

Q. So that range covers 0.03 percent. Is that what you're saying?

A. No. All I'm saying is, mathematically, 0.03 percent falls in between 0.01 and point -- and -- not .3 -- and

3 percent. Interpreting the claim would be something that an attorney would need to do.

Q. Under that rationale, 40 mg/mL falls within 40 to 50 mg/mL aflibercept, correct?

A. Mathematically, yes, it does.

Q. Now, this range on screen, 0.01 to 3 percent polysorbate, is different from a range of 0.03 to .1 percent polysorbate 20; is that right?

A. Okay. Say that again.

Q. The range on screen, 0.01 to 3 percent polysorbate, is different from 0.03 to .1 percent polysorbate 20; is that right?

A. The ranges that are described -- in that case, the ranges are different.

Q. Now, let's go take a quick look at paragraphs 11 and 12. And these, unfortunately, bridge pages 11 and 12 of the same exhibit.

And do you see here it discloses 0.03 percent polysorbate; is that right?

A. It says 0.03 percent polysorbate, yes.

Q. And that is different from a range of 0.03 to 0.1 percent polysorbate; is that right?

A. If you're asking me within the context of the patent, that's something I would need an attorney to answer.

Q. I'm just asking about the number. The number

0.03 percent polysorbate is not 0.03 to 0.1; is that right?

A. Well, all right. If I'm not talking about a patent and I'm talking about math --

THE COURT: He's just asking about the specific document, Doctor.

THE WITNESS: About the specific document?

If this is about the document, this is a patent; so I don't feel that I'm the appropriate person to answer that.

BY MR. RAKOCZY:

Q. So you're not qualified to opine or testify about patents, correct?

A. I can tell you about my invention. I can tell you about the work that I've done. If -- and you're looking at what I believe are claims within the patent or a summary of the invention. By the time you're getting down to the very specific meaning, you know, is 0.03 to 1 the same as 0.03, I'm getting to the point where I'm sorry, I'm not an attorney.

Q. So when you were -- I'm sorry, sir.

When you were comparing with your counsel the text in the provisional application compared to your '865 application, you weren't interpreting any of that; you were just telling us whether the words were the same or not. Is that right?

A. So I was looking to see if there was drift or change in the words. I was looking to see if the data was correct. And as near as I could tell, when I laid the documents down

beside one another and looked at them, the words were the same.

Q. But you weren't interpreting those words, correct?

A. I was looking to see if the words were the same.

Q. All right. Let's jump back to some of your stability studies. And I want to start with the 205 study which is at PTX 2265. And it's on screen.

Do you see that?

A. Okay. Yes.

Q. And the 205 study, I want to look at the formulation. And this formulation in the 205 study was phosphate, NaCl, polysorbate 20, and 40 mg/mL of VEGF Trap, correct?

A. Phosphate, NaCl, polysorbate 20, and 40 mg/mL VEGF Trap, yes.

Q. Now, there's no sucrose in this formulation, correct?

A. That is correct.

Q. There's no sugar or sugar alcohol stabilizer in this formulation, correct?

A. There is not.

Q. You're aware all asserted claims require a sugar stabilizer?

A. I'm not sure that that is the case. I don't know.

Q. You don't know whether the asserted claims require a stabilizer?

A. So that would be a question for my lawyer.

Q. Okay. Did you look at the asserted claims in

preparation for your testimony today?

A. I read through them, yes.

Q. Did you ask anybody what the asserted claims were?

A. Actually, I don't recall specifically asking to go through the details of the asserted claims.

Q. All right. Let's look at another study. I want to very briefly touch on the 065 study.

If we could pull up PTX 3266. That may be the wrong exhibit. No, there it is.

I just want to confirm. In the 065 study, all the formulations were 50 mg/mL concentration of aflibercept; is that right?

A. That is my recollection, yes.

Q. And I think you testified earlier you understood that all the asserted claims are to 40 mg/mL aflibercept, correct?

A. I believe that I may have made a statement to that effect, yes.

Q. So I just want to be clear, then. We can consider the 40 and the 50 mg/mL concentrations equivalent in your view?

A. No. They're different.

Q. They're different. Okay.

All right. I'd like to pull up one of your slide decks, which is PTX 3314. It should be in your binder. We'll pull it up on screen as well. You see this is entitled "ITV Review and Summary," correct?

A. Yes.

Q. And this was attached to an email at PTX 3313 from Jennifer Carrier dated March 14th, 2006. So we'll pull that up and confirm it.

If we could please see PTX 3313.

And you see the email at the top dated March 14th, 2006, from Jennifer Carrier. Do you see that?

A. Yes, I do.

Q. And she's attaching an ITV review and summary, March 14th, 2006, laptop presentation, correct?

A. Yes.

Q. All right. Let's jump back to the presentation. I want to go to page 7. And here we see at the top the title of the slide is "VEGF Trap ITV, the next steps," correct?

Do you see that?

A. Yes.

Q. And the first step or the first bullet is "a more stable ITV formulation was and is desired," correct?

A. Yes.

Q. And it says "because due to demonstration of instability to vortex in various syringe stresses," correct?

A. Yes.

Q. And then let's look at the next page, 8. Here you say that you're going to use stability analysis tools to identify superior formulations, correct?

Do you see that?

A. Okay. I see two assays. I guess, yes, that is the meaning of what is on the page, yes.

Q. Now, I want to very briefly jump to page 22 of your presentation. And here we have some data at 5 degrees C.

Do you see that?

A. I'm working on it.

Okay. 5 degrees C, yes.

Q. And you see in the left-hand column you have the formulations, right?

A. Yes.

Q. And the F2 formulation is the 40 mg/mL VEGF Trap containing 0.03 percent polysorbate 20, correct?

A. So yes. It contains -- it's listed as having those components, yes.

Q. And then for the length of stress at 5 degrees C, we have one month and five month, correct?

A. Yes.

Q. And at one month, the native VEGF Trap was less than 98 percent, correct?

A. So at one month, the native VEGF Trap was 97.9. But I'm not sure what the full composition of this formulation is based on what I'm seeing here. I know it's from Stability Study 191, which I would need that detail to know the actual composition.

Q. I'm just asking if Formulation 2 at the one month was below 98 percent VEGF Trap native. Correct?

A. It was. It started out below 98 percent.

Q. All right. Let's jump to PTX 3312. And I think you testified about this document, correct, the update on ITV syringe stability studies?

A. 3312?

Q. Yes.

A. No. I think I testified about a different document, but this might have been in my deposition.

Q. This is yours as well, correct? It's entitled "Update on ITV Syringe Stability Studies"?

A. It's mine and Dan's, yes.

Q. By Dr. Dix and yourself, dated March --

A. That is correct.

Q. I'm sorry. I'll start over.

This is one of your presentations along with Dr. Dix dated March 16th, 2006; is that right?

A. Yes, it is.

Q. Let's go to page 2 of your presentation. And here it says that "studies ongoing, examining the stability of the following formulations," correct?

A. That is correct.

Q. And at the bottom we see two of the formulations where the studies were ongoing are Formulations 8 and 9?

A. Yes.

Q. And both of those are the 40 mg/mL which contains 0.03 percent polysorbate; is that right?

A. That is correct.

Q. Now, let's go to page 27 of this same exhibit. And am I correct? Does it say that the VEGF Trap in the oncology formulation is threefold more stable than the current ITV formulation? Is that right?

A. Which page are you on?

Q. On page 27.

A. Okay. I'm going to lose my mind because I keep looking at the document page and not your page number. I apologize.

Q. They're the same on this one. Slide 27 is page 27.

A. Yeah, it is. That's pretty good. I'm going wow.

So you said the oncology formulation is approximately threefold more stable than the current ITV?

Q. Yes. Is that right?

A. That's a fair statement, yes.

Q. All right. Just a couple more, Dr. Graham.

I'd like to go to PTX 3327. And I believe I was mistaken before, but I believe you did testify about this slide deck entitled "Travels through two stability-indicating assays," correct?

A. Yes, I did.

Q. And I believe you said this was dated in March or April of 2006, correct?

A. I've seen enough dates right now, I'll take the record's word for that. But yes.

Q. I'd like to go to page -- sorry. Let's go to page 46 and look at formulations listed here.

A. Page 46?

Q. Yes.

A. At least I only have one set of page numbers this time.

Q. Are you there?

A. I am.

Q. And this one you see has total number of particles 500 nanometers or larger in 1 mL formulation; is that right?

A. That is correct.

Q. And if we look near the bottom, Formulations 8 and 9 are both 40 mg/mL concentration and they both contain 0.03 percent polysorbate.

Do you see that?

A. Yes.

Q. And unstressed, each of these particles -- strike that. Let me back up.

I apologize, Your Honor. It's getting late.

Unstressed, each of these formulations had over 60,000 particles 500 nanometers or larger, correct?

A. Yes, they did.
Q. Particles are very serious and very bad, correct?
A. They are serious and bad, yes.
Q. And when stressed, they each contained over 300,000 particles, correct?
A. Yes. They increased, yes.
Q. I apologize. I forgot to ask about one other study, and then I promise you we're going to leave the studies.
Let's jump to PTX 1860, different exhibit.
And this is the 203 study. You remember mentioning that, correct? And I want to jump to page 130 and look at the formulation.
A. So the exhibit is?
THE COURT: You said 1860, Counsel?
THE WITNESS: I don't see that.
BY MR. RAKOCZY:
Q. PTX 1860. Oh, it's in your original binder. I apologize.
THE COURT: The other book, Doctor.
THE WITNESS: Thank you.
BY MR. RAKOCZY:
Q. I want to go to PTX 1860, page 130. And I just want to confirm the test article formulation.
A. 130.
Q. Do you see it?

A. Okay. So --

Q. I'm looking at the test article on page 130. It's on screen.

A. So you're saying the document is PTX and the page is 0130?

Q. I believe it's page 130 of PTX 1860. It's on screen as well.

A. All right. Now I'm really confused. You said it was the other notebook. Oh, you mean not this other notebook; the other notebook.

THE COURT: Yes, Doctor. Yes.

THE WITNESS: Don't give me more than two notebooks at a time or I'm in trouble. Okay. And you are on page 130?

BY MR. RAKOCZY:

Q. Yes. And I want to confirm that the test article in this study did not contain sucrose or another sugar stabilizer; is that right?

A. Let me get to 130.

So ask your question. I'm there.

Q. I just want to confirm the test article -- and we have it on screen -- did not contain sucrose or another sugar stabilizer; is that correct?

A. There is no sucrose in the formulation.

Q. Now, you testified quite a bit today about the 40 mg/mL aflibercept concentration formulations, correct?

A. Yes.

MR. RAKOCZY: I have a couple more exhibits, Your Honor. May I approach?

THE COURT: You may.

BY MR. RAKOCZY:

Q. I'm going to give you two more exhibits, Dr. Graham.

A. Thank you.

Q. All right, Dr. Graham. Let's start with the first one, DTX 4121. We're going to pull it up on screen as well.

Do you see this is United States Patent Application Publication Number U.S. 2006/0217311.

Do you see that?

A. I do.

Q. It's entitled "VEGF Antagonist Formulation."

Do you see that?

A. Yes.

Q. And the inventors are two of your colleagues, Dr. Dix and Dr. Frye, correct?

A. That is correct.

Q. And do you see the file date in the middle of the page, filed March 22nd, 2006, correct?

A. Yes, I do.

Q. And I want to look below that to the column where the heading "Related U.S. Application Data" -- date -- or data. I'm sorry. It's at the top right hand of the page. My fault.

Do you see in the right "Related U.S. Application Data," correct?

A. Yes.

Q. And it says, "Provisional Application Number 60/665,125 filed on March 25th, 2005," correct?

THE COURT: Yes, Counsel?

MR. TRASK: Your Honor, objection. This is outside the scope of the direct examination. This is a document that was never shown to the doctor during his direct examination. And, in fact, it's a document that defendants didn't rely on at this point.

MR. RAKOCZY: Your Honor, he testified repeatedly about the 40 mg/mL concentration. This is a U.S. patent publication disclosing 40 mg/mL concentration that I'd like to address with the witness.

THE COURT: Overruled.

BY MR. RAKOCZY:

Q. Let's turn to exhibit page 3, paragraph 17. And I want to go to the ninth line down. And you see in the middle here the document describes "A 40 mg/mL prelyophilized solution."

Do you see that?

A. So you're on page 3?

Q. Paragraph 17.

A. And a 40 mg/mL prelyophilized solution. Yes, I see

that.

Q. Now let's look at paragraph 36 on page --

A. So --

Q. -- 5.

A. -- you know, a prelyophilized solution is not a formulation.

Q. Sir, I was just asking whether it disclose a 40 mg/mL concentration in a prelyophilized --

A. It is a prelyophilized solution, but that's never designed to be a -- I'm sorry. I'm looking at the science. And I don't understand how a lyophilized solution or prelyophilized solution matches up with a liquid formulation at the same concentration. It's two different things.

Q. Sir, I'm just asking did your boss Dr. Dan Dix disclose a "40 mg/mL prelyophilized solution" in that paragraph?

A. That is what's in there, yes.

Q. So let's go to paragraph 36, which is on page 5. I want to look at the last sentence. And here you see Dr. Dix describes, "An example of a pharmaceutically acceptable liquid formulation comprises a VEGF-specific fusion protein antagonist in a pharmaceutically effective amount of buffer, a cosolvent, and one or more stabilizers."

Do you see that?

A. Yes. That's what's written on the page.

Q. Now, I want to compare this to the provisional application which is the second document I handed you, which is DTX 8149.

I'm sorry. I misspoke.

This document, the provisional, is DTX 8194. It's the second --

A. I think we had you. Even with the dyslexia, it was good. That one, I followed.

Q. All right. And do you see in the right-hand upper corner we have a stamp? You see that? You see the stamp says "Application 60/665,125."

Do you see that in the upper right-hand corner?

A. Yes. That's what it looks like.

Q. Now, let's go to page 10 of this document, page 34 -- paragraph 34. I'm sorry. Here we see that same heading. You see stable liquid formulations, correct?

A. So page 10?

Q. Paragraph 34. We have a paragraph entitled "Stable Liquid Formulations," right?

A. All right. I'm doing it to myself again, following the document pages, not the exhibit pages. Went too far.

Okay. Paragraph 34.

Q. And you see this -- we see the same sentence, the last sentence, starting, "An example of a pharmaceutically acceptable liquid formulation comprises a VEGF-specific fusion

protein antagonist in a pharmaceutically effective amount, a buffer, a cosolvent, and one or more stabilizers," correct?

A. So you're saying the last sentence, correct?

Q. Yes.

A. Yes, that's what it says.

Q. I want to jump to the claims very quickly on page 12.

And can you confirm for me Claim 7 is directed to a stable liquid formulation of Claim 1 comprising 1- to 10-millimolar phosphate buffer, 1- to 10-millimolar citrate, 25- to 150-millimolar NaCl, 5 to 30 percent sucrose, 10 to 50 mg/mL of a fusion protein, at a pH of about 6 to 6.5; is that right?

A. This is Claim 7?

Q. Yes.

A. Yes, that's what's written on the page.

Q. Just a couple more quick questions, sir.

Let's go back to page 8 of the same exhibit, DTX 8194 -- I'm sorry -- page 5. I'm doing it as well.

Page 5, paragraph 8, of DTX 8194.

A. Doesn't that mean it's time to quit?

THE COURT: It's airborne contagious.

BY MR. RAKOCZY:

Q. Okay. I promise.

A. So you're going with paragraph 8?

Q. Yes.

A. Okay.

Q. And here at paragraph 8 we see a prelyophilization formulation of the invention.

Do you see that?

A. Yes.

Q. And then it also at the end of the paragraph says the polysorbate may also be present, for example, as polysorbate 20, correct?

A. Yes.

MR. RAKOCZY: Can you give me one moment, Your Honor?

THE COURT: Certainly.

BY MR. RAKOCZY:

Q. A couple more quick items, Dr. Graham.

Let's go back to the prior exhibit. So can you switch for me again to the first one I handed you, DTX 4121. Let's go to page 5. And in the right-hand column you see Tables 1 and 2.

A. Yes.

Q. And Tables 1 and 2 in the titles, you see they reference Stability Study 65?

Do you see that?

A. Yes, I do.

Q. That's one of the stability studies that you worked on that we talked about earlier today and that you talked about on your direct, correct?

A. Yes, it is.
Q. So you're not an inventor on this patent, correct?
A. That is correct.
Q. But that's your stability study?
A. Well, I helped it along after I joined the group, but my contributions to the patent were other things. I mean, I ran all the 200 through 207 studies, conducted the shear studies. So yeah, I'm not an inventor on that.
Q. All right. Last question, Dr. Graham. And I want to refer to the formulations in your '865 patent.
If an ophthalmologist administered the formulation from your '865 patent but without the aflibercept, would that be a safe and effective medicine for treating eye diseases?
A. Did you -- would you say that again. I'm sorry.
Q. Yes.
If a doctor administered the formulation from your '865 patent but without the aflibercept, would that be a safe and effective medication?
A. I would not expect so.
MR. RAKOCZY: All right. Pass the witness, Your Honor.
THE COURT: Thank you.
Redirect, Counsel?
MR. TRASK: Thank you, Your Honor.
THE COURT: Why don't we take five.

You're still off limits for folks to speak with you, but you can step down. We'll take a quick five-minute break and finish the doctor's testimony.

THE WITNESS: Thank you.

(A recess was taken from 4:44 p.m. to 4:51 p.m.)

THE COURT: Counsel, you may proceed.

MR. TRASK: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. TRASK:

Q. Dr. Graham, do you have the binder in front of you that defense counsel handed up?

A. Yes.

Q. Could we turn to Exhibit DTX 900 in that binder.

I'd like to turn to page 37 of that document.

And if we could zoom in on the paragraph that starts "with respect" -- actually, "Subject to the foregoing general" and then following paragraph.

Doctor, do you see that on the screen?

A. Yes, I do.

Q. Do you remember defense counsel made a bit of a show about the fact that your name is not identified in this interrogatory response served by Regeneron?

A. Yes.

Q. Do you see that this document refers to the '865

patent and it says the inventors conceived the inventions?

Do you see that?

A. Yes, I do.

Q. Who are the inventors of the '865 patent?

A. Well, that would be Dan Dix, Eric Furfine, Kelly Frye, and myself.

Q. Thank you, Doctor.

Do you remember you were asked on cross whether polysorbate 20 is a solvent?

A. Yes, I was.

Q. Is a solvent the same as a cosolvent?

A. No.

MR. RAKOCZY: Objection, Your Honor. Calls for expert testimony.

MR. TRASK: Your Honor, he asked this exact question and tried to impeach the witness about whether polysorbate is a solvent, and I'm just following up on what the doctor understands that to mean.

THE COURT: The examination was more what do the papers indicate. Sustained.

BY MR. TRASK:

Q. Let's turn to the same binder, PTX 2304. That's P as in plaintiff, PTX.

A. PTX, not --

Q. Correct.

A. Okay. Yes. I see that.
Q. And if we could turn to page 32 of that document.
Are you there?
A. I'm trying to read it on the screen, but I'm going to have to struggle. What was the number again?
Q. It's okay. If you can see it on the screen, just a quick question. If you want it, it's PTX 2304.
A. 23 -- PTX 23 -- okay. Good with it on the screen.
What's your question?
Q. So the question, Doctor, is do you remember when counsel for Biocon and Mylan pointed to the signature by your colleague Michelle Looyenga in the bottom left of this page?
A. Michelle Looyenga, yes.
Q. Can we turn to the next page of this document, PTX 2304, page 33.
And do you see that there's a page at the bottom where -- it's not the signature block, but right above that there's a signature line for study director?
A. Yes, I do.
Q. Now, that's not signed, but this is Stability Study 207, right?
A. Correct.
Q. Who was the study director for Stability Study 207?
A. That would have been me.
Q. Let's look at PTX 1825, page 85.

A. Yes, I see that.

Q. I'm sorry. Wrong page. Page 137. Sorry about that.

And do you remember -- I'll let you get there.

A. Okay. I can see this one on the screen.

Q. Do you remember when counsel for Biocon and Mylan asked you about the entry under 5C at .5 months that says, I think, clear, one filamentous particle. Do you see that?

A. Yes.

Q. Does that indicate to you that this formulation is unstable?

A. No, not necessarily.

Q. Why is that?

A. So the filamentous particle, those are typically items that come from the tech's wipes, the things that we use in the lab as part of the routine operations. If it had said one proteinaceous particle, then I might have been concerned. But the subsequent vial also showed clear, no precipitate. And having a particle is not a failure by our definitions.

Q. Thank you, Doctor.

If we could look in the same exhibit, page 111. And I'm looking at the second paragraph on this page.

A. Okay. Variability between HPLC systems and HPLC columns.

Q. Yeah. Are you there?

A. Yeah.

Q. Do you remember you were asked questions by counsel for Biocon and Mylan about the variability regarding HPLC?

A. Yes.

Q. Is this referring to SEC or HPLC?

A. So this says HPLC in terms of what it's being described.

Q. Is that the same as SEC?

A. Not necessarily, no.

Q. Okay. With respect to SEC, size-exclusion chromatography, do you consider that to be a good assay for analyzing the stability of aflibercept formulations?

A. Okay. It is a very good assay. It's what I like to call the sentinel assay.

Q. What do you mean when you say SEC is the sentinel assay?

A. So it's the one that shows something going wrong, typically, before anything else. You know, unless we have major problems, generally we don't see particles, generally we don't see increases in turbidity; but we always do see some level of change in HPLC.

Q. So, Doctor, then, if you had only one assay by which you could analyze the stability of a formulation containing aflibercept, what assay would you choose to use?

A. I would use SEC.

Q. Let's look at PTX 3314, page 22.

Do you remember being asked for counsel by Biocon and Mylan about the data under percent native VEGF Trap in this exhibit --

A. Yes.

Q. -- for Formulation 2?

A. Yes.

Q. And counsel pointed out that the percent native VEGF Trap at that condition was 97.9.

Do you remember that?

A. Yes.

Q. Was the starting percent data of VEGF Trap -- what was the starting percent native VEGF Trap with this material?

A. So it was 97.6.

Q. And what does that tell you about the stability of this material?

A. Well, so generally you have variation in your assay, but you don't go up in purity. So I started off at 97.6 plus or minus .1, .2, ended up at 97.9 plus or minus .2. It shows that there's really no change. It says that the stability is good. The fact that I started out below 98 percent, you know, I would never expect to -- if I start out below, I never would expect to come back up two.

Q. And so what does this data tell you as a formulation scientist? If you had started with material that was above 98 percent, what would you end up with?

MR. RAKOCZY: Objection, Your Honor. That's asking for opinion testimony and a prediction.

MR. TRASK: This is the very slide that counsel asked him about. I'm just asking him to explain the meaning of it, Your Honor.

MR. RAKOCZY: He's asking him to predict something that's not on the slide, Your Honor.

THE COURT: Understood.

Sustained.

BY MR. TRASK:

Q. Let's turn to Exhibit 3327, please.

And we'll look at page 46. Now, do you remember when counsel for Biocon and Mylan asked you about the last two rows of this table, Formulations 8 and 9?

A. Yes.

Q. And they pointed out that there was an increase in the number of -- I don't remember if it was aggregates or particles shown in this data?

A. I think they used the words "particles."

Q. How does -- can you explain how the HIAC analysis works that was done to generate this data?

A. So this is kind of an internally controlled experiment in that you start off by measuring the formulation and you look at whatever the base level is. Then you subject it to stress and you look for a change.

The bigger the change -- you know, that -- large changes are not good. Small changes are to be expected. You know, there's more to the story that isn't necessarily entirely captured here, but what can happen is you not only get more particles but you get bigger particles.

In comparison, if we look at all these formulations and we say, okay, how do their performances compare? 8 and 9 are probably two of the top ones. I mean, 8 started out fairly low, went up a little bit. 9 started out at 100,000 and went up.

You know, really, the only formulations that are on there that start out significantly lower are ones that are lower protein concentration. There's a couple 10 mg/mL. And, you know, they're down in the 30 thousands. You know, it basically says that these are stable to the stress or more stable to the stress more directly than everything else that's on that page.

Q. Thank you. Can we turn to 3312, please, page 27.

Do you remember when counsel for Biocon and Mylan asked a question about the fourth bullet down on this slide comparing the oncology formulation stability to the "current ITV formulation"?

A. Yes.

Q. What is the current ITV formulation here?

A. So that was what we had referred to as ITV1. It was

a formulation that contained 40 mg/mL aflibercept, 135-millimolar sodium chloride, and 0.1 percent PEG 3350.

So it was the formulation that we were seeing the issue with particulate formulation.

Q. Okay. Can we look at DTX 4121, please.

I believe this is one of the loose-leaf documents that counsel handed you. And I would like to look at page 3, paragraph 17.

Do you see that, Doctor?

A. I'm doing the wrong page number thing again; but yes, I do.

Q. So do you remember when counsel asked you a question about this statement in this document, 40 mg/mL prelyophilized solution?

A. Yes.

Q. Is a prelyophilized solution an ophthalmic formulation?

A. It is not.

Q. Why not?

A. Well, a prelyophilized solution is designed to have the drug remain stable solely --

THE COURT: One second, Doctor.

Yes, Counsel?

MR. RAKOCZY: Objection, Your Honor. This is calling for expert testimony.

THE COURT: It is. It is. Sustained.

MR. TRASK: In that event, nothing further, Your Honor. We do have exhibits to move in unless, obviously, there's further from defense counsel.

THE COURT: Understood.

Recross?

MR. RAKOCZY: Depending on the exhibits, I may have none, Your Honor.

THE COURT: Let's take the exhibits first, then. Keep our fingers crossed.

One second, Doctor, if you'll bear with us. Just housekeeping stuff.

THE WITNESS: Okay.

THE COURT: Thank you.

Slowly counsel, but go ahead.

MR. TRASK: Thank you very much, Your Honor.

PTX 3327, PTX 3326, PTX 2293, PTX 2292, PTX 1921, PTX 1825, PTX 2277, PTX 2278, PTX 1860, PTX 2238, PTX 3249, PTX 2281, PTX 2282, PTX 2283, PTX 2265, PTX 2266, PTX 2267, PTX 2275, and PTX 672.

MR. RAKOCZY: I apologize. That was going too fast for me, Your Honor. Can I compare?

THE COURT: Please. Compare notes.

MR. RAKOCZY: Your Honor, as you can imagine, I need to preserve an objection for a lot of these. I'll try to do

them in order.

No objection to PTX 672.

We object to PTX 1825, PTX 1860, PTX 1921, PTX 2238, PTX 2265, PTX 2266, PTX 2267, PTX 2275, PTX 2277, PTX 2278, PTX 2281, PTX 2282, PTX 2283, PTX 2292, PTX 2293, PTX 3326, PTX 3327.

And our objections are as I stated before, Your Honor, based on our motion in limine Number 5.

THE COURT: Understood. The Court will receive those conditionally, subject to addressing -- the parties have the opportunity to address those issues raised earlier in posttrial briefing. The Court will obviously address it in its findings of fact and conclusions of law.

MR. TRASK: Just for the record, Your Honor, we disagree with the objection. We think these documents were adequately disclosed during discovery and there's no basis for their objection here.

THE COURT: Understood.

MR. RAKOCZY: I have a few to move in, Your Honor.

THE COURT: One second.

Are those all from Regeneron's standpoint?

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

THE COURT: All right. Subject to that condition, the exhibits previously identified by counsel are deemed admitted.

(PTX 3327, PTX 3326, PTX 2293, PTX 2292, PTX 1921, PTX 1825, PTX 2277, PTX 2278, PTX 1860, PTX 2238, PTX 3249, PTX 2281, PTX 2282, PTX 2283, PTX 2265, PTX 2266, PTX 2267, PTX 2275, and PTX 672 were admitted.)

MR. RAKOCZY: And then we move to admit DTX 4121, DTX 8194, DTX 737, DTX 900.

And, Your Honor, I have several PTXs I'm not sure. They may already be in. Can I look at these overnight and then I can wrap it up in the morning?

THE COURT: Yeah. That would be fine.

MR. TRASK: Then with respect to those documents, Your Honor, I'll just note again that DTX 4121 is a document that plaintiffs had never relied on here. It wouldn't be appropriate for them to rely on that document by their experts or anyone else in this case.

But I understand that there's kind of been an agreement reached here where documents used on cross will come in. And on that basis, I understand the document will be admitted.

THE COURT: Understood.

Any other objections or concerns with the list from defendant?

MR. TRASK: No, Your Honor.

THE COURT: Those will all be deemed admitted pending closure of some PTX that may or may not have been in evidence.

(DTX 4121, DTX 8194, DTX 737 and DTX 900 were admitted.)

THE COURT: May the good doctor step down?

MR. RAKOCZY: With that, I have nothing further for Dr. Graham. Thank you.

THE COURT: Sir, you may step down. Thank you. You can leave all the binders and whatnot there. We'll tidy up.

THE WITNESS: Do you want the syringes?

THE COURT: No. Water or not. No, never mind. I'll take the Fifth on what I was going to ask.

THE WITNESS: Don't go there. Now, these have been promised to Rene, so --

THE COURT: We receive those.

MR. TRASK: I don't think those are being received.

THE COURT: I thought they were simply demonstrative, purely demonstrative.

Thank you, sir. Those are all yours.

Counsel, any progress on looming or remaining exhibits from Dr. Stewart's examination?

No, sir. Go right ahead. I'm sorry.

MR. RAKOCZY: We'll have to get back to you in the morning about Dr. Stewart along with Dr. Graham. We'll clean that up.

THE COURT: Let's have a logistics discussion. What are we down to from Regeneron's standpoint in terms of witness

presentation?

MR. BERL: Your Honor, we still have Dr. Csaky to call as well as Dr. Trout. In all candor, Your Honor, we're evaluating how the evidence comes in. And it's possible that we may not proceed with an additional witness. It's not clear that, in our view, we need to advance commercial success. And that last witness, Dr. Manning, was solely related to commercial success. And we are looking at the evidence. But it's quite possible that we may not, in fact, call Dr. Manning, which would end the case before that.

THE COURT: Would we finish Dr. Csaky and Dr. Trout tomorrow?

MR. BERL: I don't think that's likely.

MR. RAKOCZY: And, Your Honor, if I could just add, whether Dr. Manning comes, it makes a huge difference because we have the last witness, Dr. Hofmann. And so we -- it would be nice to know sooner rather than later for witness logistics just so we don't have him standing around here for no reason.

MR. BERL: Obviously, we are looking at that. We'll analyze the transcript. We will tell them as soon as we've made a decision. But that would end the trial presumably with Dr. Trout. Mr. Hofmann, I think is their commercial success witness who responded to Dr. Manning. So, obviously, no Dr. Manning, no Mr. Hofmann. And we would be done subject to their trying -- oh, sorry. I've just been reminded we have

very short videos as well. I think it's no more than half an hour at most.

THE COURT: Are those the experts in dispute at this point?

MR. BERL: Yes.

THE COURT: Okay. Any other sticky notes? Okay.

All right. When is -- I'm sorry. Is it Mr. or Dr. Hofmann?

MR. RAKOCZY: Mr. Hofmann.

THE COURT: What are Mr. Hofmann's travel plans?

MR. RAKOCZY: Well, we were having him stick around to be the last witness on Friday. So depending on what happens with Dr. Manning, whether they're going to stipulate commercial success is out of the case and then we could potentially do something about Mr. Hofmann. But we'll need that information so we can evaluate what's left of his anticipated testimony, if anything.

THE COURT: Understood.

Any idea, Counsel, when the decision on Dr. Manning might be in the offing?

MR. BERL: We hope tonight, but tomorrow at the latest.

THE COURT: Okay. All right. Yeah, as soon as a decision is made on that, if you wouldn't mind communicating that so that Mr. Hofmann can make alternative arrangements if

he's not going to take the stand.

MR. BERL: Absolutely.

THE COURT: Okay. All right. Anything else we need to take up today, then?

MR. BERL: Not from Regeneron, Your Honor.

MR. RAKOCZY: Nothing from Mylan and Biocon, Your Honor. Thank you.

THE COURT: Well, let's resume at 9:00 a.m. tomorrow with a renewed interest in being as efficient as possible.

Everyone have a wonderful evening.

(Proceedings concluded at 5:17 p.m.)

CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 21, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 21st day of June 2023.

/s/Cindy L. Knecht

_____

Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 8

Biocon Biologics,

Defendants.

- - -

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

- - -

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

Thursday morning session,

June 22, 2023, 9:00 a.m.

- - -

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

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

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

THE COURT: Okay.

From the defense standpoint, anything else?

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

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

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

THE COURT: Hello, again, Dr. Csaky.

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

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

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

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

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

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

Counsel, you may proceed.

DIRECT EXAMINATION

BY MS. OBERWETTER:

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

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

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

If we can please pull that up onto the screen.

For the record, that's PDX 8.002.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

But go right ahead.

MS. OBERWETTER: Thank you, Your Honor.

BY MS. OBERWETTER:

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

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

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

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

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

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

from the very beginning of approval of ranibizumab in particular.

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

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

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

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

Q. Can you remind us what prn stands for?

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

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

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

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

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

THE COURT: Thank you.

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

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

BY MS. OBERWETTER:

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

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

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

THE COURT: Yes, sir, you may approach.

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

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

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

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

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

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

THE COURT: Is this the same eye?

THE WITNESS: This is the same eye.

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

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

BY MS. OBERWETTER:

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

A. Correct.

Q. What was the PrONTO trial?

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

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

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

Q. And what did the PrONTO trial show?

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

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

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

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

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

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

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

Q. Okay.

We can take that slide down.

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

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

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

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

If we can put up PDX 8.0005, Slide 5.

You were here for Dr. Albini's testimony?

A. Yes, I was.

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

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

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

Q. All right.

And we can take that slide down.

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

A. Correct.

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

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

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

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

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

Q. And then Phase II?

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

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

Q. And then just very briefly, Phase III?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

And so we typically are very much aware of the fact

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

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

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

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

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

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

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

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

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

THE COURT: Can I bum a copy from someone?

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

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

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

THE COURT: Sure.

MS. OBERWETTER: Approach?

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

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

THE COURT: Is this in his opening?

MS. OBERWETTER: This is in his response.

THE COURT: Response? Okay. Paragraph 74?

MS. OBERWETTER: Yes.

THE COURT: All right. And where else?

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

THE COURT: Understood.

Objection overruled.

You may proceed.

BY MS. OBERWETTER:

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

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

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

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

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

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

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

If we can please pull up PTX 1027.

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

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

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

If we can focus in on that first paragraph for a

moment.

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

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

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

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

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

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

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

Do you see that part?

A. Yes.

Q. What were you trying to convey there?

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

Q. We can take that down.

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

A. Yes.

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

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

from page 793 of the trial transcript.

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

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

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

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

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

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

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

A. Yes.

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

A. Yes.

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

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

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

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

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

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

references Dr. Albini's Slide 6.40.

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

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

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

Why did you want to look at DME separately?

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

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

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

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

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

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

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

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

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

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

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

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

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

A. Yes, I was.

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

Slide 13.

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

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

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

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

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

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

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

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

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

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

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

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

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

Q. Okay. We can take that slide down.

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

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

the screen?

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

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

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

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

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

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

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

A. No.

Q. Did it use any loading doses at all?

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

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

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

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

Q. And what about six loading doses?

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

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

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

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

Do you see that slide?

A. Yes.

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

about this slide?

A. Yes.

Q. And let's pull up Slide 17.

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

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

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

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

A. No.

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

A. Yes.

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

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

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

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

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

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

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

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

A. That's correct.

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

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

A. Yes.

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

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

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

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

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

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

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

A. Yes.

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

And what does this slide show?

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

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

A. Correct.

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

A. No.

Q. Why not?

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

based off of a prn strategy.

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

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

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

A. Yes.

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

A. No.

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

A. No.

Q. And why not?

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

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

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

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

Do you recall that generally?

A. Yes, I understood that.

Q. Do you agree with that position?

A. No.

Q. And why not?

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

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

Q. Thank you, Dr. Csaky.

We can take that slide down.

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

If we can pull up Slide 20, please.

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

A. Yes, I cited this report.

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

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

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

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

something that I'm used to dealing with.

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

Q. Thank you.

We can take that slide down.

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

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

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

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

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

A. It's a slow progressing disease.

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

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

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

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

If we pull that up.

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

A. Yes, I did.

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

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

that time.

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

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

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

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

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

Do you see that?

A. Yes.

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

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

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

Q. Right below this section --

If we can take that down.

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

A. Yes.

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

A. Yes.

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

A. No.

Q. Okay.

We can take that document down.

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

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

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

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

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

A. Correct.

Q. So let's take a look at Do 2012, which is DTX 3105.

What is this article that we are looking at? What is Do 2012?

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

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

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

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

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

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

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

A. No.

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

A. No.

Q. Or for DR?

A. No.

Q. And why not?

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

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

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

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

Do you see that?

A. Yes.

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

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

Q. Okay.

We can take that down.

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

Do you see that?

A. Yes.

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

A. Yes.

Q. Are diabetic retinopathy and DME the same thing?

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

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

A. Yes.

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

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

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

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

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

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

THE COURT: Okay. One at a time.

MR. McLAUGHLIN: Sorry.

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

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

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

MR. McLAUGHLIN: Look --

THE COURT: I'm going to say this one more time.

One at a time.

Ms. Oberwetter?

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

THE COURT: Counsel?

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

THE COURT: Sustained. Sustained.

BY MS. OBERWETTER:

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

A. Yes.

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

A. No, I did not.

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

A. The PANORAMA study.

Q. And if we pull up PTX 1794.

What is PTX 1794?

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

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

A. That's correct.

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

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

to think that way.

Q. Okay.

We can take that document down.

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

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

A. Yes. I heard him claim that.

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

A. Yes, I did hear him say that.

Q. Okay.

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

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

A. Yes, I have.

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

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

The other thing that is really interesting about this

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

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

A. No. No, not at all.

Q. And why is that?

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

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

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

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

A. No, it doesn't.

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

A. No, it doesn't.

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

A. No, it doesn't.

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

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

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

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

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

A. Correct.

Q. Okay.

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

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

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

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

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

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

Q. Okay.

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

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

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

fundamental difference between a loading dose and a prn injection.

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

A. No.

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

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

Q. Okay.

We can take that slide down.

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

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

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

I want to start with the words of an independent

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

A. Yes. Correct.

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

A. Correct.

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

A. Correct.

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

If we can pull up PDX Slide 30.

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

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

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

as it relates to anticipation.

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

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

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

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

We can take this slide down.

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

A. Yes.

Q. Okay.

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

that, DTX 204.

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

A. Yes.

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

A. Yes.

Q. I'd like to take a look at -- if we scroll forward to page 3 and take a look at that 2.3 section called "Chemistry."

Do you see that part?

A. Yes.

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

A. No.

Q. And why do you say that?

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

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

solutions or even what an isotonic solution is.

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

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

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

A. Oh, absolutely.

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

A. No.

Q. Okay. I want to --

We can take that slide down.

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

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

Do you see that, Dr. Csaky?

A. Yes, I do.

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

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

little more readable?

A. Yes. Yes.

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

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

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

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

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

A. Yes.

Q. What is the PIER trial?

And we can call up Slide 35, please.

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

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

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

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

A. Correct.

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

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

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

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

A. Correct.

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

A. Yes.

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

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

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

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

A. Correct.

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

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

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

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

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

A. Yes.

Q. If we go forward one more?

A. Yes. Yes.

Q. What have you added here?

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

every 12 weeks.

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

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

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

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

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

A. Yes. Yes.

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

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

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

going on in AMD, correct?

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

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

A. Yes.

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

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

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

A. Correct.

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

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

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

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

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

Do you remember that?

A. That is true.

Q. Is she just talking about European studies here?

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

Q. Okay. We can take that slide down.

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

Do you recall him talking about that generally?

A. Yes.

Q. Okay. Do you know Dr. Brown?

A. Yes, I know Dr. Brown.

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

Dr. Albini's Slide 37.

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

A. Correct.

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

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

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

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

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

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

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

THE COURT: Counsel.

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

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

THE COURT: Overruled.

BY MS. OBERWETTER:

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

A. Not a fixed eight-week dosing interval.

Q. We can take that slide down.

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

If we can please pull that up.

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

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

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

A. That's correct.

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

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

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

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

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

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

A. Nothing.

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

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

makes sense, right?

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

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

A. Yes.

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

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

A. Correct.

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

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

there's articles written about this.

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

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

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

Q. Okay. We can take that slide down.

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

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

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

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

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

A. I have -- I was here.

THE WITNESS: Thank you.

THE COURT: You're welcome.

BY MS. OBERWETTER:

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

A. Yes, I do.

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

Do you see that?

A. Yes.

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

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

THE COURT: Yes, Counsel.

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

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

MR. McLAUGHLIN: Which part?

MS. OBERWETTER: The responsive part.

THE COURT: Overruled.

BY MS. OBERWETTER:

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

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

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

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

A. Correct.

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

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

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

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

A. No. No.

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

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

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

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

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

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

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

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

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

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

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

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

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

Q. Okay. We can take that slide down.

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

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

A. I was also here for that.

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

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

A. Yes.

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

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

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

A. Yes, I did.

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

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

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

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

A. Yes.

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

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

And what does this language of the '572 patent

discuss?

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

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

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

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

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

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

disorders.

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

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

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

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

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

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

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

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

Do you recall that generally?

A. I do recall that.

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

A. Correct.

Q. Do you recall him also mentioning corneal neovascularization?

A. Correct.

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

A. Yes, I do.

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

A. Yes, I am.

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

A. I did.

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

A. Not officially.

THE COURT: One second, Doctor.

Yes, Counsel.

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

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

Dr. Stewart's reply.

THE COURT: Rebuttal evidence. Overruled.

BY MS. OBERWETTER:

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

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

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

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

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

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

A. Yes.

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

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

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

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

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

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

A. No.

Q. And why not?

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

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

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

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

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

A. Correct.

Q. And is that your opinion as well?

A. Yes. Yes.

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

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

A. Yes.

Q. And why?

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

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

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

THE COURT: Yes, Counsel?

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

THE COURT: Counsel?

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

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

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

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

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

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

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

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

MS. MAZZOCHI: Your Honor, if I may.

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

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

MS. MAZZOCHI: Right.

THE COURT: Objection overruled. Thank you.

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

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

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

Thank you all very much.

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

THE COURT: Good afternoon, Doctor.

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

MS. OBERWETTER: Thank you, Your Honor.

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

BY MS. OBERWETTER:

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

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

A. Well, I mean, the approval --

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

A. Sure.

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

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

A. Yes.

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

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

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

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

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

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

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

Q. Okay.

And we can take that slide down.

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

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

A. Yes.

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

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

A. Yes.

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

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

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

A. Correct.

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

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

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

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

A. Yes.

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

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

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

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

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

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

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

A. Absolutely. These are all in the specifications.

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

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

Q. Okay. I want to focus --

We can take that down.

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

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

A. Yes.

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

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

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

A. Correct.

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

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

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

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

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

You reviewed Example 7 that's in the specification?

A. Correct.

Q. What does Example 7 contain?

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

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

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

What does this disclosure tell the POSA?

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

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

Q. Okay.

We can take that slide down.

With respect to -- sorry.

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

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

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

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

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

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

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

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

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

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

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

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

A. Yes. Yes.

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

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

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

A. Yeah, absolutely.

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

A. Yes.

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

So if we take that slide down for a moment.

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

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

A. Yes.

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

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

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

Q. Okay.

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

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

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

Q. Okay.

We can take that slide down.

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

A. Correct.

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

A. I did.

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

A. Yes.

Q. Do you have any disagreement with the way he

highlighted that demonstrative?

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

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

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

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

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

Do you see that?

A. Yes.

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

A. Yes.

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

A. That's correct.

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

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

that I agree with him on that.

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

A. Yes.

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

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

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

A. Right.

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

A. Yes.

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

A. Correct.

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

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

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

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

Do you recall --

A. Yes.

Q. Okay.

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

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

A. Yes.

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

Do you remember that?

A. Correct.

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

A. That's correct.

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

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

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

A. No.

Q. Okay. And why not?

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

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

A. I would have no concerns.

Q. Okay. We can take that slide down.

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

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

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

A. I have.

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

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

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

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

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

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

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

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

Which of these machines are we talking about?

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

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

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

BY MS. OBERWETTER:

Q. Thank you, Dr. Csaky.

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

Had others besides Regeneron attempted to develop such regimens?

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

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

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

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

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

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

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

A. Yes.

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

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

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

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

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

A. Yeah.

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

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

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

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

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

Do you agree with that suggestion?

A. No.

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

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

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

MS. OBERWETTER: Thank you, Dr. Csaky.

I pass the witness.

THE COURT: Understood.

Cross.

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

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

MR. McLAUGHLIN: May we approach, Your Honor?

THE COURT: You may.

Whenever you're ready, Counsel.

MR. McLAUGHLIN: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. McLAUGHLIN:

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

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

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

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

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

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

A. Yes. Exactly.

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

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

Do you see that?

A. Yes.

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

A. I did say that, correct.

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

Do you see that?

A. I do see that.

Q. We can take that down now.

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

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

Q. Heier 2012.

A. Is that this?

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

VIEW 2 results.

A. Yes.

Q. You relied on that publication, correct?

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

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

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

A. I have been told that, correct.

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

Do you remember that?

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

Q. Their opinions are widely read and respected.

Would you agree with that?

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

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

pulmonary, cardiology, cancer, everything.

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

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

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

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

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

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

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

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

MR. McLAUGHLIN: Okay. May I approach?

THE COURT: You may.

BY MR. McLAUGHLIN:

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

Do you see that?

A. Yes.

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

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

Is that what he said?

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

Q. Do you know who Andy is?

A. Yes.

Q. Who is Andy?

A. Andy Schachat.

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

A. At that time he was.

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

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

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

appropriate, what their initial thoughts are.

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

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

Q. We can take that down.

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

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

A. I did.

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

A. I did.

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

A. I did not.

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

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

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

A. Yes, I did.

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

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

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

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

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

A. Yes. Thank you.

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

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

Q. This was in 2009?
A. This was in 2009.
Q. That's well before the filing dates of the '601 and '572 patents, correct?
A. That's my understanding.
Q. Now, at this point we pull up Claim 10 of the '601 patent, PTX 1, page 21.
Is it in front of you on your screen?
A. Could you just repeat that DTX number. I'm sorry.
Q. That is PTX 1.
A. PTX.
Q. It's also on the screen in front of you.
A. Okay. I'll look at the screen.
Q. Could we agree there's nothing in Claim 10 requiring a Phase III efficacy result?
A. Correct. I mean, this is a claim and doesn't relate anything to clinical trials.
Q. And, in fact, the word "efficacy" doesn't appear anywhere in this claim, correct?
A. Correct. Again, my understanding is there were subsequent claims that were dismissed that related to efficacy. But in this alone, there are no efficacy details.
Q. While we're here on this claim, it doesn't say "loading" anywhere in this claim, does it?
A. The word "loading" is not used. But, again, you

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

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

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

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

Do you see that highlighted text up there?

MS. OBERWETTER: Objection, Your Honor. Foundation.

THE COURT: Fair. What's the --

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

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

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

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

MR. McLAUGHLIN: This is an IPR. This is a decision from the Patent Trial and Appeal Board that I think would have been very informative to Dr. Csaky had he considered in formulating his opinions on whether efficacy was something that was read in these claims.

THE COURT: Let's start there and see whether he's ever been provided this, reviewed it, or researched it at all.

MR. McLAUGHLIN: Sure.

BY MR. McLAUGHLIN:

Q. First of all, let me ask you this: Do you recall relying on a declaration by Dr. Diana Do in the process of formulating your opinions?

A. There were portions -- as I recall, portions of her declarations that I relied on.

Q. And that declaration, you understand, came from these IPR proceedings?

A. I would have to review exactly those declarations that I reviewed in relationship to this document.

Q. Well, I'll represent to you that those did, in fact, come from these prior IPR proceedings.

Have you seen this document before, Dr. Csaky?

A. I said in -- if I reviewed it, I was reviewing it in the context of forming my opinion as it related to infringement, for example, and gathering information that would inform my opinion as it related to, in this case, infringement.

So I -- if I did review it, it was specifically for that purpose.

Q. Okay. And if I could go back to page 23 of that document. I'm going it read this language to you briefly here.

"Based on the foregoing and our review of the record as a whole, we find no persuasive support for considering the preamble recitation of a method for treating a patient with an angiogenic eye disorder as requiring such treating to achieve any particular level of effectiveness, much less a high level of efficacy."

Do you see that?

MS. OBERWETTER: Objection, Your Honor. I think Mr. McLaughlin has established there's no foundation for him to ask Dr. Csaky about this document with respect to these opinions even if the preference would be to put PTAB decisions in front of the Court.

THE COURT: Overruled.

MR. McLAUGHLIN: I'll also note this is also in his Tab B of things that he's considered in the context of formulating --

THE COURT: It's been overruled. Ask your question again.

BY MR. McLAUGHLIN:

Q. Did you factor this language into your opinions as you were developing your opinions in this case?

A. I may have -- you know, I can't recall exactly the specifics of this since I'm not that familiar with PTAB and those proceedings; so I couldn't put that into context of my world and what informed my opinion.

So these are the kinds of discussions and, again, that I may have seen, but I don't know how much role it played. I would have felt uncomfortable about allowing it to form my opinion if I wasn't sure what the context, who was it, what are the different requirements and things like that, as opposed to a -- something that someone that I'm familiar with, another POSA and what other folks commented on about their use of Eylea in their clinical settings.

So I can only comment at this point about I may have seen it, but again, because of my uncertainty about, again, all the details and the impact and where it was being -- so I may have seen it, but I don't think I would have used it to -- in a big way because of my uncertainty about the context.

Q. Let me ask you this, Dr. Csaky: Even with the Phase III data in hand from VIEW 1 and VIEW 2, we can agree that, when it comes to treatment of angiogenic eye disorders, there's still many patients with these disorders whose needs are still not met. Isn't that correct?

A. That's true.

Q. And in fact, you're the moderator of an HCP live peer exchange review titled "Unmet Needs for Patients with AMD."

Isn't that right?

A. That's very true.

Q. If we put up DTX 9204.

Do you recall participating in this discussion?

A. Yes. And it's pretty recent, December 2021. So yes.

Q. The title is "Unmet Needs for Patients with AMD"; is that right?

A. That's correct.

Q. If we go to page 1 of that document, is that you in the upper left?

A. It's a resemblance of me. I hope that isn't the best picture you have of me, but yes, it is.

THE COURT: You're an adverse expert, Doctor. They picked that one on purpose. Just kidding. Just kidding.

MR. McLAUGHLIN: Promise that's not the case, Your Honor.

THE COURT: I know.

BY MR. McLAUGHLIN:

Q. So I'd like to turn to this selection on page 1. There's a quote attributed to you where you asked one of your colleagues a question, "Jennifer, is the race over? Are we going to be able to crack the durability nut? Is that the only nut that we have left to crack?"

Do you recall asking that?

A. Yes. I asked it. I don't recall, but I asked it.

Q. Dr. Jennifer Lim, her response is that "I believe the durability question has been addressed to some point between the PDS" -- port delivery system -- "and faricimab."

Do you see that?

A. Yes.

Q. Lim does not mention -- Dr. Lim does not mention aflibercept, does she?

A. No.

Q. When this question was posed to another one of your colleagues, Dr. Holekamp, she mentioned visual acuity. And she says, "I must throw up my hands and say we don't control visual acuity. There's no agent we've tested so far reliably, at least in Phase III, that produces superior visual acuity outcomes."

Do you see that?

A. Yes.

Q. We can take that down.

I want to move on and try and get a little bit of clarity from you about where you stand on this question of the value of fixed regimens versus office visits.

Now, we can agree that there is nothing in the claims -- we just looked at Claim 10 of the '601 patent -- there's no language in the claims about excluding office visits, correct?

A. Correct.

Q. And now, even once clinicians had the VIEW 1-VIEW 2 data, you were still of the position that ultimately the issue for retina specialists will be which of those patients you were going to be able to inject and see back in three to four months versus patients who received an injection and may need to come back in every six to eight weeks. Until we can figure this out, we will have to continue to see our patients on a regularly frequent basis.

Was that a position you took in front of your peers?

A. Yes. I think it's always important to understand the context. And I'm assuming -- can you give me the date of that discussion?

Q. Sure.

Why don't we actually pull that up. That's DTX 9022.

And is that you that's third from the right there on the cover of this magazine?

A. Yes. Yes, that's me.

Q. If we go to page 10.

I'm sorry. Let's stay here for a second.

Top right, do you see the date, January-February 2012?

A. Correct.

Q. That refreshes your recollection about when this occurred?

A. Yeah. Exactly.

Q. If we go to page 10, the title of this selection in this magazine is "Ophthalmic Formulations: Safety and Efficacy of VEGF Neutralizing Drugs."

Do you see that?

A. Yes.

Q. So let's jump over to the page where you made that statement. This is on page 13, bottom left corner.

Can you see this?

A. Yes.

Q. And it's true that you made this -- you made these comments in the context of the VIEW trials; isn't that right? If you look at the top of this paragraph.

A. Yes.

Q. And yet, again, even with that data in hand, you still don't know which patients you're going to need to see in three to four months and which you're going to need to see in six to eight weeks; isn't that right?

A. That's correct.

So I think, again, it's important to understand the context in which we were -- so this is very soon after Eylea became available, right? And in many ways it's -- we're learning, obviously, as I think I've said multiple times, that prn and treat and extend were the directions that we were going. Right?

It doesn't mean that this is -- that I exclusively --

or anyone at that point exclusively used prn and treat and extend. This was in the context of trying to figure out how best to use Eylea. You know, we've learned a lot over the years.

For example, it's a very interesting aspect that when I -- even in this context I look back in 2012, and we thought -- I'll give you a good example. We thought that fluid -- I've showed you the prns. And we had to dry things completely. Turns out that wasn't always necessary. So a lot of this, you know, was a work in progress.

And it was clear that, while that was the direction that we were heading as a group, it was nice and of course to have this availability of fixed dosing if we needed it under certain circumstances.

So I don't think this necessarily indicates that I never used fixed dosing. I think it kind of reflects our enthusiasm at the time of trying to see where we were with prn, treat and extend. So it's kind of -- it's context- and time-dependent. But at the same time, under certain circumstances, as I've testified on numerous occasions and as we've seen Dr. Do's testimony that I relied on and other forms, that there was a role for a fixed every-other-month dosing in certain patient populations in certain conditions.

So while this is -- and we've said this over. This was the direction of the field. It didn't preclude the fact

that we had this in our back pocket, fixed dosing.

Q. And turning now to those -- the fixed-dosing regimens that you're talking about having in your back pocket back in that time frame, you, in fact, called these fixed-interval dosing regimens, including the eight-week regimen, burdensome; isn't that right?

A. Well, again, if you were going to think about this from a -- from every patient, it could have been construed at that time as burdensome. But at the same time, I would have hoped that I would have also said that prn dosing was burdensome. And so there were different approaches that we were trying to take.

And, again, I would have said that, for certain patients -- again, this was not a treatment regimen that I would have given to everybody, but it's something that I definitely would have said -- given to certain patients under certain circumstances. And, again, we're always trying to balance -- when we say burdensome -- all of the context for that patient and his or her family.

Q. Sure. And let's go ahead and take a look at what you've said about prn treatments and treat and extend in relation to fixed dosing.

A. Sure.

Q. Let's go to DTX 9013.

This is an article from just last year, is it not?

A. Correct.
Q. From 2022?
A. Correct.
Q. This is titled "YOSEMITE and RHINE Phase III Randomized Clinical Trials of Faricimab for Diabetic Macular Edema: Study Design and Rationale."
So in this -- and you're a coauthor on this publication, correct?
A. Yes, I am.
Q. Here in the bottom left of page 1, going from the left-hand column to the right-hand column, you say, "Personalized treatment regimens such as treat and extend and pro re nata are often used to reduce treatment burden associated with fixed interval, every-four-to-eight-week intravitreal injections."
Is that what you said in 2022?
A. That was in the article, correct.
Q. And the reasons that a POSA like yourself would use personalized regimens is because, unlike in a clinical trial where you try to have a defined patient population, in the real world, as you state here, these personalized approaches may also address heterogeneity in individual anti-VEGF responses; isn't that correct?
A. Yes.
Q. Let's turn to another document, DTX 9009, and page 7.

I want to direct you to page 7. I want to direct you to a quote from a Dr. Singh where he states near the bottom of this paragraph, that "In CATT, ranibizumab and bevacizumab had equivalent visual outcomes when injected on the same schedule. But that's not how we treat patients in the real world. We use treat and extend. We try to get them as dry as possible as fast as possible. We need to extend them as quickly as we can."

Do you see that?

A. Yes.

Q. Now, it doesn't sound like an endorsement for a rigid, extended fixed-dosing regimen, does it?

A. So again, I think with -- I think, as you've seen and as I think as I've presented to the Court, clearly this treat-and-extend prn dosing was a strategy that we were all pushing for, right? But the reality is that even in treat and extend, it can be burdensome because in some cases you can have patients that come in even more frequently than fixed every other month.

So while this is a nice general statement, the reality is that, as you pointed out, there's lots of heterogeneity. And in some cases this idea of having a fixed-schedule approach with a drug and a patient can obviate multiple visits and trying to find in certain patients that sweet spot.

The other issue, of course, is, you know, treat and extend is such an unusual concept for patients, right? As we try to explain to certain patients how this is going to work, there are -- again, as I mentioned in my initial deposition, there are circumstances where, again, just explaining something simple is -- it's a very easy way to communicate to a patient to make sure that that patient understands what's happening.

So yes, this is the world -- this is relatively, you know, recent after CATT and HARBOR. And so we are still in this world of struggling what's the best way to treat. And as I said, even some of this data is what I would call outdated. So when Dr. Singh said dry as possible, there's now newer publications that says a little bit of fluid, actually, you do okay.

So this is the constant evolution. And I think in many ways it allows us to think about, in some cases, looking back at these fixed-dosing schedules and seeing that there was some degree of certainty that you would have these great outcomes that we saw in VIEW 1 and VIEW 2.

Q. Would it surprise you to learn that this was published in 2021?

A. No, not at all.

Q. Further down after Dr. Singh made his comment, you were quoted as saying, "Where I practice in Texas, it can take some time to process the insurance paperwork. We start with

bevacizumab, but usually the patient is approved for a branded treatment in time for their second visit."

Do you see that?

A. Yes.

Q. Was that a true statement?

A. Yeah, there are some patients -- depending -- the majority of patients who are on anti-VEGF are on -- usually have CMS and copay. And then depending on the type of CMS and copay, you may or may not have to have prior authorization and other aspects that dictate what you can begin with and then what you can follow up with.

So yes, it's -- this is not an uncommon situation. It's also -- there's been many patients where I've started right off the bat with Eylea without having to have preauthorization.

Q. There are many patients that you've started off with bevacizumab; is that right?

A. For some patients, I start off with bevacizumab.

Q. And that's an off-label use of bevacizumab; is that right?

A. That's an off-label use of bevacizumab.

Q. So you're not discouraged from using bevacizumab in the absence of an FDA-approved intravitreal injection label; is that right?

A. Well, it's -- you know, it really depends on kind of

the time frame of bevacizumab. So I do think we have to be careful. It depends on the time period, right? So if we're talking when Phil Rosenfeld first presented his early data with using bevacizumab in 2005, that enthusiasm about bevacizumab is dramatically different than what happened in 2012, 2013, '14, and going forward.

So there was an evolution in bevacizumab. And having been involved in a lot of those discussions and at the CATT trial, there was a fair amount, as I think -- of concern about using an off-label drug. I mean, you use an off-label drug, guess who bears the liability burden? Thank you, attorneys.

And so there was a lot of concern, which is one of the reasons that Dan Martin -- and I actually helped Dan Martin with the CATT study because there were some people who either wouldn't use it because it wasn't absolute evidence that it worked. We actually in some cases had a separate consent form to make sure that patients fully understood that it was off-label back then.

So the evolution of bevacizumab is an interesting and -- evolution -- you really need to tell me if this is now in 2005 or '6 or is this in 2010, '11, or '12 when I made this comment.

Q. I think we just established this is 2021, Doctor.

A. Oh. So even more so that now in 2021 we've got CATT data, we have, obviously, millions of injections. And I think

we now have a much higher comfort level with bevacizumab.

Q. And you've been using bevacizumab for years; isn't that right?

A. Yes.

Q. Now, I'd like to direct your attention to page 10 of this article. Specifically, I'd like to direct your attention to this portion here that's highlighted on the screen where you say -- this is attributed to you, Dr. Csaky, right?

A. Yes.

Q. It says, "Aflibercept is an immunoadhesin, which is essentially a synthetic antibody but it's still the construct of an antibody."

Did you make that statement?

A. I did.

Q. Let's go on to page 12.

A. Can I just -- I really want to make sure I clarify that statement. Okay?

Q. No. That's okay. I'm moving on to the next question, Doctor.

THE COURT: Just respond to the questions posed, Doctor.

THE WITNESS: Okay. Thank you.

BY MR. McLAUGHLIN:

Q. Let's flip to page 12 of this document. There are a couple of quotes attributed to you on this page. And I'd like

to direct your attention to one towards the bottom where it says "Dr. Csaky" -- this is attributed to you, Dr. Csaky, where you say, "My hope is that we'll have agents with better durability a year from now to help relieve that treatment burden for our patients."

Do you see that?

A. Yes.

Q. Was that a true statement you made in 2021?

A. Yes.

Q. Now let's turn to the second page of this article, page 2. Now, that's you pictured here in the center top?

A. Yes.

Q. Now, in connection with publishing this article, you had to disclose your financial relationships and commercial interests; isn't that right?

A. Correct.

Q. If we turn to page 3, it states here you're a paid consultant for Regeneron Pharmaceuticals; is that right?

A. That's correct.

Q. And also Genentech?

A. Correct.

Q. And then below your name is Diana Do, MD; is that right?

A. Correct.

Q. And is that the same Diana Do whose IPR declaration

you relied upon in this matter?

A. Correct.

Q. You'll see that here Dr. Diana Do discloses her financial and commercial interests, right?

A. Correct.

Q. And there she lists Regeneron Pharmaceuticals; is that right?

A. Correct.

Q. I'm going to shift gears a little bit. Let's turn to PTX 311. This should be the Heier 2012 article that you've relied upon in formulating your opinions in this case.

So, first of all, let me take you to the back. I just want to establish some information. This is on page 12, where it indicates the -- who the authors are associated with, which entities the authors are associated with.

Do you see that?

A. Yes.

Q. And the superscript 10 indicates a Regeneron Pharmaceutical association; is that right?

A. Correct.

Q. And superscript 11 indicates a Bayer HealthCare association; is that correct?

A. Correct.

Q. So if we turn back to page 1 of this article, there are at least one, two, three, four, five authors that are

Regeneron employees or associated somehow with Regeneron that are authors on this article, correct?

A. Yes.

Q. And one of those is George Yancopoulos, the listed inventor of the '572 and '601 patents.

Do you see that?

A. Yes.

Q. Then there are four authors here with associations with Bayer; is that correct?

A. I'm assuming. I don't know those individuals, but their references seem like they work for Bayer.

Q. Because they're indicated with the superscript 11?

A. Yes.

Q. Now, you understand that in this VIEW trial both monthly ranibizumab and monthly aflibercept were evaluated head to head?

A. Correct.

Q. And aflibercept was never shown to be superior when dosed at the same frequency as ranibizumab; isn't that right?

A. Can you show me the -- I think -- can we look at the article VIEW 1. I think -- do we have that -- am I allowed to look at the entire article? Would that be okay?

THE COURT: Yes, Doctor.

BY MR. McLAUGHLIN:

Q. You don't recall, sitting here today?

A. Well, I haven't -- no, I have not memorized the VIEW 1-VIEW 2 results. So if I could look at the results, I could refresh my memory, if that's possible.

Q. Sure. Let's take a look at those.

So I believe what you're looking for is found in Table 2?

A. No. It would be the --

Q. Page 67.

A. -- the visual acuity results --

Q. Yep.

A. -- of the two trials, VIEW 1 and VIEW 2.

Q. Let's go to change in ETDRS. Do you see that?

A. Right. But the way we look at these is similar to what I show with the PIER where we show the change in visual acuity over time. I think that is part of these -- of this publication. If you look at the -- there are these line graphs. I'm sorry to make this complicated, but that's the way we analyze this data. If you can go to --

Q. Sure. Why don't we look at that. That's Figure 3.

A. Okay. Yeah, there we go. Okay.

Q. Why don't we take a look at Graph C, the integrated data for the VIEW 1 and VIEW 2 trials.

A. Well, I also want to look at VIEW 1 as well.

Q. So let's start by looking at Graph C. 2q4 is the aflibercept monthly dosing arm, correct?

A. Correct.

Q. And R q4 is the ranibizumab monthly dosing arm, correct?

A. That's correct.

Q. And the integrated data across both those studies shows that aflibercept was only -- the patients on average gained 9.3 letters of visual acuity.

Do you see that?

A. Yes. 2.2 milligrams q4, 9.3, correct, yes.

Q. And the ranibizumab arm patients showed on average gains in visual acuity of 8.7 letters.

Do you see that?

A. That's correct.

Q. Now, this data presented here was never considered adequate enough to come to the conclusion that monthly aflibercept was superior to monthly ranibizumab; isn't that correct?

A. The integrated data was, but there was some, you know, suspicion, if you look at the VIEW 1 data in particular, that -- if you look in that -- remember, there were two trials, VIEW 1 and VIEW 2. And if you can highlight the VIEW 1 results --

Q. I'm not asking about the VIEW 1 results. We looked at the integrated data. My question was about the integrated data.

A. Okay.

Q. And based on that integrated data, aflibercept has never been determined to be superior or show statistical superiority when dosed monthly compared to ranibizumab monthly; isn't that correct?

A. If you limit your analysis to the integrated data, that's correct.

Q. I'm going to switch focus a little bit here and let's -- I want to ask you some questions about some of the related patents in this family that you've reviewed in the process of formulating your opinions in this case.

So you've considered the prosecution histories of the '601 and the '572 patents; is that right?

I can show you the covers of those. We didn't bring them today because they're huge.

We can provide digital copies to the Court.

If we show you DTX 28, the cover page.

A. So these are -- I'm sorry. Refresh -- these are the -- what documents? These are the --

Q. These are the prosecution histories --

A. Okay.

Q. -- that, according to your Tab B, you've reviewed in connection with formulating your opinions in this case.

Do you recall reviewing that?

A. Yeah. To some degree as needed for my -- in forming

my opinion, correct.

Q. What's shown here is the file history from the '601 patent. Do you see that?

A. Yes.

Q. Did you also review DTX 29? Do you recall doing that?

A. Yes. Again, as much as I was not aware of all of the details, I did a cursory review of these to begin to understand how this might help form my opinions.

Q. And did you -- and you also reviewed DTX 33, didn't you, the prosecution history for the '338 patent from this family?

A. Inasmuch as I could understand and how it might help in forming my opinion as a POSA as it related to these claims, I did that review, correct.

Q. Okay.

I'd like to call up PTX 3 at this point, the '572 patent. Now, what's shown here is a list of related U.S. applications. Do you see that?

A. Yes.

Q. And do you see there are a number of patents listed there --

A. Correct.

Q. -- that are related to the '572 patent?

A. Correct.

Q. Those include the '338? That's at the bottom.
A. Correct.
Q. This is going kind of in reverse chronological order. Then next is '069. Do you see that?
A. Yes.
Q. Then '681?
A. Yes.
Q. '345?
A. Yes.
Q. And then the patent we're talking about here today, the '601.
A. Yes.
Q. The '205 patent?
A. Yes.
Q. Then, of course, the '572 patent, which all of this appears on the face of, correct?
A. Correct.
Q. Now, if we look at the earliest patents in this chain, U.S. Patent Number 9,254,338, are you aware that Mylan challenged and then the Patent Trial Appeal Board invalidated claims from that patent?
A. No, I was not aware.
Q. Are you aware that the '338 patent is directed to the same eight-week dosing regimen that's claimed in the '601 patent?

MS. OBERWETTER: Objection to the foundation with this witness.

THE COURT: Let's rewind a little bit, Counsel.

BY MR. McLAUGHLIN:

Q. I'll represent to you, Doctor, that the eight-week dosing regimen was claimed in the '338 patent.

And then are you also aware that Mylan challenged and then the Patent Trial and Appeal Board invalidated claims of the '069 patent?

A. So, again, you know, just so we're clear, if I stated or -- in my report these documents, I just want to make sure I'm clear to the Court that I'm not a patent attorney. So when I'm looking through these, I'm looking for help in forming my opinion as an ophthalmologist, as a POSA, right, not as a patent attorney litigating various aspects of patents and various procedural steps.

So I feel I'm entering into an uncomfortable area where that's not my role as an expert. I don't have expertise in assigning what the import is of various decisions and how this relates to the various claim constructions and things that are kind of patentese, we want to call it, rather than ophthalmology stuff.

THE COURT: Understood.

Repeat your question, Counsel.

BY MR. McLAUGHLIN:

Q. Actually, why don't we do this.

Can we pull up DTX 4135 and put it next to DTX 9007.

You see on the left-hand document it says, "Determining all challenged claims unpatentable"?

Do you see that?

A. Correct.

Q. Under "Judgment"?

A. Correct.

Q. And this is with respect to the 338 patent?

A. Yes.

Q. And then on the right-hand side, same final judgment, determining all challenged claims unpatentable? And that's with respect to the '069 patent?

A. Correct. That's what's stated here.

Q. So is it safe to assume, then, that you've not factored these decisions into your analysis in this case?

A. I was asked kind of to -- specifically to look at the '572 and '601 patents in particular as an expert witness. And so I did not go back into the patent history of the various issues that are within the Court's purview. And so no, I did not do an extensive legal analysis of these types of documents, the implications, what the rulings mean. That's not what I did.

I was looking through these and seeing if there was anything that might help. And, again, recognizing the

limitations of my knowledge base, my review was very cursory. So this is really not -- my area of expertise is not, surprisingly, patent law.

Q. Let's go to DTX 9015.

This relates to the '205 patent, which is directed to monthly dosing of aflibercept. Do you see at the top here it says, "I hereby disclaim the following complete claims in the above-identified patent, 1, 2, and 3"?

A. I see that written.

Q. Were you aware that Regeneron, rather than contest Mylan's IPR petition, chose to disclaim all claims of the '205 patent?

A. Again, I was -- I'm not aware -- and these are, again, documents that I may have used very cursorily in my report. But I'm not aware or I'm not really perhaps experienced enough to make any comment about what the implications, what's happening here, who are the parties, what this means in terms of disclosures. This is really not something that I would feel is in the area of my expertise.

Q. Let's move on to DTX 6444. This is Docket Number 433 from this case, titled "Regeneron's Stipulation Regarding Summary Judgment and Claim Narrowing."

So looking at the second bullet, the stipulation states, "Regeneron accepts summary judgment of invalidity of Claims 5 and 6 and 9 of U.S. Patent Number 10,888,601."

Do you see that?

A. I see that.

Q. And those were claims that you've previously opined are all valid; isn't that right?

A. I opined at the time -- when I reviewed these documents at the time, my working constructs were -- I was instructed on which claims were being contested, and I made my opening report based off that. And so I was told, I think, at some point that there was some changes in the visual acuity outcomes, as I was told. And that's the extent to which I then went back and said -- looked at my opinions and looked at, again, the -- kind of the sections and my perspectives kind of -- you know, in the absence of these claims.

Q. Turning to DTX 405, this is another patent disclaimer filed by Regeneron in connection with the '601 patent.

Did you know that, prior to this litigation, Regeneron had disclaimed Claims 3, 4, 13, 14, 22, 29, and 30 of the '601 patent?

A. Again, I'm not -- I can't comment on any of these. I wasn't involved in the litigation. I wasn't involved in the discussions. This is not something that I'm privy to or can offer or render an opinion or any statement in this regard.

Q. So you did not incorporate these developments into your opinions in this case, correct?

A. No. I was simply told to -- here were the specific

claims that were now under considerations, and went back into my reports and looked at how I had constructed my arguments as it related specifically to the claims that we've been discussing during this trial.

Why and how it came to be that those were, I was not privy to any of those discussions and to the reasons for those decisions.

Q. So now that we've gone through some of the things where invalidity is decided or not contested, let's focus on a few elements that you think are contested.

So let's start with your Slide 30, PDX 8, and talk about the '572 patent, Claim 6.

A. Sure.

Q. The only thing you've pointed to as a disputed element is the isotonic solution element; is that correct?

A. For the anticipation analysis, that's correct.

Q. And you did not offer any opinions here on isotonic; is that correct?

A. I deferred all of my opinions to Dr. Trout.

Q. All right. Let's turn to the September 14th, 2009, DME press release. This is DTX 3198. You can go to page 2.

Your only complaint with respect to this reference is that it expressly says three loading doses rather than five loading doses; is that right?

A. That's correct. The major -- when I reviewed this

press release as it related to the five loading doses, I did not see a five-loading-dose regimen outlined here.

Q. But you admit that there is a 2-milligram as-needed regimen after three monthly loading doses, correct?

A. Correct.

Q. There's also a 2-milligram monthly arm, correct?

A. There is a 2-milligram monthly arm, correct.

Q. So Regeneron went with a 2-milligram every-single-month arm despite these systemic side effects that you were talking about earlier today, correct?

A. So I think, again, it's critical to put this in context, right? Well, for one thing, this is a --

Q. That was a yes-or-no question, Doctor.

You opined earlier today that there were systemic side effects that would have discouraged somebody from going from three loading doses to five; isn't that right?

A. That's correct.

Q. What Regeneron did was design an arm of their Phase II trial that was straight monthly dosing; isn't that correct?

A. That is correct.

Q. It's also true, when you were discussing the Lalwani reference, what she did or what she described was the doubling of doses, correct, in the treatment of DME?

A. Yes. If I recall, it was a doubling from .5 to 1.

It may have been .3 to .5. I can't recall the details of the result. It was an increase in the dose, for sure.

Q. That's despite these supposed concerns about systemic side effects; is that correct? That she made that proposal?

A. Well, I don't know -- I mean, these considerations at the time -- first of all, we were focusing on ranibizumab. And so we had some data from ranibizumab, but the -- as I recall, she would -- she did not recommend continued dosing with multiple high doses of ranibizumab. I don't think that was part of the strategies.

And the issues of safety still existed. I mean, we're still in the -- in this period of time when we're trying to navigate what exactly is happening as it relates to patients and their potential for stroke and heart attacks when getting intravitreal anti-VEGF injections.

Q. And in view of those concerns, in Lalwani they still recommended the doubling of ranibizumab doses, correct?

A. Yes.

Q. Now, I want to talk to you about the -- this hypothetical -- a hypothetical prn protocol. So I'm going to take you to PDX 1.124. This may be a slide that you've seen before. And I want to talk about the prn dosing for DME as it relates to the press release, DTX 3198, okay, as if you were one of the clinical inventor investigators in that study.

Do you understand?

A. Correct.

Q. So I want you to assume for purposes of my next set of questions that we're going to be using the row here that says 2q prn. Do you see that?

A. 2q prn, correct.

Q. So you don't dispute that in the press release were described three monthly loading doses, correct?

A. Correct.

Q. So that's a dose at Week 0, one at Week 4, one at Week 8; is that correct?

A. That's correct.

Q. Then at Week 12, according to the DA VINCI protocol, the clinical trial subject would come into the office for evaluation at Week 12; isn't that right?

A. That's correct.

Q. And you performed an assessment on that subject, right?

A. Correct. Along with OCT and vision and a full examination, correct, to assess activity or no activity of the macula in terms of dryness or not.

Q. And then upon performing that assessment, if the patient meets the re-treatment criteria, you would provide an injection at that visit, correct?

A. Correct. If it met the -- typically on these prn trials, there are strict criteria that dictate when you could

not re-treat, right? So there are -- whether it was a little bit of fluid, maybe not; if there was more fluid, maybe yes. So there's these criteria that investigators would use during these prn visits that will then inform us as to whether or not we should or should not inject.

Q. Right. So this patient came in, they met the re-treatment criteria, they got an injection at Week 12. Okay?

A. Correct.

Q. The subject comes back to your office at Week 16. You perform the assessment. And once again, the subject meets the re-treatment criteria. You inject at that visit, correct?

A. If they met the injection criteria, then you would inject.

Q. Okay. It's now Week 20. And as before, the subject returns to your office for an evaluation, but here now the retina looks dry. The patient doesn't meet any of the re-treatment criteria. You withhold an injection; is that correct?

A. You would not inject at that visit, correct.

Q. And that brings us to Week 24, where once again the subject comes in for their monthly visit. If they meet the re-treatment criteria, you administer an injection; is that correct?

A. That's correct.

Q. And that's one scenario that any competent

ophthalmologist could work out under the 2q prn regimen; isn't that correct?

A. If you mean the regimen that a competent ophthalmologist would have said is three loading doses plus prn, you can't look into the future and say if a patient will or will not need an injection. That's why it's a conditional injection, right?

So an ophthalmologist would have said, question mark, does that person need an injection? Question mark, does that person need an injection? So that would have been the protocol that an ophthalmologist would have designed under a prn dosing regimen.

Q. And what we see here is one scenario in which that would have happened. And what we're looking at are five monthly injections, correct?

A. We see -- again, we see injections being given on a conditional basis, right? So I think --

Q. That wasn't the question, Doctor. I'd like for you to answer my question.

What we're seeing here are five monthly injections, correct?

A. These are injections, if the patient meets prn criteria, that they would receive injections on a monthly basis.

Q. Now, Dr. Csaky, before the patent's issued here, you

had used Avastin to treat AMD; isn't that right?

A. That's correct.

Q. And you recognized back then even that some patients may need more injections for DME; isn't that right?

A. That's correct.

Q. So let's turn to DTX 9014.

This is a January 2010 article from *EyeNet* titled "Avastin: New Hopes and Hesitations." Now, if we go to page 4, there's a quote that's attributable to you, Dr. Csaky, where you say, "Avastin is becoming standard of care for AMD."

Do you see that?

A. Correct.

Q. And you go on to say, "Sometimes you have to give more injections for DME."

Do you see that?

A. So I just want to make sure we qualify, "standard of care for AMD if you use the definition of what the community is doing."

Q. Was this a true statement that you made in front of your peers at this meeting in January of 2010?

A. Yes.

Q. So you managed to figure out how to give more injections even without any FDA-approved label for Avastin for ophthalmic use; isn't that right?

A. Again, in this scenario it's -- in this construct

during this period of time, as I was talking about, where we were actively interrogating patients, right, using OCT, determining how many injections, what the degree of fluid was, with the caveat again that with DME we had a little bit more wiggle room. So yes, we could, depending on that individual patient, change and manage their strategy on this kind of personalized approach.

Q. And then you go on to comment about the use of Avastin further. This is from page 1, where you say, "We don't know how to use Avastin. We don't know when to stop it. We don't know if the dose is correct."

Do you see that?

A. Correct. And --

Q. The article goes on to say, "Who will respond? Do you give seven injections and then stop? It's all seat of the pants, and it's made more implicated because we don't have guidelines."

You said that, correct?

A. Remind me of the date of this.

Q. January of 2010.

A. Right. So again --

Q. You said those words, correct, Doctor?

A. I did say those words.

Q. All right. I'm going to shift gears a little bit here.

Do you recall providing opinions pertaining to the written description of the claims of the '601 and '572 patents?

A. I did.

Q. And in connection with providing your opinions on written description support regarding the five monthly injection DME-DR claims, you relied on Example 5; is that right?

A. Can I pull up the patent to remind myself what Example 5 is?

Q. Sure. Actually, why don't we bring up your -- call up a snippet from your report, DTX 2027, page 224, paragraph 406.

Here you state, "Example 5 clearly identifies the treatment of DME using a similar dosing regimen," correct?

A. Can I just have one second to find the patent? Would that be all right?

Q. Sure.

THE COURT: What exhibit tab is the patent available at, Counsel?

MR. McLAUGHLIN: Should be PTX 1.

BY MR. McLAUGHLIN:

Q. Do you have that, Doctor?

A. Yes, I have it. Thank you so much.

Q. Example 5 shows up on page 17 of PTX 1.

A. I'm sorry. Example 5, we're on page 17, correct?

Q. We're on page 17 of the PTX number, Column 14.
A. Correct. Yes. I see that now.
Q. Towards the top, Example 5.
A. Yes.
Q. You understand this to be a recitation of the DA VINCI Phase II clinical trial?
A. That's correct.
Q. Is it still your opinion that Example 5 clearly identifies the treatment of DME using a similar dosing regimen to those that are claimed?
A. This is an example that -- in the specifications as one of several areas in the specification that outlines the treatment of DME.
Q. Do you recall using Example 7 of the '572 patent to illustrate that the specification provides various examples of a finite number of secondary doses?
A. I'm sure I did if you're going to bring it up for me.
Q. Okay.
Why don't we pull up DTX 2027, page 211, paragraph 378. You state here, "The patent specification provides various examples of regimens with a finite number of secondary doses."
Do you see that?
A. Correct.
Q. You state that "Example 7 discloses dosing regimens

having two, three, four, five, six, and seven secondary doses."

Do you see that?

A. Correct.

Q. I want you to keep that statement in mind, and I want to turn to PTX 722, which I believe you've seen before. This is the October 1st, 2007, *Retinal Physician* article. Do you recognize this document?

A. Yes.

Q. And if we go to page 1 and we look at this comment from Dr. Hariprasad where he describes one of the ways that he treats AMD, he states that "I treat with ranibizumab monthly until optical coherence tomography (OCT) shows the macula to be completely free of fluid. Some patients reach that point after two injections. Others require as many as eight injections."

Do you see that?

A. Correct.

Q. So he talks about starting off loading doses with as few as two, as many as eight; isn't that right?

A. Well, he's defining these injections in order to achieve using OCT a macula which is free of fluid.

Q. Right. And, actually, I'm going to come back to that.

Let's use the parlance of the '601 and '572 patents and its use of the term "secondary doses." Okay?

A. Sure.

Q. So using that definition, what he's talking about is anywhere from one to seven secondary doses; isn't that correct?

A. In the context of evaluating patients, he's defining -- again, the minute you start using conditions like -- he even says, "I use OCT to demonstrate the macula to be completely free of fluid." Then in -- my perception of this is he is not necessarily in this sense using a fixed-dosing approach; he's using a prn approach or a regimen that requires that he create a dry macula.

Q. And in that context he identified one to seven secondary doses, correct? Yes or no.

A. Yes.

Q. And that same article articulated the concept of eight-week dosing intervals, correct, as explained by Dr. Brown?

A. No.

Q. That's not an eight-week dosing interval that we're looking at right there?

A. No.

Q. "I give three monthly injections and see them in eight weeks."

Do you see that?

A. Correct.

Q. So that's an eight-week interval that he's seeing the patients; isn't that correct?

A. He's seeing them; he's not necessarily treating them.

Q. In the act of seeing them, he's going to evaluate them. And if they need an injection at that eight-week mark, the patients are going to get that injection, correct?

A. Well, it depends.

Q. It depends on what?

A. So, for example, if I see --

Q. It depends on the OCT readings, correct?

A. OCT and vision. And so in doing my -- like I said, this conditional evaluation, what happens is -- for example, let's say there was fluid. Could very well be that at that step I start to rethink my diagnosis. I start to think about doing additional testing.

So this approach of seeing them first -- and it's critical that he says I see them -- or that I treat them and see them, but I see them, is exactly what's meant by this personalized approach. You're seeing these patients. And then based off what you see, you can make a treatment decision. There is situations -- I'm just asking -- I mean --

Q. Are you making a statement, or are you answering my question, Doctor?

THE COURT: We need to get back to a question-and-answer setup here.

THE WITNESS: Sure.

BY MR. McLAUGHLIN:

Q. We're going to be here for a very long time.
A. I'm sorry. So say that again.
Q. Let me take you to the very next sentence in his statement. He says, "If fluid is absent at that visit, I give another injection."
Do you see that?
A. Yes.
Q. Thank you.
THE COURT: Counsel, why don't we take a break at this point.
MR. McLAUGHLIN: Sure.
THE COURT: We'll take ten minutes.
Doctor, you are still off limits for conversation.
But we'll take ten minutes and resume at that point. Thank you all very much.
(A recess was taken from 2:35 p.m. to 2:51 p.m.)
THE COURT: Counsel, you may continue.
MR. McLAUGHLIN: Thank you, Your Honor.
BY MR. McLAUGHLIN:
Q. Let's go to DTX 3089.
Doctor, this is a Chun reference from 2006 reporting on ranibizumab in DME. I'd like to take you to page 3.
Can you confirm that -- and I want to go to the visual acuity and central retinal thickness measurements

section of this on page 3.

Can you confirm that this reference reports the low-dose group gained a mean of 12 letters?

A. Yes.

Q. Let's move on to DTX 4069.

This is the Nguyen 2009 reference looking at ranibizumab again in the treatment of DME. If we look at the abstract, this involved 126 participants, correct?

A. Yes.

Q. And under the results it's reported that the patients in Group 1 achieved 7.24 letters in visual acuity gain, correct?

A. Yes.

Q. Let's go to DTX 3096.

This is a DRCRN 2010 article. This is a report of the design and outcome of a clinical trial using ranibizumab in the treatment of DME.

If we go down to the results, you see that patients gained on average nine letters in visual acuity?

A. Yes. The ranibizumab and deferred laser group gained nine letters.

Q. And it further reports that no systemic events attributable to study treatment were apparent.

Do you see that?

A. Yes.

Q. Let's get on to DTX 4215.

It's the Arevalo reference from 2007.

In this reference under "Participants," it reports there are 110 eyes that were assessed.

Do you see that?

A. Yes.

Q. Then this study reports in the "Results" section that 55.1 percent improved by greater than or equal to two ETDRS lines of BCVA.

Do you see that?

A. Yes.

Q. That's the same as a ten-letter gain?

A. Yes.

Q. Now, I want to ask you a little bit about PrONTO. I know that's been a topic of discussion today.

Let's pull up DTX 3215.

This is the Engelbert 2010 reference. And let's go to page 2, where the Engelbert authors were commenting on the PrONTO study on the left-hand column.

And they note -- towards the bottom of that paragraph that begins "the PrONTO study," they note about midway there, "As a result of the PrONTO study, PrONTO-style dosing has become popular in the retina community."

Do you see that?

A. Yes.

Q. So now I'd like to turn to paragraph 352 of your responsive expert report. This is DTX 2027 at pages 201 and 202.

Do you recall providing a chart along with your opinions that described the ranibizumab clinical trial dosing regimens?

A. Yes.

Q. So it's the case, though, that the prn PrONTO-style protocol that had become popular and has shown visual acuity gains was omitted from your chart on this page; isn't that correct?

MS. OBERWETTER: Objection. Outside the scope of direct.

THE COURT: How is this related to the direct, Counsel?

MR. McLAUGHLIN: This goes -- all he did today was talk about prn and PrONTO, and this goes right to the heart of that matter.

THE COURT: Overruled.

THE WITNESS: So this graph is --

BY MR. McLAUGHLIN:

Q. I'm not asking you what it is; what I'm asking you is you left PrONTO off this graph, correct?

A. I did not make this graph.

Q. And you didn't endeavor to correct the graph to add

PrONTO?

A. I did not add PrONTO to this graph.

Q. All right. Now I want to turn to talking about the q12 regimen that you've talked about today. And you've provided an opinion in your opinion that Genentech repeatedly tried and failed to demonstrate that Lucentis could be used effectively on extended dosing regimens, right?

A. I indicated there were several trials on quarterly following three monthly doses that did not get to the same visual acuity as monthly dosing.

Q. But you are aware that the FDA approved Lucentis for 12-week dosing, are you not?

A. Yes.

Q. And that's in the Lucentis label, correct?

A. That's correct.

Q. Since 2006?

A. That's correct.

Q. It's not your testimony that the FDA would approve a drug dosing regimen that it deemed a failure, right?

A. That's correct.

Q. Let's go to the Mitchell reference. That's DTX 4061.

And I'd like to draw your attention to page 6. What's shown here, as indicated in the Figure 3 legend, is a subpopulation study of the PIER trial patients. I'd like to direct your attention to the top line with the triangles.

Now, according to this substudy, 40 percent of initial responders in the PIER study were able to maintain the gains from the loading-dose phase; isn't that correct?

A. That's correct.

Q. So for these 40 percent of patients that were able to maintain their vision while receiving far fewer injections in their eyes, this was certainly not a failure, correct?

A. Unless you were -- happened to be in the other groups that lost vision, then you're --

Q. I'm asking you about the 40 percent of the patients that were in this arm that showed the ability to maintain vision while receiving far fewer injections. They would not have considered that a failure, would they?

A. If you happened to be fortunate enough to be in that group in this one study, then this would not have been a failure.

Q. And you agree that the PIER 12-week regimen was a fixed-interval dosing regimen, correct?

A. Correct.

Q. Now let's go back to Dixon. That's DTX 0204.

I'm going to ask you a little bit more about Dixon. Let's see what the prior art was saying about the CLEAR 2 trial, the Phase II trial aflibercept.

So let's get to page 5 of Dixon.

While we're waiting for Dixon to come up, I'll ask

you this: You understand that there were several treatment arms in the CLEAR-IT 2 trial, right?

A. Correct.

Q. And one of those arms involved the administration of four monthly injections followed by prn dosing?

A. That's correct.

Q. Do you recall that?

A. Yes.

Q. Now, if we go to page 5 of Dixon in the right-hand column, there's a paragraph that begins "data from the Phase II study."

A. Correct.

Q. This states, "Data from the Phase II study of VEGF Trap-Eye were positive," correct? It says that?

You see that, Doctor?

A. Yes, I see it says "were positive." Correct?

Q. And it also goes on to say, "Results from the noninferiority Phase III trials will establish its efficacy versus ranibizumab."

Do you see that?

A. Yes.

Q. Let's look and see what else Dixon disclosed about the CLEAR-IT 2 regimen and results.

Do you recall providing testimony today about the CLEAR-IT 2 study design?

A. Yes.

Q. But in that discussion you didn't touch on the CLEAR-IT 2 results, did you?

A. No.

Q. All right. Let's go to page 4 of Dixon and Section 2.6.2. And the Phase II section there on the left.

So you would agree --

Actually, let's go to the next paragraph, the one just below this, where it says, "Patients initially treated with 2 milligrams of aflibercept, or VEGF Trap-Eye, monthly achieved mean improvements of 9.0 letters."

Do you see that?

A. Yes.

Q. And 29 percent of those same patients achieved greater than or equal to 15 ETDRS letters at 52 weeks.

Do you see that?

A. Yes.

Q. It also reports that the median time to first reinjection in all groups was 110 days.

Do you see that?

A. Yes.

Q. That means that after the loading dose phase, the median time to patients receiving their first -- the next first injection was 110 days, right?

A. In all the groups, correct.

Q. That's almost four months, correct?
A. Almost four months, correct.
Q. And Dixon cites to Reference 45 of the Dixon reference, correct, for this clinical trial data?
A. Correct. That's the 45 reference.
Q. Okay.
Why don't we pull up DTX 3173.
And this is entitled "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results."
Do you see that?
A. Yes.
Q. And it's indicated this was presented on September 28th, 2008?
A. Yes.
Q. Let's turn to page 6. This section that's highlighted here, that's the arm that received four monthly injections of aflibercept, correct?
A. Yes.
Q. Followed by prn treatment?
A. Yes.
Q. Let's see what happened to those patients. Let's go to page 12. If we highlight the Row 2 2 mg q4, what this reports is that these patients needed on average only 1.6 injections over the course of that prn dosing period from Week 12 to Week 52, right?

A. Yes.

Q. And the range is indicated as 0 to 4, meaning that one or more patients required no injections between Week 12 and Week 52, correct?

A. Yes.

Q. Let's go to slide -- or page 13 of this document.

And again, the 2 mg q4 arm, the second row, indicates that the median number of days to first reinjection was 150 in this arm.

Do you see that?

A. Yes.

Q. That's about five months, is it not?

A. Yes.

Q. Let's jump to page 19 of this document. You understand that the fewer than 15 letters lost is a common primary end point in these types of clinical trials?

A. Yes.

Q. And in this clinical trial, the 2q4 arm showed that 100 percent of the patients in that arm hit that end point, correct?

A. Yes.

Q. Let's go to page 26. "Safety: Serious Adverse Events" is the title of this slide. It says, "Systemic serious adverse events: None deemed to be drug-related."

Do you see that?

A. Yes.

Q. Let's jump to the conclusions slide, page 28.

"VEGF Trap-Eye achieved clinically meaningful and durable vision improvement over one year."

Do you see that?

A. Yes.

Q. Up to nine mean letters gained in Week 52?

A. Yes.

Q. And up to 160 microns reduction in central retinal lesion thickness, correct?

A. Yes.

Q. I want to shift gears a bit here and pull up a DTX 917. This is a November 22nd, 2010, email from -- looks like somebody called newsdesk@broadcast.shareholder.com to George Yancopoulos.

Do you see that?

A. Yes.

Q. And it states, "Today announced" -- I'm sorry. Regeneron and Bayer "today announced that in two parallel Phase III studies in patients with neovascular form of age-related macular degeneration (wet AMD) all regimens of VEGF Trap-Eye (aflibercept ophthalmic solution), including VEGF Trap-Eye dosed every two months, successfully met the primary end point compared to the current standard of care, ranibizumab, every month."

Do you see that?

A. Yes.

Q. And then going down further where it says "About VEGF Trap-Eye."

Do you see that section on page 2?

A. You have to highlight it for me, please.

Q. It states there on November 22nd, 2010, that "VEGF Trap-Eye is specially purified and contains iso-osmotic buffer concentrations allowing for injection into the eye."

Do you see that?

A. Yes.

Q. This is what is disclosed here?

A. Yes. It says that it's an iso-osmotic buffer concentration.

Q. Let's jump to DTX 918, page 1.

This is an email from the same date, November 22nd, 2010, that reports that more than 33 million -- there were more than 33 million views of that morning's announcement.

Do you see that?

A. Yes.

Q. So if the person of ordinary skill in the art needed to have these Phase III results to ensure the need was solved, those results were publicly known before the earliest filing date for the '572 and '601 patents, correct?

A. This would have been shared with those individuals

who were seeing this report, correct.

Q. All right. Dr. Csaky, you've reviewed Regeneron's '758 patent in offering your opinions in this matter, correct?

A. Correct.

Q. If we could pull up DTX 4213.

Would you agree that the cover page of this document states this patent term extension petition is with respect to 7,374,758 U.S. patent number at the top there?

A. Yes.

Q. And if we go to page 2 of this document, do you agree, looking at Bullet 1, that Regeneron identified Eylea as the relevant approved product covered by the '758 patent?

A. Yes.

Q. Then turning to page 4, Bullet 9.

Let's go down a little bit further where we see the claims.

Regeneron stated to the patent office that at least the following claims of the '758 patent claim a method of using the approved products, Claims 1 and 2.

Do you see that?

A. Yes.

Q. When you were looking at questions of nexus in this case, did you consider that fact?

A. Again, I'm not sure I included a comprehensive understanding and perspective of nexus as it relates to claims.

I looked at this simply from the viewpoint of a POSA as whether or not this was informing us about the claims.

Q. Okay. Let's go to another document, DTX 3501. We'll go to page 1, the cover here.

This indicates that this relates to U.S. Patent Number 7,070,959. Do you see that?

A. Yes.

Q. This is another patent term extension petition. Do you understand that the '959 patent expired last Friday?

A. No, I did not.

Q. And when you were looking at questions of nexus, did you consider this document?

A. Again, I don't think I went into a complete detail of nexus as I was making my opinions on the -- from the POSA's perspectives on patents that were under consideration.

Q. Let's go to another document, DTX 4956.

This is a Regeneron 10-K form filed with the SEC in March 2005.

Do you see that?

A. Yes.

Q. Are you aware that in March 2005 Regeneron filed a Form 10-K with the SEC publicly disclosing that Regeneron was starting clinical trials of aflibercept through intravitreal injection in mid-2005?

A. No.

Q. If we could turn to another document, PTX 1027.

So you mentioned your publication coauthored with Dr. Diana Do in your direct exam. Do you remember that?

A. Yes.

Q. You talked about these systemic safety risks associated with aflibercept?

A. Correct.

Q. So if we turn to page 9 of this document, can you confirm that when you wrote this paper you -- both you and Dr. Do reported that this study had been supported by research funding from Genentech?

A. Did we report that?

Q. You did report that, did you not?

A. Yes, I did report that.

Q. So you were receiving -- so at the time that you were talking about potential risks of using aflibercept, you were a paid consultant with Genentech, correct?

A. Yes, but --

Q. All right. Next --

THE COURT: Yes is good enough for now, Doctor. Thank you.

BY MR. McLAUGHLIN:

Q. Let's take a look at DTX 2027.

This morning at around 9:47 a.m. you talked about justification of striking references from Dr. Albini's slide

for loading doses.

A. Yes.

Q. That a POSA won't apply any results from CRVO or AMD to DME. Do you remember that?

A. Yes.

Q. Why don't we take a look at DTX 2027, your responsive expert report in this case, page 213.

And in the middle of paragraph 382 here's what you say:

"The POSA would have understood that the specification defined angiogenic eye disorders as any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage according to the common characteristic of their etiology and thus their ability to be treated by anti-VEGF therapy."

Do you see that?

A. Yes.

Q. So your report you said that when you're looking at angiogenic eye disorders, which includes AMD and DME and DR, you said that a POSA would have understood that they had a common etiology; namely, they're able to be treated by anti-VEGF therapy. Correct?

A. Yes, but --

THE COURT: Yes is good enough for now, Doctor.

BY MR. McLAUGHLIN:

Q. Let's turn to PTX 1145.

This is the Schmidt-Erfurth publication that you were talking about earlier today. At the time that she wrote this publication, are you aware that she was running the VIEW 2 clinical trial for Regeneron?

A. She was involved, as far as I recall, in the -- part of the -- I think, one of the VIEW trials.

Q. And you talked about there being no reasonable expectation of success that a POSA could use these regimens to maximize vision gains.

Do you recall saying that?

A. And "these regimens" would be?

Q. The claimed regimens that are at issue in this case.

A. Yes.

Q. Let's use the '601 patent Claim 11 as an example.

Does the '601 patent Claim 11 -- actually, I'll withdraw that.

Actually, I want to bring you to DTX 5431.

I believe this is another publication that you were presenting information about earlier today, the Shahraki publication?

A. Yes.

Q. Let's go to page 11 of that document.

A. Yes.

Q. Let's see what the authors say here.

So starting with the "Shenasi and colleagues" comment, they say, "Shenasi and colleagues evaluated the effect of subconjunctival bevacizumab immediately after the excision of primary pterygium. They concluded that the combination therapy is well tolerated, but it cannot significantly reduce the recurrence of pterygium."

Do you see that?

A. Yes.

Q. Now let's go to the first page of that Shenasi reference that they refer to there, DTX 9030.

MR. McLAUGHLIN: And we have copies.

MS. MAZZOCHI: May I approach?

THE COURT: You may.

BY MR. McLAUGHLIN:

Q. Let us know when you have that in front of you, Doctor.

A. I do have that in front of me.

Q. Let's go to the first page, the "Methods" section.

A. Uh-huh.

Q. Here it says that bevacizumab was being injected into the eye, correct?

A. Into the -- under the "Methods" section in the first page?

Q. Correct, about halfway through this paragraph.

"Subconjunctival bevacizumab, 1.25 milligrams,

injected immediately after surgical excision."

Do you see that?

A. Correct. That was not into the eye.

Q. So that was a direct injection into the eye?

A. It's not into the eye.

Q. I'm sorry. I didn't hear that?

A. That's not into the eye.

Q. What is that?

A. That's into the conjunctiva.

Q. And the conjunctiva, that's the surrounding tissues --

A. Correct.

Q. -- around the eye?

A. Correct. You don't enter into the eye.

Q. It's not intravitreal?

A. At this point it's not intravitreal. That's correct.

Q. And the conclusion was still that this administration of bevacizumab cannot significantly prevent the recurrence of pterygium, correct?

A. Correct. This study did not show that.

Q. Now, let's turn to the other one that you relied upon, the Kasetsuwan paper.

I believe this is DTX 9031. And if we blow up the methods section and the purpose.

Let's go about halfway down where it begins

"Topical" -- I'm sorry. Also under purpose.

"This study was designed to assess the efficacy and tolerability of topical bevacizumab."

Do you see that?

A. Yes.

Q. And if we go down into the methods section, it states, "Topical bevacizumab and placebo were applied in the respective groups four times daily for three months."

Do you see that?

A. Yes.

Q. That is not a method as claimed in the claims of the '601 or '572 patents, correct?

A. As far as -- it is not intravitreal.

Q. And it's not on the same schedule, correct?

A. It's not on the same schedule.

Q. Let's look at the next reference that the Shahraki publication referred to.

This is DTX 5431. This is at paragraph 11 -- I'm sorry -- page 11.

This is the Shahraki reference, and it mentions on page 11 a Hwang and Choi article.

Do you see that?

A. Sure. Yes.

Q. What they report here about that study is that they compared the recurrence rates of pterygium removal surgery

associated with topical MMC, cyclosporine, and bevacizumab. And what they reported is that they observed no difference between the control group and the group that received topical bevacizumab.

Do you see that?

A. Yes.

Q. And then the last reference that the Shahraki publication mentions -- this goes over onto the next page. And it has a citation of 148.

Do you see that?

A. Yes.

Q. What they report there is that "In a recent study, two different concentrations of topical bevacizumab were used following pterygium removal of 90 patients, and the recurrence rates were compared between the groups. Pterygia recurred in 13.3 percent in the 5 mg/mL group, while no recurrence was observed in the 10 mg/mL group. Thus, the authors concluded that the 10 mg/mL concentration of topical bevacizumab is more effective than the 5 mg/mL dose in preventing pterygium recurrence."

Do you see that?

A. Yes.

Q. So, again, that is not an intravitreal injection of bevacizumab, is it?

A. At this stage it is not an intravitreal injection.

Q. Let's go to page 20 of DTX 5431. And there's a reference to -- a reference number 148 which cites to an author Motarjemizadeh.

THE COURT: Would you mind spelling that for the record, counsel?

MR. McLAUGHLIN: Absolutely. That's M-O-T-A-R-J-E-M-I-Z-A-D-E-H.

THE COURT: Thank you.

MR. McLAUGHLIN: We're going to mark that paper as DTX 9032. Let's pull that up on the screen.

BY MR. McLAUGHLIN:

Q. If we take a look at this one, at the abstract, what we see again is that bevacizumab was given topically, correct?

A. Correct.

Q. And not only that, but it was given topically four times a day for one week, right?

A. Yes.

Q. And the low dose didn't work; only the high-dose group did?

A. Yes. The 10 mg/mL concentration was more efficacious.

Q. We can agree that Claim 6 does not permit dosing regimens of topical administration four times a day for a week, right?

A. That's correct.

Q. Now, you also mentioned that you believed aflibercept would work for PVR. Do you recall that?

A. Yes.

Q. Let's take a look at what we will mark now as DTX 9033, "Efficacy of Intravitreal Injection of Bevacizumab in Vitrectomy for Patients with Proliferative Vitreal Retinopathy, Retinal Detachment: A Metaanalysis of Prospective Studies."

Do you see that on the screen?

A. Yes.

Q. And if we go to the conclusion on the first page, can you confirm that the conclusion there reads, "Based on the available evidence, intravitreal injection of bevacizumab in vitrectomy for patients with PVR-related retinal detachment did not decrease retinal redetachment rate or improve visual acuity," correct?

A. That's what it states.

Q. This was published in 2018; is that right?

A. That's correct.

Q. Let's take a look at a couple more. Let's start with DTX 9034. This is a Tousi reference, "Intravitreal Injection of Bevacizumab in Primary vitrectomy to Decrease the Rate of Retinal Redetachment: A Randomized Pilot Study."

And if we can go to the abstract.

So, again, this was an intravitreal injection of bevacizumab, correct?

A. It is intravitreal bevacizumab.

Q. And if we look at the conclusion there, it says, "Our preliminary results show neither benefit nor any harm from intervention in both anatomic and visual outcomes."

Do you see that?

A. Yes.

Q. Let's take a look at DTX 9035. This is a Falavarjani reference.

And I can spell that again. That's F-A-L-A-V-A-R-J-A-N-I.

This relates to the "Intrasilicone Oil Injection of Bevacizumab at the End of Retinal Reattachment Surgery for Severe Proliferative Vitreal Retinopathy."

Here again, if we take a look at the abstract, bevacizumab was injected, correct?

A. Yes.

Q. It was injected into the silicone -- I'm sorry -- injected into the silicone oil at the end of retinal reattachment surgery for rhegmatogenous retinal detachment.

Do you see that?

A. Correct.

Q. All right. If we go to the conclusion, it states here that "intrasilicone injection of bevacizumab at the end of vitrectomy for RRD with severe PVR does not eliminate the risk of postoperative PVR."

Do you see that?

A. Yes.

MR. McLAUGHLIN: I have no further questions. Pass the witness.

THE COURT: Redirect?

REDIRECT EXAMINATION

BY MS. OBERWETTER:

Q. All right. Good afternoon, Dr. Csaky.

A. Good afternoon.

Q. I have a few additional questions based on some of the questions that Mr. McLaughlin had for you.

First of all, if I can direct you back towards the beginning of the cross-examination, you had some questions about what was marked as DTX 9024, which was a roundtable discussion that I believe you participated in.

Do you still have DTX 9024 in front of you?

A. Just please project it. If I have to look for it, it's going to be a problem.

Q. I'm not sure we actually have it loaded onto our system as it was not a produced document.

THE COURT: Do you know in which binder or stack that might be? I'll join the doctor's position on finding something.

MS. OBERWETTER: I do not know, unfortunately, which binder it was in.

THE COURT: What's the exhibit number again?

MS. OBERWETTER: It's DTX 9024. And I'm sorry we're doing this old school.

THE WITNESS: DTX --

MS. OBERWETTER: I believe it was Volume 2.

THE COURT: Yeah, Volume 2, Madam Clerk indicates. Thank you.

The smaller of the two binders, Doctor.

Bear with us at the front of the room, please. Thank you.

BY MS. OBERWETTER:

Q. And if it's helpful, it has the picture that Dr. Csaky was not enamored of. And it's called "Unmet Needs for Patients with AMD."

THE COURT: It's in cross exhibits, Volume 2, 9024.

THE WITNESS: 9024. Yes, that's my mug. Okay.

BY MS. OBERWETTER:

Q. Do you have it, Dr. Csaky?

A. Yes, I do have it.

Q. Mr. McLaughlin directed your attention to the bottom of page 2 and the top of page 3 of that document and had some questions about one of your comments about durability.

Do you recall that?

A. Yes.

Q. And do you recall that one of the potential responses

to that offered by the panelists was the port delivery system?

A. Yes.

Q. What's a port delivery system and what has happened to that?

A. Yeah. So the port delivery system is -- was a new technology that was developed by Genentech. It's essentially a -- basically a piece of plastic that goes into the eye, and it allows the injections to go through this little port rather than going through the skin of the eye.

We surgically place it. And the idea is that this little device can contain ranibizumab for longer periods of time and therefore increase the durability as it slowly releases ranibizumab.

Q. Is that device currently in regular and active use by a large number of doctors?

A. No. It's been recalled by the FDA because of problems with manufacturing. And the device actually has issues with consistency and was a probable safety concern.

Q. And the other reference in that paragraph I believe was to a drug called faricimab. How long after Eylea was approved did faricimab come out?

A. Faricimab was just approved as of February of last year.

Q. I'm going to change topics a little bit. And I'd like to direct your attention to some questions that

Mr. McLaughlin had for you about whether aflibercept is an antibody.

Do you remember those questions?

A. Yes.

Q. Can you explain what is an immunoadhesin and whether aflibercept is a, quote, antibody?

A. Yes. So I happen to -- I actually worked on immunoadhesins. I actually made these. And so the idea is that they are a purely synthetic recombinant protein. Yes, they have a synthetic portion of the antibody, but they're not generated in any form or fashion like an antibody.

You make these in a purely genetic way. And so the construct has a portion that is -- has some sequences that are similar in the Fc portion; but unlike being made like an antibody is being made, you make these purely with recombinant DNA technology. And then of course the other portion is purely recombinant. So it's completely different than a naturally occurring or even any type of modified antibody.

So that's a very important distinction that I actually happen to have personal experience with.

Q. Thank you.

I'd like to change topics a little bit and take a look at the Heier 2012 reference, which was PTX 311, please.

And this one we should have -- we should be able to put up on the screen. And if we could take a look at that page

marked 8 that had the tables that Mr. McLaughlin asked you about. You recognize this as the Heier reference, Dr. Csaky?

A. Yes.

Q. And we'll advance forward to page 8.

Mr. McLaughlin had some questions for you about the integrated table and what that showed. Could you please comment on what the VIEW 1 table that you wanted to comment on shows?

A. Yeah. I think one of the interesting aspects -- and it's one of the things that Regeneron was actually looking at. If you look at the VIEW 1 results, what you actually see at the top line is the 2-milligram aflibercept given every month. And what you see is that says 10.9 letters of gain, and in the exact same trial, that's the top line there. And, interestingly, if you look at the ranibizumab same regimen every four weeks, it actually is almost three letters worse.

So there was some interesting initial data from VIEW 1 that there could be the possibility that aflibercept was, in fact, better than ranibizumab.

Q. Okay. Was the primary benefit the extended interval?

A. Yes. So the ultimate -- because of the ultimate outcome and the fact that it was not inferior, the actual, as it went to the label, was this idea of extended fixed dosing.

Q. Okay.

We can take that document down.

I want to go back to the September 2009 press release that Mr. McLaughlin asked you about.

If we can pull up DTX 3198 again. And, again, if we look at the second page of this document and pull out the DME paragraph there toward the top.

Mr. McLaughlin had some questions for you about the 2-milligram monthly arm. Do you remember that?

A. Yes.

Q. Can you please comment on whether the use of the 2-milligram monthly arm in the Phase II trial would have affected the reasonable expectation of success as to safety?

A. Again, in these kinds of trials, there's several limitations, right? One is the fact that there was a restriction. In this study in particular, some of the inclusion criteria included restricting patients who potentially were at risk for developing strokes and heart attacks. So, again, there was a reduction in the type of profile that we're having.

And the other thing that's really important to remember is in these trials there's data safety monitoring boards. And these review the data very, very carefully. And if there's any even hint of a safety concern, that arm gets stopped.

So in the context of a trial, as we're trying to decipher signals -- small signals, big signals -- the decision

to include this in a trial carries with it lots of restrictions and boundaries that really relates to ensuring the safety of this type of 2-milligram monthly dosing.

Q. Thank you.

We can take that document down.

I'd like to talk about another document that Mr. McLaughlin showed you. And, again, I think this one you may need to fish out of your pile. It's DTX 9014. And it's that article printed in color that says "Avastin: New Hopes and Hesitations."

THE COURT: 9014?

MS. OBERWETTER: Yes, Your Honor.

THE COURT: I have 9015. There it is.

MS. OBERWETTER: It sounds close.

THE COURT: It does sound close.

Yeah, same binder, Doctor, second smaller binder.

THE WITNESS: Thank you.

DTX -- say that again.

BY MS. OBERWETTER:

Q. It's 9014, and it's that article printed in color.

A. Yes, yes, yes. I got it. Thank you.

Q. So I'm going to direct you to the bottom of the first page of the article. And it's one of the paragraphs that Mr. McLaughlin directed you to that contained one of your quotes. It's the one that includes the phrase "it's all seat

of the pants."

Can you please explain what you were -- what that paragraph of this article is about.

You have me on the first page. You're looking down toward the bottom right of the first page.

A. I got it. Here we go.

So, again, this is now -- we've had some beginning experiences with Avastin. We don't have any clinical trial guidelines yet. This was in 2010. So we don't have any guidelines about the whole idea behind Avastin. And so I think the point of Avastin, even more so than with ranibizumab, we had very little guidelines as to, A, how effective it was, what type of approaches we should be using in patients.

So I think it's fair that, with Avastin in particular, we were really trying to kind of work out and figure out what were treatment regimens and approaches that we could use with Avastin since we really had only had it for five years, and we were beginning to get kind of some -- we didn't really have lots of guidelines.

So we were all a little bit -- not just me, but I think all of us were a little bit undirected. And we were trying to figure out exactly what was the full potential for Avastin.

Q. And how much experience was there with aflibercept at this point in time in clinical practice?

A. None.

Q. I'd like to talk about a different document. And this one, I think we can put up on the screen. It's PTX 722. And this is the October 2007 reference that Mr. McLaughlin showed to you.

There's a quote that he showed to you on the first -- I believe it was on the first page that we looked at earlier.

If we can highlight or pull out those -- yes. Thank you. That is exactly the paragraph I was looking for.

And just to clarify for the record, is this a reference to a prn dosing strategy?

A. Yes.

Q. And how can you tell that?

A. So very simply. I mean, you look at these qualifiers, when the macula is completely free of fluid, when the macula is dry. So, again, these are all indicators that this OCT machine was being used and that in this case the physician was using those tools -- it even says that -- to make treatment determinations.

Q. Okay.

We can take that document down.

Mr. McLaughlin had a series of questions for you using the word "nexus."

Do you recall that generally?

A. Yes.

Q. Were you able to tell from his questions exactly what nexus he was asking you about?

A. No.

Q. I'm going to change topics a little bit. And I'd like to talk about some of the references that arose toward the end of the examination. And, in particular, Mr. McLaughlin asked you a series of questions about pterygium.

Do you recall those?

A. Yes.

Q. You recall those additional references?

A. Yes.

Q. Did the additional references that were provided to you by Mr. McLaughlin affect the point that you were making about angiogenic eye disorders?

A. No.

Q. And why not?

A. No, because the point of these diseases is -- and of course they are much more complete and comprehensive review articles and ongoing trial results.

And the point of this was to indicate that these are angiogenic eye disorders and they could be treated with an anti-VEGF agent. Whether we're using topical or, down the road, some form of intravitreal is still to be determined, but the point is that these references -- there are, of course, many more. My colleagues -- in particular, my cornea

colleagues -- are very excited about using anti-VEGF agents in the treatment of pterygia.

Q. And Mr. McLaughlin also asked you some questions about PVR.

A. Yes.

Q. And my question is the same. Do the additional references affect your point about angiogenic eye disorders in light of what you know about how aflibercept is being used?

A. No. I mean, I found an article -- an article, clinical trial, that showed that intravitreal bevacizumab was effective, right? And, again, if you look at the work of Andrius Kazlauskas and his work with the clinicians at the University of Chicago, Illinois, there was an ongoing trial -- actually, the beta trial -- that was in bevacizumab for PVR.

So there's been a lot of interest in interrogating with some success in the biology in particular of VEGF and anti-VEGFs in PVR. It's really good science. And so there's a lot more that we could add to this -- to the repository of articles that support my opinion.

Q. I'd like to take a look at -- I'm going to change topics a little bit. I'd like to take a look at PTX 1027, which is that article that you coauthored with Dr. Diana Do.

If we could pull that back up.

Mr. McLaughlin had some questions about a passage toward the end of the article where he pointed to who

participated in funding some of the work for the article.

Can you please provide the context and explanation for how this article came to be.

A. Yes. I mean, this is something that Diana and I talked about doing. It's not uncommon for us to reach out for kind of writing support. You know, we write the manuscript and then we need somebody to help kind of wordsmith it. And so the key thing that every journal wants to see -- and I think this is the key point. Both authors were involved in the design and conduct of the study, collection of data management analysis and interpretation of data and preparation, review, and approval of the manuscript. That was left up completely to Diana and I to write this in the way that we thought represented the state of the knowledge when we wrote this article.

Q. And what was going on in the art at the time that made you interested in writing this article?

A. Yes. It's exactly this point, that there was already some data, if we'd looked at ongoing trials, SAILOR, for example showed a slight difference in stroke rates between .5 and .3. There was this concern -- Bob Avery had started to look at systemic levels following an intravitreal injection.

And then we had this molecule, aflibercept, that again had these higher affinities and potentially higher duration in the systemic circulation. So we wanted to really

call attention to our colleagues. And, again, it's not something that we typically think about in our day-to-day lives. And suddenly here we were faced with giving new medicines into old people, into diabetics who potentially were sick. And we really wanted to make sure that we raised the specter for everybody to be aware of this potential issue.

MS. OBERWETTER: Nothing further, Your Honor.

THE COURT: Recross?

MR. McLAUGHLIN: Just one question, Your Honor.

THE COURT: I'm going to hold you to that.

MR. McLAUGHLIN: Understood.

RECROSS-EXAMINATION

BY MR. McLAUGHLIN:

Q. Dr. Csaky, you just made reference to some various articles, references, clinical studies. However, today, despite having multiple opportunities to do so, you've not been able to identify anything from the published medical literature that showed intravitreal aflibercept dosed on the Claim 6 schedule that actually worked to treat formed corneal neovascularization, proliferative vitreal retinopathy, pannus, or pterygium in humans, correct?

A. That's correct.

MR. McLAUGHLIN: Thank you.

Thank you, Your Honor.

Thank you, Dr. Csaky.

THE COURT: Redirect?

MS. OBERWETTER: No, Your Honor. Only exhibits if we should do that at this point.

THE COURT: Yeah. Let's go ahead and do that. If I could ask you, Ms. Oberwetter -- you can remain seated if you'd like. Just get closer to a mic so we can hear you clearly. And slowly, of course, the newest local rule we have.

Doctor, if you'll bear with us for one moment.

MS. OBERWETTER: Yes. We have DTX 212, which I believe we previously used on day two. And we probably misspoke and called it PTX 212, but it's DTX 212.

DTX 3105, DTX 3112, DTX 3186, PTX 821, PTX 841, PTX 1027, PTX 1143, PTX 1145, PTX 1146, PTX 1155, PTX 1447, PTX 1794, PTX 3225, and DTX 9014.

THE COURT: Seeing no objections from your own table, Counsel.

Any objections to any of those from the adverse party?

MR. McLAUGHLIN: No objection, Your Honor.

THE COURT: Without objection, each of those identified by Ms. Oberwetter will be hereby admitted.

(DTX 3105, DTX 3112, DTX 3186, PTX 821, PTX 841, PTX 1027, PTX 1143, PTX 1145, PTX 1146, PTX 1155, PTX 1447, PTX 1794, PTX 3225, and DTX 9014 were admitted.)

THE COURT: Exhibits from Mylan.

MR. McLAUGHLIN: Yes, Your Honor. I tried to deduplicate as counsel was reading them off. I apologize if I repeat any.

DTX 9, DTX 10, DTX 12, DTX 28, DTX 29, DTX 33, DTX 405, DTX 917, DTX 918, DTX 2027, DTX 2733, DTX 3082, DTX 3089, DTX 3096, DTX 3051, DTX 4069, DTX 4135, DTX 4213, DTX 4215, DTX 4956, DTX 9007, DTX 9008, DTX 9009, DTX 9013.

DTX 9014, that might have already been read in.

DTX 9015, DTX 9022, DTX 9024, DTX 9030, DTX 9031, DTX 9032, DTX 9033, DTX 9034, DTX 9035, PTX 1027.

And then -- actually, I'm having to actually withdraw one of these, DTX 2027.

THE COURT: Off the list.

MR. McLAUGHLIN: Off the list. Thank you.

THE COURT: Thank you, Mr. McLaughlin. Does that comport with the rest of your table's list?

It seems so. Outstanding.

Any objections from the adverse party?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, the list -- with 2027 being withdrawn?

MR. McLAUGHLIN: 2027.

THE COURT: 2027 being withdrawn. Otherwise, Mr. McLaughlin's list, without objection, is hereby deemed admitted.

(DTX 9, DTX 10, DTX 12, DTX 28, DTX 29, DTX 33, DTX 405, DTX 917, DTX 918, DTX 2027, DTX 2733, DTX 3082, DTX 3089, DTX 3096, DTX 3051, DTX 4069, DTX 4135, DTX 4213, DTX 4215, DTX 4956, DTX 9007, DTX 9008, DTX 9009, DTX 9013, DTX 9015, DTX 9022, DTX 9024, DTX 9030, DTX 9031, DTX 9032, DTX 9033, DTX 9034, DTX 9035, and PTX 1027 were admitted.)

THE COURT: Doctor, thank you, sir. You may step down. Thank you very much. Whatever's there, leave. We'll tidy up.

Why don't we take a ten-minute break. We'll let everyone reshuffle in here. I'd ask folks to use that time wisely and efficiently to distribute binders and the rest. I'm assuming we're going to do Dr. Trout next; is that correct?

MR. BERL: Correct, Your Honor.

THE COURT: All right. Let's take ten while we rearrange the courtroom. If I could ask counsel to grab whatever's left here from Dr. Csaky and pass out the rest, and then we'll get started with Dr. Trout. Thank you all.

(A recess was taken from 3:50 p.m. to 4:05 p.m.)

THE COURT: Yes?

MS. MAZZOCHI: A quick housekeeping matter, Your Honor. I know that you said that, as we got closer to the end of the trial days, people would either be happy with or angry with the keeper of the time. The way in which we've been

calculating things, just based on Your Honor's average trial day, et cetera, by our estimates, defendants have about three hours left; plaintiffs have about 90 minutes left.

If we were to subtract out some of the time that plaintiffs have indicated they want to use for deposition designations, we can lower that a bit more.

Since there was an agreement for an even split between the parties in terms of time and we've been -- we've tried to be very judicious to make sure we have enough time for a full and effective cross-examination at the end, we just want to make sure that we're going to be able to get our full time to do the complete cross-examination of Dr. Csaky.

THE COURT: Trout?

MS. MAZZOCHI: I'm sorry. Trout. Apologies.

THE COURT: Yeah, I would assume we'll start and stop Dr. Trout, resume tomorrow with him. And then I know we've yet to talk about -- how long are the videos?

MR. BERL: Your Honor, I actually have some good news in that regard. We've decided, in view of how the evidence came in, we are not going to play any of those videos. So Dr. Trout is the last witness. I think we have some differences from the calculations. Honestly, I don't really think it matters. We're going to finish tomorrow.

THE COURT: Indeed we are.

MR. BERL: They'll have the time that they need.

THE COURT: We don't have any choice.

Yeah. Okay. Noted. Understood.

MS. MAZZOCHI: Thank you.

THE COURT: Let me ask this before we get started. Any issues if we resume tomorrow at 8:30 a.m. to get a running start on the day?

MR. BERL: No issues at all.

THE COURT: All right. And for those lucky associates in charge of ordering lunch and the rest, I will know in the morning if we're taking another early lunch tomorrow based on the weather forecast and my 11-year-old daughter's softball schedule tomorrow. So I'll let everybody know as soon as I can tomorrow what our outlook looks like. But let's get started at 8:30 tomorrow and hit the ground running.

With all that, Regeneron may call its next witness.

MR. BERL: Your Honor, Regeneron calls Bernhardt Trout.

THE COURT: Doctor, if you wouldn't mind repeating from last week, I believe.

THE WITNESS: Yes, Your Honor.

BERNHARDT TROUT, PHD, PLAINTIFF'S WITNESS, SWORN

THE COURT: Thank you, sir. Once you're comfortable, if you wouldn't mind adjusting that mic.

With that, you may proceed.

DIRECT EXAMINATION

BY MR. BERL:

Q. Good afternoon, Dr. Trout.

A. Good afternoon, Mr. Berl.

Q. We're here to talk about validity today. Did you evaluate validity from the perspective of the person of ordinary skill?

A. Yes, I did.

Q. Okay.

Can we put up Demonstrative 2 on the screen.

Can you read into the record your definition of the person of ordinary skill.

A. Yes.

"The POSA would have held an advanced degree such as a master's in a biopharmaceutical science or related discipline such as chemical engineering and several years of experience in the development of biologics product. Alternatively, the POSA could have a PhD in such discipline and less experience."

Q. Did you meet the definition of a person of ordinary skill in 2006?

A. Yes, I did.

Q. How so?

A. Well, I actually had a PhD then, and I had been doing relevant research since 1998, at least. So I met that definition.

Q. Do you understand Mylan's definition of the POSA to differ substantially from yours?

A. No, not much.

Q. Would any of your opinions be different if Mylan's definition were used instead of yours?

A. No.

Q. And did you apply the Court's claim constructions in your validity analysis?

A. Yes, I did.

Q. I'd like to ask about some background issues before we get into the prior art itself.

What is aflibercept?

A. Well, aflibercept, as we've heard for the past couple weeks, is what's known as a fusion protein. So it's made up of three different pieces of three different proteins. And we could call it a Frankenstein molecule because it's a nonnatural molecule.

Q. Let's look at PTX 1826, the Aruffo article. Did you review this article in connection with your work in the case?

A. Yes, I did.

Q. And if we look at page 1 and blow up one excerpt, beginning with "fusion proteins" and "these proteins consist," can you explain what Aruffo is telling us.

A. Yes. And I guess just to be clear, it continues, "These proteins consist of the constant regions of

immunoglobulin, typically mouse or human, fused to an unrelated protein or protein fragment."

So basically what I said, they're nonnatural proteins that are made by fusing various parts of other proteins.

Q. And what are the parts of the aflibercept fusion protein?

A. So one of the parts is what's called the constant domain of an antibody, so a piece of an antibody. And then there are two other parts from two different receptor proteins.

Q. You heard Dr. Rabinow testify last week about a fusion protein and an antibody being largely the same thing.

Do you agree?

A. No, I don't agree.

Q. How are fusion proteins different from antibodies?

A. Well, as I've been emphasizing, fusion protein is made of different pieces of other proteins. It's not natural. Antibodies have evolved over time or are part of nature.

Q. Were fusion proteins known as of 2006?

A. Yes.

Q. Were any commercially available?

A. Yes.

Q. Let's look at one of the slides shown by Dr. Rabinow. It was his Slide 47.

Let's put that on the screen.

Do you remember this chart you put up of stable

protein formulations?

A. Yes, I do.

Q. Did Dr. Rabinow identify any fusion protein drug products on this slide?

A. No. And as a matter of fact, each of those is highlighted because they're all antibody, noting that ranibizumab is an antibody fragment, a piece of an antibody.

Q. And the next one in the chart, that's bevacizumab, is that also called Avastin?

A. Yes. That's correct.

Q. And is that a fusion protein or an antibody?

A. No. That's an antibody.

Q. Now, do fusion proteins and antibodies have the same properties?

A. No.

Q. Okay.

Let's bring up the Fast reference. That's PTX 1835.

Did you review this article in connection with your work on the case?

A. Yes, I did.

Q. And if we go to page 15. And we'll also show an excerpt from page 19 below it, beginning in the paragraph that starts "intact antibodies."

Can you explain the relevance of the Fast disclosure?

A. Yes. And I've highlighted, I think, the relevant

pieces of that section.

"In comparison with native IgG proteins" -- like the ones on the previous slide -- "wherein interdomain interactions presumably here evolved to provide mutual stabilization, fusion proteins may lack such stabilizing interdomain stabilization."

And then a little skip there, but goes on to say, "This has been seen in other artificial fusion proteins as well."

And this referenced the Souillac, which is a bit more of a technical article.

Q. What is this conveying with respect to the relative expected stability of antibodies on the one hand compared to fusion proteins on the other?

A. Well, this is conveying that the skilled person or the person of ordinary skill in the art would expect that fusion proteins could be less stable than antibodies.

Q. And the Souillac reference that's cited for this proposition, in what year was that published?

A. That was published, as highlighted here, in 2005.

Q. And the proposition about the expected relative stability of fusion proteins compared to antibodies, would that have been consistent or inconsistent with the POSA's thinking as of 2006?

A. That would have been consistent. This is illustrative of what the POSA would expect.

Q. Now, I'd like to turn to obviousness and invalidity over the prior art now, Doctor.

Do you understand that Dr. Rabinow testified that the asserted claims of the '865 patent are invalid on three bases: Fraser plus Lucentis; Fraser plus Liu; and, thirdly, Dix?

A. Yes.

Q. Do you agree with Dr. Rabinow's opinions?

A. No, I do not.

Q. Let's take them one at a time. And let's start with Lucentis plus Fraser.

Let's take a look at 2.13.47.

Now, you heard Dr. Rabinow -- or did you hear Dr. Rabinow testify first about Claim 1 and then about the asserted claims?

A. Yes, I did.

Q. Is that how you conducted your anticipation and obviousness analyses?

A. No, that is not. I started with the asserted claims -- for example, Claim 4 here -- noting that Claim 4 depends on Claim 2. Claim 2 depends on Claim 1. And I looked at all of that together.

Q. Now, in order to reference Dr. Rabinow's testimony and demonstratives, I'm going to go back to his demonstratives even though they address Claim 1 and the dependent claims separately.

Is that okay?

A. Okay.

Q. Before we get into the various limitations of the claims and the details of these references, do you think a POSA looking to make a formulation to treat eye diseases would have selected Fraser and the Lucentis references from all of the available prior art?

A. No.

Q. Why not?

A. Well, there was quite a bit of prior art. And there's no particular reason why the POSA would be pointed to those two references.

Q. Do you think the POSA would have any reason to choose to combine Fraser and the Lucentis references of Gaudreault and Shams?

A. No. There's no reason.

Q. Is that how formulation research is done, to take a formulation form from one molecule and combine it with another and put them together?

A. No, it is not.

Q. Is there any reason that Dr. Rabinow provided that you heard to choose these references from amongst all of the prior art?

A. No.

Q. Now, Doctor, I understand your opinions, but unless I

specifically say otherwise, I'd like you to assume for the rest of your testimony about this combination that the POSA would have combined Fraser with Lucentis as Dr. Rabinow urges.

Can you make that assumption?

A. Okay.

Q. Now, let's go back to Claim 1 for a moment.

What does Claim 1 recite with respect to the claimed VEGF antagonist?

A. Well, it's what's highlighted here. It's a VEGF antagonist. But it's not just any; it's a specific one. It's got to be glycosylated. And it comprises a specific sequence of amino acids that is specifically defined and described in the patent.

Q. Let's go to Dr. Rabinow's Demonstrative 51.

And what did Dr. Rabinow rely on to meet those limitations in his Fraser plus Lucentis combination?

A. Well, Dr. Rabinow relied on this disclosure in Fraser which says VEGF Trap R1R2.

Q. And does Fraser disclose the limitations that we're discussing relating to the VEGF antagonist in Claim 1?

A. No, it doesn't. It doesn't disclose this sequence.

Q. Do you recall that Dr. Rabinow relied on Holash as somehow being incorporated into Fraser?

A. Yes.

Q. And if we look at the next -- does Fraser incorporate

Holash?

A. No. Holash is just one of the many references in Fraser.

Q. Now, I understand your opinion there, but I'd like to look at Holash nevertheless. That's DTX 3549. And we've shown part of page 2 of the Holash reference.

Does that disclose the amino acid sequence recited in Claim 1 of the '865 patent?

A. No, sir, it does not. It just discloses this schematic here which does not disclose or relate the sequence.

Q. Are these disclosures from -- are these the disclosures from Fraser and Holash that Dr. Rabinow relied on to meet these claim limitations about the amino acid sequence of aflibercept?

A. Yes.

Q. And to be clear, do either disclose the claimed amino acid sequence?

A. No, neither do.

Q. And did you highlight in red boxes for the disclosures that don't meet the claim limitations in Dr. Rabinow's demonstrative?

A. Yes, I did, right here on the screen.

Q. Now, do you recall Dr. Rabinow discussing the Papadopoulos reference, DTX 3619?

A. Yes, I do.

Q. Do you understand Papadopoulos to be part of either of Dr. Rabinow's obviousness combinations?

A. It is not.

Q. Do any of the references in Dr. Rabinow's obviousness combinations cite or discuss Papadopoulos?

A. No.

Q. Now, Doctor, did you prepare a demonstrative exhibit summarizing the fusion proteins disclosed by Papadopoulos?

A. Yes, I did.

Q. And were those sequences voluminous in Papadopoulos?

A. Yes.

And the summary, Your Honor, is here in this table, all the different -- I just have the names here. You can imagine each of those sequences is about a page or longer. But the Papadopoulos discloses all of those.

MR. BERL: And for the record, this is marked as DTX 3619A.

BY MR. BERL:

Q. Doctor, can you explain what is shown here.

A. Yes.

So this is a list that I've prepared. On the right side are different names as disclosed in Papadopoulos. On the left side are the figures that are in Papadopoulos. Those figures actually contain the sequences listed out.

Q. Doctor, there are a lot of letters on this table.

I'd like to discuss a couple of them with you. What is Flt1, or Flt1?

A. Yes.

So that, Your Honor, might be new in terms of the abbreviation, but all it means is the same as this VEGR1. Biologists may have a certain sense of humor in naming different proteins, but that's just the VEGF R1.

Q. So that's VEGF Receptor 1?

A. Yes. Correct.

Q. And there's also something in here that's referenced as Flk1. What's Flk1?

A. Well, again, Flk1 is just another name for the VEGF Receptor R2. So the Flt and the Flk together are the R1R2.

Q. And we saw earlier that there was a description in the references that Dr. Rabinow testified about to VEGF R1R2.

Do you remember that?

A. Yes.

Q. And how many fusion proteins does Papadopoulos describe that fall within that categorization?

A. Well, it describes these two. I've just highlighted in the table, the small reproduction of the table, the two that I just mentioned. And here on the upper right side is where they are in the text. And, again, it tells you that R1R2 are just the Flt1 and the Flk1.

Q. And are you showing on the right-hand side part of

page 60 of DTX 3619, the Papadopoulos reference on about lines 4 to 5?

A. Yes. That's correct.

Q. Do these two fusion proteins that are denoted R1R2 have the same sequence or different sequences?

A. They have different sequences.

Q. How do you know?

A. Well, I did a comparison. I talked about a different comparison last week that I did. But I did a comparison here using the same National Institute of Health software. And I showed that the sequences, as we say, do not align. In other words, they're different.

Q. How would the POSA interpret the references to VEGF Trap R1R2 in the literature such as Fraser?

A. Well, the POSA would interpret them as meaning a multiplicity of different sequences.

Q. Now, the claims also require that the VEGF antagonist is glycosylated; is that right?

A. Yes. Correct.

Q. Very briefly, Dr. Trout, what is glycosylation again?

A. Very briefly, it's the addition of carbohydrate groups, or kind of extended sugar groups, to various sites in the protein.

Q. And why does glycosylation matter?

A. Well, I think it could be a number of reasons. But

for the standpoint here, I think it matters because, if a molecule is glycosylated, it makes it bigger, more voluminous.

Q. You said that proteins can be glycosylated at certain sites; is that right?

A. Correct.

Q. Now, if those sites are present, if those amino acids are present, will the protein always be glycosylated?

A. Not necessarily, no. Not always, I should say.

Q. And let's look at the Sinclair reference. That's PTX 1773. Did you review this reference?

A. Yes, I did.

Q. And let's look at page 2 of that reference beginning with the sentence that says, "Most naturally occurring consensus sequences in secreted proteins are not glycosylated."

What is this conveying as relevant to your opinions?

A. Well, it's conveying, again, what a POSA would know and what I just stated, which is that not all proteins are glycosylated.

Q. And is that true even if they have the sites that would potentially permit glycosylation?

A. Yes. That's correct.

Q. Let's turn back now to Dr. Rabinow's slides and focus on the glycosylated requirement.

Now, does Fraser teach that VEGF R1R2 is glycosylated?

A. No, it does not.
Q. Does Fraser say anything about glycosylation?
A. No, it does not.
Q. Did you hear Dr. Rabinow refer to Papadopoulos with respect to glycosylation?
A. Yes.
Q. Did Papadopoulos describe glycosylation of the sequence recited in the '865 patent claims?
A. No.
Q. Is that disclosed anywhere in the prior art, as far as you know?
A. Not as far as I know. Not as far as I've seen.
Q. Now, if we go back to Papadopoulos at page 82 of the reference, what sequence did Papadopoulos disclose the glycosylation of?
A. Well, as I've showed here in this excerpt that there are five possible glycosylation sites. And it describes a different molecule or different fusion protein than the one in the '865 patent.
Q. So to be clear, what we have here at line 20 in Papadopoulos at page 82 of the exhibit, is -- that protein that's identified with the glycosylation sites, is that aflibercept or is that a different protein?
A. No. That's different protein. Again, I did a comparison between that and aflibercept. And this one is not

the same.

Q. Would you know from the glycosylation of a different protein that the protein in the claims of the '865 patent, aflibercept, would be glycosylated?

A. No, you would not.

Q. Now, let's look at the claims of the '865 patent again and, in particular, if we could look to Claim 14 on page 13 of the reference.

Doctor, what does Claim 14 require?

A. Well, it requires glycosylation at these specific sites. There are five sites in sequence ID Number 4. These are asparagine sites, and they're numbered right here.

Q. Does Papadopoulos teach the glycosylation of aflibercept at those sites recited in Claim 14 of the '865 patent?

A. No, it does not.

Q. As far as you're aware, is that disclosed in any prior art that's been advanced by Dr. Rabinow?

A. No, it does not.

Q. Does Holash -- also I recognize not part of the obviousness combination -- teach glycosylation at these residues?

A. No, it does not.

Q. I'd like to shift to a different topic, Dr. Trout. I'd like to talk about retinal penetration and aflibercept.

A. Okay.

Q. Based on the prior art as a whole, what kind of molecule would the POSA have wanted to use for intravitreal injection?

A. Well, the POSA would have wanted to use a relatively small molecule relative to aflibercept, for example, because of the limit of going through the various membranes to reach the retina.

Q. Now, Mylan's combination of Lucentis and Fraser relies on the Gaudreault reference as one of the Lucentis references, correct?

A. Yes.

Q. Okay. We've placed on the screen part of page 6 of the Gaudreault reference. That's Exhibit PTX 1839.

What does Gaudreault teach with respect to retinal penetration?

A. Well, it teaches what I've basically just said, highlighted here, "Notably, penetration of ranibizumab into the retina is critical for its clinical use. Retinal penetration suggests the availability of ranibizumab to inactivate VEGF at the site of AMD."

Q. Now, let's go back to page 1 of Gaudreault, Exhibit 1839 and beginning with this paragraph that starts "ranibizumab."

Can you explain what Gaudreault is teaching a person

of ordinary skill as it relates to retinal penetration?

A. Yes. So, again, with respect to ranibizumab, I'll just focus on that larger highlighted portion of this excerpt.

"Ranibizumab has also been shown to penetrate all layers of the rabbit retina, the first demonstration of retinal penetration of an anti-VEGF therapy intended for AMD."

Q. And was it the understanding -- what did the POSA understand about why ranibizumab was being developed by Genentech? For what kinds of diseases was it being developed?

A. Well, for anti-VEGF diseases; in other words, diseases of angiogenesis.

Q. Where in particular?

A. In the eye, of course, yes.

Q. Now, if we go further down on page 1 of the reference, Gaudreault, 1839, was the size of ranibizumab disclosed to be relevant for that purpose?

A. Yes. Extremely relevant.

Q. What is Gaudreault saying in that regard?

A. Well, again, just right below what I had read before, the "ability" -- that is, for retinal penetration -- "has been attributed to the small molecular size (48 kilodaltons) because a full-length antibody, trastuzumab (148 kilodaltons) was not able to penetrate all the retinal layers of rhesus monkeys."

It continues, "The small molecular weight of ranibizumab probably also contributes to its demonstrated

ability to penetrate the retina."

Q. What is that conveying?

A. Okay. All that sort of technical terms basically says if you have a relatively small molecule, 48 kilodaltons -- I understand that's a weight, but it can also be reflected in the volume. So it's a small molecule. That can penetrate the retina -- or layers to get to the retina, I should say; whereas larger molecules, like antibodies or aflibercept, were thought not to be able to get through to the retina.

Q. What is molecular radius that's being described here by Gaudreault?

A. Okay. So that is the important term here. That's basically the size of the molecule. So it's related to the molecular weight in kilodaltons, but it's the size. And that's what's, at the end of the day, most important.

Q. Does glycosylation affect a protein size?

A. Yes, it does.

Q. And in what way?

A. Well, again, glycosylation means that carbohydrates are added, they're extended carbohydrates. So they're going to be added to these sites, extend out, and increase the effective volume.

Q. Was ranibizumab glycosylated?

A. No.

Q. Now, Gaudreault was a Genentech paper. Did

literature from other researchers inform your opinions as to the issue of size and retinal penetration?

A. Yes.

Q. And let's look at the Ghate reference. That's PTX 576. Did you review this article?

A. Yes, I did.

Q. And what did it disclose with respect to retinal penetration?

A. Well, here I've just highlighted an excerpt. It says, "The internal limiting membrane" -- that's the membrane to get from the vitreous to the retina, "that membrane is impermeable to" -- and then it talks about linear molecules, which aren't so important for this situation.

But what it also talks about are globular molecules greater than 70 kilodaltons. So the larger macromolecules would have a longer retention time, possibly weeks, but their effect on the retina after an intravitreal injection is limited.

Q. Did you look at other references as well?

By the way, was that pages 8 and 9 of Exhibit PTX 576?

A. Yes.

Q. Did you look at other references as well?

A. Yes.

Q. Okay.

And let's put up the Jackson reference. That's PTX 1842.

Did you rely on Jackson in connection with your opinions?

A. Yes, I did.

Q. Okay.

And if we can put up page 1 of Jackson in the conclusion.

What is it disclosing?

A. Well, sort of the beginning of the conclusion here, "In humans, the inner and outer plexiform layers are sites of high resistance to the diffusion of large molecules, resulting in an REL of" -- about 76, 77 kilodaltons -- it says 76.5.

And REL is the retina exclusion limit.

Q. And did you prepare a demonstrative to help show the relative sizes of aflibercept compared to ranibizumab?

A. Yes, I did.

Q. Okay. And if we take a look at that, that's Demonstrative 4 on the screen.

Can you explain how these compare.

A. Yes.

And, Your Honor, I'll just focus on the middle and the right one.

So this is the aflibercept that we've been talking about. It's about 115 kilodaltons, remembering that the

retinal exclusion limit is in the 70s. It's close enough. Ranibizumab, on the other hand, is 48 kilodaltons, so below that limit.

Q. Now, Doctor, as of the priority date, was the efficacy of larger VEGF R1R2 proteins like aflibercept in treating retinal diseases compared by the intravitreal route and the subcutaneous systemic route?

A. Yes.

Q. Let's take a look at the Saishin article, Exhibit 1785, and at the time at the Ferrara review article, Exhibit 701.

Did you review both of these references?

A. Yes, I did.

Q. Now, Ferrara, is that a review article?

A. Yes.

Q. And what is a review article?

A. Oh, a review article is an article that summarizes what's already in the literature. It typically does not include new results, but it's an analysis of results that are already in the literature.

Q. And does it generally reflect the conventional wisdom in the field at the time?

A. Yes.

Q. Okay.

So if we look to -- if we can put up the

demonstrative showing both of those together.

On the left-hand side, do we have Figures 1 and 2 of Saishin, PTX 1785?

A. Yeah, we do.

Q. And on the right-hand side, do we have Ferrara at page 5, also page 862?

A. Yes. Yes.

Q. And Ferrara is PTX 701.

Can you explain first what the left-hand side shows, Saishin, and then what the right-hand side, Ferrara, is saying about it?

A. Yes, I can.

And, Your Honor, you've seen this perhaps a couple times before.

So this is a comparison of the effect of the VEGF Trap. Well, the first one is without the VEGF Trap and the second one is with it. And this is subcutaneous injection; in other words, not intravitreal injection. And I think the analogy was used before this is like golf, not basketball. You want to have as low a score as possible.

And that's compared here with the intravitreal administration. And so this is, again, the baseline. You can see a much lower differential here versus subcutaneous.

Q. And what was said about this data in the literature?

A. Well, so Ferrara, in referencing this -- we can turn

to the screen here -- says, "The limited efficacy occurred in spite of the high binding affinity of the VEGF Trap for VEGF. And it may be due, at least in part, to the existence of a barrier to the transretinal penetration of large molecules such as the VEGF Trap."

Q. Does this reflect what the POSA would have thought at the priority date?

A. Yes. Exactly.

Q. And does Ferrara analyze the Saishin reference and account for the details of its experimental design?

A. Yes. Clearly, Ferrara looked at it closely and analyzed it and led to that conclusion, which would be the conclusion of a POSA.

Q. Doctor, on the basis of these data, if the POSA wanted to use a VEGF R1R2 Trap like aflibercept to treat retinal diseases, what kind of administration would the POSA have used?

A. Well, if it's going to be the VEGF Trap, the POSA would have used subcutaneous or some kind of systemic injection.

Q. Would the POSA who made that choice have practiced the claims of the '865 patent?

A. No.

Q. Does the '865 patent require intravitreal administration?

A. Yes, it does.

Q. Now, were there risks and drawbacks associated with intravitreal injection?

And we'll bring up on the screen PTX 576 again, the Ghate reference, at page 8.

A. Yes. And, again, just highlighted this one sentence from Ghate.

"It is also the most invasive and the route with the most serious complications," referring again to intravitreal injection right here in the header.

Q. And does it further in the next sentence explain one or more of those complications?

A. Yes. In the next sentence it talks about the various complications and the rates varying from 0.15 percent to as high as 0.87 percent.

Q. And it talks about endophthalmitis. Do you understand that to be infection inside the eye?

A. Yes. I wasn't going to go into the details of that term; but yes, my understanding is an infection. But it's a very serious infection.

Q. Now, does Saishin teach anything about the appropriate formulation for aflibercept?

A. No.

Q. Does Saishin indicate anything with respect to whether the VEGF Trap stays in native conformation in a

formulation?

A. No, nothing.

Q. Now, if the POSA had decided to treat retinal diseases using an intravitreal injection, on the basis of all of the information you've reviewed, what molecules would the POSA have wanted to use, what kind of molecules?

A. Well, the POSA would have wanted to use smaller molecules such as ranibizumab.

Q. Was there also a VEGF Trap that fit into that category?

A. Yes, there was.

Q. If we bring up Demonstrative 6.

You've labeled now a third molecule in the demonstrative as Mini-Trap. Can you explain what that is.

A. Yes. The Mini-Trap is another molecule that Regeneron was working on.

And, Your Honor, you've already seen these two. So this is our favorite molecule here, aflibercept, and this is the ranibizumab.

The Mini-Trap is just this top part of aflibercept with a bottom part cut off to make it smaller. So it's about the same size as ranibizumab, maybe even slightly smaller.

Q. And did you look at literature relating to the Mini-Trap?

A. Yes, I did.

Q. Okay.

Let's pull up Exhibit 1757.

Do you understand this to be the Daly application?

A. Yes. That's correct.

Q. And can you explain what Daly is disclosing here on page 11, paragraph 48.

A. Yes.

At the top it's referring to this Mini-Trap, nonglycosylated and glycosylated. And then it says this Mini-Trap has optimized characteristics for local intravitreal delivery, i.e., shorter serum half-life for faster clearance, and minimizing unwanted systemic exposure.

In addition, due to its smaller size, the Mini-Trap has the ability to penetrate through the inner limiting membrane, ILM, in the eye, and diffuse through the vitreous to the retina/retinal pigment epithelial RPE layer, which will help to treat retinal disease.

Q. Doctor, on the basis of the prior art as a whole, would the POSA who wanted to use intravitreal injections of a VEGF Trap have wanted to use aflibercept or the Mini-Trap?

A. No, the Mini-Trap, the smaller molecule.

Q. And was that designed specifically for intravitreal delivery into the eye?

A. Yes, it was.

Q. Now, we've heard a lot about Avastin during this

trial. Wouldn't that have taught to use a large molecule for intravitreal injection?

A. No.

Q. Now, Dr. Rabinow addressed the Avery reference. That's DTX 2264. And for now I want you to assume that Avery is prior art.

Let's turn to page 368 of Avery. What is the article conveying to the person of ordinary skill?

A. Well, it's conveying, as you see in these two excerpts that I've highlighted -- this is in the discussion section -- "We acknowledge the shortcomings of this study: retrospective design, limited number of patients, nonstandard visions, and limited follow-up."

And then it further says in the same paragraph a little ways down there, "However, the visual results of this study are difficult to interpret."

Q. And did the Ferrara reference you've been discussing, PTX 701, did that address Avery's findings as well?

A. Yes, it did.

Q. Okay.

And if we can pull that up again at page 8.

What did Ferrara have to say?

A. Well, Ferrara says, "Although intriguing, these early findings are difficult to compare with data from rigorous double-masked controlled Phase III trials."

And then it continues. It's talking about ranibizumab, among others. And then it says, "It is noteworthy that initial uncontrolled Phase I or II studies with pegaptanib or verteporfin photodynamic therapy suggested a considerably greater benefit in AMD patients than that eventually demonstrated in randomized Phase III studies, further emphasizing the difficulty of interpreting early clinical results."

Q. So in view of all the references, including Saishin and Avery, what did Dr. Ferrara ultimately suggest and conclude in his 2006 review article?

A. Well, Dr. Ferrara concluded, again, what the person of ordinary skill in the art would understand, which is that that person of ordinary skill in the art would be turned to use the smaller molecules like ranibizumab and others.

Q. And so the record's clear, that excerpt that you were discussing on page 8 a moment ago from Ferrara, and it had the Footnote 114, was Ferrara discussing the Avery reference there?

A. Oh, yes. And you can see that on the right on the slide, the same Avery reference, correct.

Q. And that's the Avery reference that Dr. Rabinow discussed last week at trial?

A. Yes.

Q. Now, I'd like to shift again, Dr. Trout, and discuss the concentration required by the claims.

What is the concentration that all of the asserted claims require?

A. Well, of the aflibercept, it's highlighted here, 40 mg/mL.

Q. And let's go back to the prior art on which Dr. Rabinow relied, Fraser at DTX 729 on the second page.

Does Fraser teach 40 mg/mL of VEGF Trap?

A. No, not at all. Fraser teaches, as underlined here, 24.3 mg/mL.

Q. Did you hear Dr. Rabinow's testimony that the POSA would have used the 40 mg/mL concentration from the Lucentis references if we look at Slide 93 of Dr. Rabinow's presentation?

A. Yes, I heard him say that.

Q. Now, let's look at the Lucentis references. Do you recall that Dr. Rabinow relied on two Lucentis references, Shams and Gaudreault?

A. I do recall.

Q. Let's take a look at Shams first. That's DTX 726. And we're showing on the screen page 32 of the exhibit.

What does Shams teach regarding the concentration of ranibizumab?

A. Well, just what's highlighted here regarding that concentration, 6 mg/mL or 10 mg/mL.

Q. And just to be clear, is that 40?

A. No.

Q. And I think this was discussed last week, but what was the purpose for which Shams was using this ranibizumab?

A. Oh, so Shams is disclosing clinical approaches to using ranibizumab, so clinical trials.

Q. And let's look at Gaudreault, PTX 1839, and we'll look at page 2.

What concentrations does Gaudreault discuss?

A. Well, Gaudreault discusses 10 mg/mL and 40 mg/mL.

Q. Would Gaudreault have taught the POSA to use 40 mg/mL of aflibercept, Dr. Trout?

A. No, sir. On the contrary, Gaudreault teaches away from that. You can see some excerpts here. Actually, if we go back to the previous -- previous one.

Thank you.

It says that at the 2000 micrograms, that's the 40 mg/mL, it causes, at that concentration, moderate to severe inflammation; whereas it is not moderate to severe at the 10 mg/mL.

Q. And you're reading from pages 2 and 3 of Gaudreault, Exhibit 1839?

A. Yes.

Q. And how would the person of ordinary skill in the art have interpreted the findings of Gaudreault with respect to the 10 mg/mL compared to 40 mg/mL concentrations of ranibizumab?

A. Well, that person again would understand that the 40 mg/mL is problematic from an immune response standpoint versus the 10 mg/mL. And this would teach the person away from the 40 mg/mL. And I emphasize the bottom two. It basically lasted two to eight days, so seven days.

Q. Why do you say that it lasted seven days?

A. Well, it says that the inflammation was present at day two. It was a monkey study. The eyes were monitored throughout. So it was present at day two but had completely resolved by day eight.

Q. And is that good news or bad news?

MR. RAKOCZY: Your Honor?

Objection, Your Honor. He obviously has testified about it from the protein formulation perspective. The witness is not an ophthalmologist; so I don't think he's qualified to talk about good or bad from a clinical standpoint here.

THE COURT: Understood. Sustained.

BY MR. BERL:

Q. Doctor, let's take a look -- well, what happened to the 40 mg/mL dose of ranibizumab?

A. Well, it wasn't used going forward.

Q. Now, I think we had another excerpt that we put on the screen from a moment ago from Gaudreault. Can you explain the relevance of the sentence beginning after administration of 500 micrograms per eye?

A. Yes. This is another point from Gaudreault focusing on the 500 micrograms per eye. Again, in the table, you can see that corresponds to 10 mg/mL. And Gaudreault is saying that the retinal exposure was greater than 3,000-fold larger than the retinal exposure to VEGF.

So -- and it says suggesting that this ranibizumab dose provides maximum inhibition of VEGF. So the 10 mg/mL dose, according to Gaudreault, provides maximum inhibition. So you don't get more if you go higher anyway.

Q. Doctor, are you aware of any use of 40 mg/mL of ranibizumab after Gaudreault?

A. No, I'm not.

Q. Now, how does the potency of ranibizumab compare to the potency of aflibercept?

A. Well, aflibercept has a much higher potency than ranibizumab, 10 to 100 times more. I think I said in my report, 20 times more, so significantly more.

Q. Now, if the POSA had relied on ranibizumab as Dr. Rabinow suggests, how would the POSA have applied the teachings of Gaudreault and Shams regarding ranibizumab to the concentration of aflibercept?

A. Well, if anything, the POSA would choose a lower concentration. Again, as I said, aflibercept is much more potent than ranibizumab. Even accounting for the difference in the size or the weight, there would be much lower concentration