macular edema, and diabetic retinopathy.

Q. For the next bit of your testimony, I want to ask you just to focus on the AMD indication. Okay?

A. Uh-huh.

Q. So let's take down PTX 3097 and go back -- actually, before we do that let me ask this.

Can we check off the box in Claim 6 for the first limitation that Mylan or Biocon recommends the first step of Claim 6?

A. Yes, that would be correct.

Q. Let's take down PTX 3097, and then let's keep moving.

What's the next limitation of Claim 6 that you analyzed to determine whether Mylan's label or Biocon's label recommends infringement?

A. So the next limitation is that the treatment, the method, comprises sequentially administering to the patient by intravitreal injection a single initial dose of 2 milligrams of aflibercept.

Q. Dr. Csaky, does the proposed Yesafili labeling encourage, recommend, or promote doctors to sequentially administer to the patient by intravitreal injection a single initial dose of 2 milligrams of aflibercept?

A. Yes.

Q. Let's bring back up the label. That's PTX 3097, and we're looking at page 1 and the "Dosage and Administration"

section for AMD. Excuse me. We're looking at page 2, and that's the "Dosage and Administration" section for AMD.

Where does Mylan or Biocon's label recommend that doctors sequentially administer to the patient by intravitreal injection a single initial dose of 2 milligrams of aflibercept?

A. Right. So under the, again, "Dosage and Administration," it says the recommended dose for Yesafili, 2 milligrams, to be administered intravitreal injection every four weeks, monthly.

Q. Okay. And you said every four weeks, monthly. Are any of those monthly doses a single initial dose?

A. Yes.

Q. Which one?

A. Well, it's the first -- first one would be the initial dose.

Q. Fair enough.

We're going to move to the next requirement of Claim 6 here in just a second, but before we do I want to talk about a few issues that I think we're going to see over and over again, and I want to see if we can clear the air on those first to streamline things.

The patent claims on the right, they refer to administering aflibercept. Do you see that?

A. Yes.

Q. Yesafili's label on the left -- that's PTX 3097 --

refers to administering Yesafili. Do you see that?

A. Yes.

Q. What is the active ingredient in Yesafili?

A. Aflibercept.

Q. So whenever PTX 3097 recommends administration of Yesafili, is it recommending the use of aflibercept?

A. Yes.

Q. The patent claims also all require that the doses of aflibercept be 2 milligram doses.

Do you see that?

A. Yes.

Q. And that will appear in the other claims we look at, right?

A. Yes.

Q. Turning back to the "Dosage and Administration" section we looked at earlier -- that's again PTX 3097, page 2 -- what dose of aflibercept does Yesafili's label recommend that doctors administer?

A. 2 milligrams.

Q. I know we're only looking at AMD on the screen right now, but have you reviewed PTX 3097 -- that's the proposed labeling -- in full?

A. Yes.

Q. Is there any dose referred to in PTX 3097 that is not a 2-milligram dose?

A. Not that I could find.

Q. Okay. So whenever PTX 3097 recommends administration of Yesafili, is it recommending the use of 2 milligrams of aflibercept?

A. Yes.

Q. All right. Last but not least, the claims are all going to require intravitreal administration, I think an image that is now burned into our brains.

How does Mylan or Biocon recommend administering aflibercept in PTX 3097?

A. Through intravitreal injection.

Q. Again, any kind of administration other than intravitreal administration that's described at all in this label?

A. Not that I could find.

Q. For shorthand, whenever PTX 3097 recommends administering Yesafili, is it, in fact, recommending that doctors administer a 2-milligram intravitreal dose of aflibercept?

A. Yes.

Q. All right. Then let's keep cruising here. You can take down PTX 3097 for a moment and turn back to your slides.

Can we check off this box that Yesafili's label recommends sequentially administering to the patient by intravitreal injection a single initial dose of 2 milligrams of

aflibercept?

A. Yes.

Q. All right. Then let's turn to the next set of limitations, and I see you've highlighted two.

What are the next limitations of Claim 6 that you'll address?

A. So the next limitations are these idea of secondary doses. And the claims are that there should be one or more secondary doses of 2 milligrams of aflibercept and that each of these secondary doses be administered approximately four weeks following the immediate preceding dose.

Q. Let's bring back up PTX 3097, still looking at page 2.

Does Mylan or Biocon's labels recommend that doctors administer -- excuse me -- does Mylan or Biocon's label recommend that doctors follow the initial dose with one or more secondary doses of 2 milligrams of aflibercept wherein each secondary dose is administered approximately four weeks following the immediately preceding dose?

A. Yes.

Q. Where?

A. So, again, it says under "Dosage and Administration," the recommended dose of Yesafili is 2 milligrams to be administered every four weeks for the first 12 weeks or three months.

Q. And of those first three injections, which, if any, of those correspond to the secondary doses of the claim language?

A. So the secondary doses in this case would be the second and third injections.

Q. Those are the ones after the initial one?

A. Correct.

Q. Does PTX 3097 recommend that doctors administer those secondary doses approximately four weeks following the immediately preceding dose?

A. Yes.

Q. Where does it do that?

A. It says right here that these injections should be administered every four weeks, approximately every 28 days or monthly.

Q. So then let's turn back to your slides. We're looking at PDX 4028.

Dr. Csaky, can we check off these boxes? Does the label recommend -- excuse me -- does PTX 3097 recommend both of these steps of the method of Claim 6?

A. Yes.

Q. All right. What's next? What's the next limitation of Claim 6 you analyzed?

A. So the next are the "followed by one or more tertiary doses of 2 milligrams of aflibercept," and this too has another

limitation in that each tertiary dose be administered approximately eight weeks following the immediate preceding dose.

Q. Okay. After recommending the initial and secondary doses we just looked at, does PTX 3097 encourage, recommend, or promote that doctors administer one or more tertiary doses of 2 milligrams aflibercept wherein each tertiary dose is administered approximately eight weeks following the immediately preceding dose?

A. Yes.

Q. Let's pull back up the label. That's PTX 3097.

Dr. Csaky, where is that recommendation?

A. So, again, it states here under "Dosage and Administration" that, after the initial doses, they should be followed by 2 milligrams of the intravitreal injection once every eight weeks or two months.

Q. And just in the language of the claims, which of those 2-milligram intravitreal injections once every eight weeks or two months are the tertiary doses of the claim?

A. All of them.

Q. Any of them that are administered?

A. Any of them that are administered would be considered tertiary doses.

Q. And, again, does the label explicitly recommend administering tertiary doses once every eight weeks?

A. Yes.
Q. Where is that?
A. Again, it says to be -- injection once every eight weeks under the dosage and administration label.
Q. All right. So turning to Slide 29, that's PDX 429, can we check off these boxes? Does Mylan/Biocon's label recommend that doctors perform the tertiary dose steps of Claim 6?
A. Yes.
Q. All right. Looking at PDX 430, we've now made it to the crossed-out limitation. Can we skip this one for purposes of your analysis?
A. Yes, I did.
Q. Then let's turn to Slide PDX 431. What's the last limitation of Claim 6, Dr. Csaky?
A. It says, "wherein the aflibercept is formulated as an isotonic solution."
Q. Dr. Csaky, did you evaluate whether the Yesafili aflibercept that Mylan's label recommends doctors administer is formulated as an isotonic solution?
A. I did not.
Q. Why not?
A. I'm not a formulation expert.
Q. Do you know if anyone did address that limitation?
A. I've been informed that Dr. Trout performed that

analysis.

Q. And just to set expectations, Dr. Trout will testify as to infringement shortly. I expect him to address that limitation. And so with that in mind, Dr. Csaky, let's turn to the next slide, PDX 432. And I just want to ask you, for the rest of your testimony about Claim 6, I need you to assume that Dr. Trout will testify that the aflibercept recommended by Mylan Biocon's label to be administered is formulated in an isotonic solution.

Do you understand that?

A. Yes.

THE COURT: While those boxes are checked, Counsel, would it be a good time to take our morning break?

MS. KAYALI: Absolutely, Your Honor.

THE COURT: We'll do that, then. We'll take 15 minutes. If everybody could be ready to resume at ten after 11:00, we'll resume the doctor's testimony.

Sir, you can take a break if you'd like, and you can step down. I'll give you the same speech. I recognize you're an expert; but for purity of our circumstances, yes, the same speech you heard me give Dr. Yancopoulos yesterday applies to you. You're a man without a country. No one's being rude or discourteous, but they're not allowed to talk you midstream. So we'll go with that.

Otherwise, we'll see everyone here in 15 minutes.

Thank you all.

(A recess was taken from 10:59 a.m. to 11:15 a.m.)

THE COURT: Counsel, you may proceed.

MS. KAYALI: Thank you, Your Honor.

BY MS. KAYALI:

Q. Dr. Csaky, we're going to hop right back to Slide 32 where we left off. But before I ask the next question there, earlier in your testimony, I believe you testified that about 1 million patients suffer from AMD. Is that about 1 million in the United States?

A. Correct.

Q. And DME and DR, you also explained that those diseases are common. Are they common in the United States?

A. Correct.

Q. So then let's turn back to where we left off. We had just checked off all the boxes. Let me just ask this: Is there anything else in Claim 6 we need to look for in Mylan's label?

A. No.

Q. We got them all. That's all the limitations?

A. Correct.

Q. All right. So then let's go to the next slide. And I want to turn back to the question we started with. That's PDX 433.

In view of your testimony, in your opinion, does the Mylan Biocon label, PTX 3097, recommend that doctors perform every step of the method of Claim 6 to treat AMD using Yesafili?

A. Yes.

Q. Okay. In view of that, does the Mylan Biocon label recommend that doctors perform a method that infringes Claim 6?

A. Yes.

Q. Let's turn to the next slide, then, and ask -- let's focus now on Question Number 2. Okay?

And, actually, I should back myself up.

Before we focus on Question Number 2, I want to see if we can do something to help us move just a little faster through the rest of this examination. We've been looking at page 2 of PTX 3097.

If we could bring that back up, please. And if we could call out the -- there you go, Section 2.2, the dosing instructions for AMD.

Is there anywhere else other than this section on page 2, "Dosage and Administration," that communicates the same information about Mylan or Biocon's label recommends that doctors use Yesafili to treat AMD?

A. Not that I can see.

Q. Let's take a look at page 1 of the label. And page 1, are they what's called the "Highlights of the

Prescribing Information"?

A. Yes.

Q. Okay. Do the highlights of the prescribing information say the same thing about how doctors should administer Yesafili to treat AMD as the more -- the longer section on page 2 of the exhibit?

A. When I read these, they are identical.

Q. Okay. So, really, what I'm asking is, to avoid flipping back and forth, can we stick with the highlights of the prescribing information as we move forward?

A. That would be fine.

Q. It says the same thing as the more detailed stuff later?

A. Yes.

Q. All right. Now, let me ask while we have this up, I see three bullet points under -- on the left. This is PTX 3097, page 1, the dosage and administration section and the highlights of the prescribing information. I see three bullet points that look like they correspond to the three sentences in the full Section 2.2 dosage and administration on page 2.

Do you see that?

A. Yes.

Q. Which of those bullet points have you focused your testimony on today?

A. The first bullet point.

Q. Why did you do that?

A. I did that because that's the only place in reviewing this document that I could see that the term "recommended" was used.

Q. So how many recommended dosing regimens are there in Mylan or Biocon's label as to how doctors should administer Yesafili in order to treat AMD?

A. There's only one recommended way.

Q. Is that the one you've offered testimony on today?

A. That's the one I've offered testimony on.

Q. Now, let's look at this briefly, because we're going to get there, for diabetic macular edema and diabetic retinopathy too.

Are there also highlights of the prescribing information for diabetic macular edema and diabetic retinopathy?

A. On here all I'm seeing is neovascular wet AMD.

Q. Okay. If we go back to page 1 of PTX 3097, could we pull up the highlights of the prescribing information at the bottom for diabetic macular edema and diabetic retinopathy?

Will we also be referring to the highlights of prescribing information -- let me ask a better question.

Do the highlights of the prescribing information also instruct doctors about how to use Yesafili to treat DME and DR?

A. Yes.

Q. And we're going to come back to that in a minute. I just wanted to sort of establish where we're headed next.

Let's go back. Let's go back to PDX 4/34 and turn back to Question Number 2. We're in a world where you just answered yes to Question Number 1, and now we're asking ourselves -- you're asking yourself -- will any doctor perform infringing methods as a result of Mylan or Biocon marketing Yesafili using the proposed labeling we've just looked at?

And so I want to get into the nitty-gritty of your answer in just a second, but let's answer that at a high level first.

In your opinion, if Mylan or Biocon sell Yesafili with the proposed labeling we've just looked at, will doctors perform the method of Claim 6 and infringe Claim 6 as a result?

A. Yes.

Q. Okay. I want to talk a lot more about how and why you know that. Let's ask some prefatory questions first.

Do ophthalmologists like yourself read labels?

A. Yes.

Q. Why?

A. Well, there's several reasons. Especially when a drug comes onto the market, it gives us a good synopsis of the important information of that drug, right? It tends to be a synopsis of the data that supported its approval. So there typically is a recommended usage that we now can be understood

should be an approach that we should consider. It outlines again some of the issues, contraindications, reasons why you would not want to use it, what to look for.

Other reasons -- for example, we have continuing medical education lectures, right? And those typically require that, if you're going to give a lecture on a drug, that you give it on-label, which means that, as you're talking about the aspects of the drug, that you're talking about it per the label. So that's typically either a requirement or that you have to notify the audience that you're going to be going off-label.

And then of course in many cases sometimes insurance carriers, they utilize the label for reimbursement purposes, and so it's something you have to be aware of. So it's something that all of us from time to time will be either exposed to, read, or understand what's in the label.

Q. Well, does what the label say influence the way that ophthalmologists use ophthalmic drugs?

A. Of course.

Q. Why?

A. Well, because, again, I mean, we have to understand that there's several reasons that we'd want to look -- you know, as we look at a label, these are the guideposts, right? These are the instructions. And for many people, these are kind of a good way to start. They're going to say, okay,

here's how the agencies like the Food and Drug Administration, who has approved the drug, is -- has recommended that it be used. So, again, it gives us a starting point for how do we utilize the drug.

So, again, there's lots of reasons to begin to review that, especially with a new drug as it comes out, that's something that we'll be exposed to and read.

Q. So in view of that, Mylan or Biocon sells Yesafili with a label that recommends that doctors infringe Claim 6. Will some doctors actually do what that label says and use Yesafili according to the method of Claim 6?

A. Some doctors will in some patients.

Q. So I want to break things down a little bit because you're offering testimony about Yesafili, and I think we've established that drug's not on the market yet, right?

A. Yes.

Q. So how is it that you can form an opinion about how ophthalmologists will use Yesafili even though it hasn't been sold yet?

A. Well, in forming my opinion I looked at how people use Eylea. And I reviewed the Eylea label and I asked myself is there any doctor with any patient that follows the label of Eylea in order to make my decision.

Q. And if we bring back up PTX 917 on the left and PTX 3097 on the right, is there any difference between how

Regeneron recommends that doctors use Eylea and how Mylan or Biocon recommends that doctors use Yesafili?

A. Not that I can see.

Q. All right. In view of the fact that these labels make the same recommendations and in view of the fact that we just walked through your opinion that Mylan or Biocon's label encourages, recommends that doctors perform every method of claim -- excuse me -- every step of the method of Claim 6, does Eylea's label also recommend that doctors perform every step of the method of Claim 6?

A. Yes.

Q. Now, we touched on this at a high level before, but let's be a little more granular now. Do some doctors use Eylea in the way that Regeneron's label recommends?

A. Yes.

Q. How do you know?

A. Well, in doing my assessment, I kind of reviewed several aspects. One, of course, is thinking back on how I have used Eylea. And, again, as I said, there are certain circumstances with certain patients, certain situations, where I have followed the label for lots of reasons.

I've also -- when we sit on these committees and talk about various approaches, clearly there are lots of alternatives that people use, but there's still people who feel as if these label indications still in many cases they have

that comfort in knowing that this will give them good visual acuity in the patients that they want to treat.

So I used several kind of indicators of trying to determine our -- again, are there some doctors in some patients who will utilize this approach? And the conclusion I came to was yes.

Q. I want to take each of those reasons that you just offered in turn and dive in in a little more detail.

You said you have used Eylea in the way the label recommends in accordance with the method of Claim 6. When and why?

A. So, again, sometimes -- again, if you look -- I mean, the label basically suggests that, you know, I need to be giving three injections, which is again a very common approach for neovascular AMD. And then it instructs me to say, okay, wait eight weeks after that initial injection and do eight-weeks injections.

And, again, there's certain circumstances, especially when there is -- I think back specifically to times when, for example, patients had challenges with scheduling, right? They want to know exactly kind of what to expect. They want to be able to figure out, Dr. Csaky, tell me exactly when I'm going to be coming in. I can give them some guideposts and metrics using this kind of approach.

So there again, it's lots of reasons to have this

wider range of treatment options for patients as you talk with them and you ask them questions about what specifically -- remember, this is a burdensome approach. And if somebody, especially in areas where they have trouble getting back and forth and they have to arrange certain trips, you know, having kind of a known schedule in certain circumstances can be really helpful for the patient. So, again, there have been some cases where I tried to and I have reviewed with the patient and I've used this approach.

Q. Are there particular circumstances that stand out?

A. Again, I think, you know, when I look back -- again, and this is typically in areas where getting to and from certain regions are challenging -- like, again, sometimes in these rural communities, it can be very challenging. If I'm there once a week and I don't have the luxury of being there often, it's nice to have that comfort to know the patients are coming back and forth.

Also sometimes when I'm sharing a clinic with -- in this case in one of my satellite clinics, we can easily share patients because we kind of know what the schedules are going to be like. So, again, there's certain circumstances in which this type of approach can have some benefits.

Q. And this type of approach, that's the fixed-dosing approach that's recommended by Eylea's label and covered by Claim 6?

A. Correct. So this is a -- an approach where, again, if you look at this label, it suggests that you want to have that patient come in once every month for three months and then start extending it to eight weeks.

Q. Well, I understand that's your experience, Dr. Csaky. Is the retinal community such that you're familiar with how other doctors use Eylea?

A. Yeah. I mean, I have -- like I said, I'm involved in lots of committees, discussions. Even with some of my fellow colleagues at Texas Retina, we talk about various approaches that people use. So, again, this is -- it's part of our armamentarium. What we want is we want to have different approaches in our armamentarium that we can offer patients and try to meet some of their needs and what they can have in terms of their scheduling and things like that.

So that's really kind of a critical aspect to work with patients and fully appreciate what's the best for them in trying to get the best treatments.

Q. And just to be very clear, in your conversations that you mentioned with other doctors, have you become aware as to whether other doctors used the fixed-dosage regimen recommended by Eylea's label and covered by Claim 6?

A. Yeah, I've had certain -- like I said, discussions. And also I've seen certain documents where people have talked about using these kinds of approaches.

Q. Okay. During the course of preparing your opinion, did you come across a document reflecting how any particular doctor used the fixed-dosing approach?

A. Yes.

THE COURT: One second, Doctor.

Yes, Counsel?

MS. LESKO: Objection, Your Honor. I believe what -- the document that counsel's about to refer to is the declaration of Dr. Do, who was an expert on behalf of Regeneron in a separate proceeding. That is hearsay. It should not be admissible. If they wanted to introduce Dr. Do as an expert in this case, they could have done it.

THE COURT: Agreed, but, Counsel, go ahead.

MS. KAYALI: Your Honor, we don't intend to seek admission of this document. Under Rule 703, Dr. Csaky is permitted to rely on such things. And he only intends to testify as to what that declaration said and how he relied on it.

THE COURT: Understood. Assuming that foundation is laid, objection overruled; but we'll keep an eye on it.

MS. KAYALI: Thank you. So let's bring up -- well, I'm not sure if we got an answer to the last question; so let me just ask it again.

THE COURT: Yeah, let's repeat that question.

BY MS. KAYALI:

Q. In the course of your work on this case, did you come across a document reflecting how any particular doctor -- or whether any particular doctor uses a fixed-dosing regimen recommended by Eylea's label and covered by Claim 6?

A. Yes.

Q. And what document is that?

A. So this was a document that was -- there was some testimony by a good friend of mine, Dr. Diana Do, and I reviewed part of that in coming to my opinion about -- in this case.

Q. Okay. Well, let's bring up PTX 1527.

And, Dr. Csaky, is this the declaration of Diana Do you are referring to?

A. It is.

Q. And do you see highlighted above her name, "Inter Partes Review Number 202100881"? Do you see that, Dr. Csaky?

A. I do.

Q. Do you understand that this is a declaration Dr. Do submitted in a different litigation before the patent office about a different Regeneron patent?

A. Yes.

Q. And if we flip to the last page of the document, that's page 67, do you see that she signed this declaration under penalty of perjury?

A. Yes.

Q. Let's take a look at what she said. If we could go to paragraph 137. I believe that's on page 54.

What does Dr. Do say in her signed declaration about how doctors use Eylea to treat wet AMD?

A. Right. And, again, I want to make it clear that I know Diana very well, and I value -- I think she's a phenomenal doctor; so I really respect her opinion and her approach. And so that's why it was important for me when I used this document to come to my opinion.

And what she says here is that physicians, including herself, typically and frequently treat wet AMD in particular by administering one or more monthly doses subsequent to the initial dose. And she calls these out, secondary doses, approximately four weeks after the immediate preceding dose.

And then she goes on to say -- and, again, in the second paragraph, she talks about patients following these loading doses, she talks about physicians, including herself, and that typically and frequently follow the monthly loading doses by transitioning, like I have, from monthly or four-week visits to bimonthly or eight-week visits and injections.

Q. If -- we just walked through the steps of Claim 6. If a doctor uses Eylea in the way Dr. Do describes here, will that doctor perform the method of Claim 6 for the treatment of AMD?

A. Yes. That is my opinion.

Q. And just to be clear, this is what Dr. Do does and what she says other physicians do. Is this also something you do?

A. Yes.

Q. And I know that this document is going to surface again in our later discussions, but I want to again see if we can save a little time. And so I'm just going to ask does Dr. Do also describe using the method of Claim 6 for indications like DME and DR?

A. Yes. So she includes these other diseases. And when I formed my opinion on these other diseases like diabetic macular edema, DME, or diabetic retinopathy, she points out in both cases that she too uses this approach of these initial dose and secondary dosing and then transitions to these bimonthly or eight-week visits and injections.

MS. KAYALI: I think we can take that down.

BY MS. KAYALI:

Q. Dr. Csaky, in the course of forming your opinions, did you come across any other documents reflecting how physicians use Eylea according to the method of Claim 6?

A. I did.

Q. Let's pull up PTX 586.

What is this document, Dr. Csaky?

A. So this is a manuscript in the public domain

published in 2023 by Mark Gallivan. And what Mark did here was to review this database called the IRIS Registry.

Q. Well, if we turn to page 2 of Exhibit 586, Plaintiff's Exhibit 586, can you explain to the Court what the IRIS Registry is.

A. Yes. So the IRIS Registry is a database, very -- you know, a kind of interesting database that the American Academy of Ophthalmology started many years ago with the intent of collecting real-world data -- anonymized real-world data. Many of us have EHR, or electronic health records. And so the idea was an anonymized way you could upload some of that data to a central server and then have availability of that data to be studied and reviewed.

Q. The records in the IRIS Registry, are those records of patients that were treated in a clinical trial or records of patients that were treated in just normal clinical practice?

A. These are primarily just in normal clinical practice. So these are -- it's a voluntary registry and -- but it's been very successful, and people want to be able to upload so we can analyze what's happening in the real world.

Q. When the authors in Dr. Gallivan's papers -- so Dr. Gallivan and his colleagues -- reviewed the IRIS Registry for patients treated during their normal clinical practice, did they find any patients who received an initial dose of aflibercept, one or more secondary doses of aflibercept four

weeks after the preceding dose, and one or more tertiary doses of aflibercept eight weeks after the preceding dose?

A. Yes. And so the purpose of this study was really interesting. They wanted to -- we knew what the VIEW 1-VIEW 2 data -- clinical data showed. And so what the intent was to say, okay, those are clinical trial patients. Can we find patients in the real world that emulate those trial -- those approaches that we took?

And of course one of the approaches in the VIEW 1 and VIEW 2 was exactly what we're talking now, this approach where we give monthly dosing and then switch to every-eight-week dosing. So, indeed, they went through and they found a group of patients that fulfilled that criteria.

Q. And if we skip ahead in the document to page 6, let's pull up Table 5.

Dr. Csaky, how many patients in the IRIS Registry did Dr. Gallivan and his colleagues find that received, essentially, the method of Claim 6?

A. Right. So they went through -- and, of course, these registries, you have to remember, when you're trying to emulate a VIEW 1 or VIEW 2 trial data, there's lots of data that wasn't available, but what was available was in some cases the dosing schedule that these patients underwent. And in this case they were able to identify 154 patients who were following exactly the approach that was -- that we're discussing now, this

approach of giving, as it says right there, three initial monthly doses and then converting 2 milligrams every two months after that.

So these were a group of patients that they identified in the real world who were being treated this way.

Q. Just to be very clear, if doctors administered aflibercept 2 milligrams intravitreally every two months after three initial monthly doses, did those patients receive the method of Claim 6?

A. Yes.

Q. One last question, Dr. Csaky. Does the IRIS Registry contain data about every patient who's ever received Eylea?

A. No.

Q. So this is a sampling?

A. Yeah. So the IRIS Registry, again, it's a voluntary approach. It's a significant portion, but it clearly does not capture everybody who's being treated with Eylea in the real world.

Q. So let's turn back to your slides. Let's look at PDX 434.

Dr. Csaky, let's focus on the second question here on the slide. In view of everything we've just discussed -- in view of your own experience, your discussion with colleagues, Dr. Do's declaration, the Gallivan article -- can we answer Question 2?

A. Yes. I did answer Question 2.

Q. Well, then, what's the answer? What is your opinion as to whether, if Mylan or Biocon market Yesafili in accordance with the proposed labeling in PTX 3097, will some doctors follow the label's instructions and use Yesafili to treat AMD in a way that infringes Claim 6?

A. Yes.

Q. Any doubt in your mind about that?

A. No, no doubt.

Q. All right. Then let's turn to PDX 4.35. And I want to take a step back.

Having answered both these questions, that is in view of your opinion that Mylan or Biocon's label recommends that doctors perform a method that infringes Claim 6 and in view of your opinion that some doctors will, in fact, perform the method of Claim 6 as a result of the recommendations in the label, have you formed an opinion as to whether or not Mylan or Biocon will induce infringement of Claim 6 if they sell Yesafili?

A. Yes.

Q. And what is your opinion?

A. My opinion was that Mylan or Biocon will infringe Claim 6 by promoting Yesafili.

Q. At this point I have some good news, which is that we are done with Claim 6 for wet AMD.

I also have some really good news, which is that we get to do it again.

We are going to now discuss Claim 6 in the context of DME and DR. And I promise we're going to do those far more quickly and that we're going to take them together, but I just want to set the stage.

So let's go back to the beginning of Claim 6. Can we please put up the Mylan -- excuse me. That would be Slide PDX 4.26. Thank you. Can we please bring back up the Mylan/Biocon label on the right. Let's focus on the "Indications and Usage" section for DME, and that's -- we're looking now at page 1 of PTX 3097.

Dr. Csaky, we're taking it from the top here. If Mylan or Biocon market Yesafili with the labeling that's PTX 3097, will Mylan or -- will that label recommend that doctors perform a method of treating an angiogenic eye disorder in a patient in need thereof in the context of DME and DR?

A. Yes. The answer is yes.

Q. How do you know?

A. So, again, under the "Indications and Usage," we see that Yesafili will be indicated for the treatment of patients with diabetic macular edema and diabetic retinopathy.

Q. And are both of those angiogenic eye disorders?

A. Yes.

Q. So excuse me. Looking back to PDX 4.26, can we check

off the first limitation of Claim 6, understanding that Mylan and Biocon's label recommends doctors perform this step?

A. Yes.

Q. Right. We're going to be talking about both DME and DR at the same time for the next few questions. So I want to, again going back to the difference between the highlighting and the full label, see if we can move this along more quickly.

Let's pull up the full dosage and administration instructions for DME. That's on page 2 of 3097.

Dr. Csaky, how does Mylan or Biocon recommend that doctors use Yesafili for the treatment of DME?

A. Yes. Under "Dosage and Administration," it recommends that Yesafili be given 2 milligrams by intravitreal injection every four weeks, or approximately 28 days monthly, for the first five injections.

Q. And just like I asked for AMD, can we find this information in the highlights of the prescribing information as well?

A. Yes.

Q. Let's take a look at that on page 1.

Dr. Csaky, is there any difference in how the full dosage and administration section recommends that doctors use Yesafili to treat DME and how the highlights of the prescribing information recommend that doctors use Yesafili to treat DME?

A. No.

Q. Sorry. Let's turn to DR. Can we bring up the full dosage and administration instructions for DR on page 3 of PTX 3097.

Dr. Csaky, on the right we now have the highlights of the prescribing information under "Dosage and Administration" for DR. That's page 1 of 3097.

So do you see we have page 3 on the left and page 1 on the right?

A. Yes.

Q. Same question. First, how does Mylan/Biocon's label instruct doctors to administer Yesafili for the treatment of DR?

A. Again, it recommends that the treatment for DR be 2 milligrams intravitreal injection every four weeks for the first five injections.

Q. And comparing that to the highlights of the prescribing information on the right, is there any difference at all between recommended dose on page 3 and the recommended dose on page 1?

A. No.

Q. So we're going to use the highlights of the prescribing information moving forward since it's going to be a little faster, but do you have any problem with that?

A. No.

Q. One more question about the highlights of the

prescribing information here.

For both DME and DR -- and we're look at PTX 3097, page 1 -- how many bullet points are there under the highlights of prescribing information for DME and DR?

A. There's two bullet points.

Q. Which one of those are you going to focus your testimony on today?

A. My testimony is on the first one.

Q. Why?

A. Well, again, it's before this was -- this -- it states the recommended dose for Yesafili in this bullet point.

Q. How many recommended dosing regimens are there for the treatment of DME and DR using Yesafili and Yesafili's label?

A. Only one.

Q. And that's the first bullet point here, right?

A. Yes.

Q. Okay. With that background out of the way, let's go back to your slides and look at the next limitation of Claim 6 in the context of DME and DR.

Can we pull up PDX 427. Thank you.

Dr. Csaky, we just checked off the first box a minute ago. What's the next limitation of Claim 6?

A. So the next limitation is that it be administered by intravitreal injection with a single initial dose of

2 milligrams of aflibercept.

Q. Does the Mylan or Biocon label recommend that doctors administer an intravitreal injection of a single initial dose of 2 milligrams of aflibercept for the treatment of DME and the treatment of DR?

A. Yes.

Q. Let's bring back up page 1 of PTX 3097.

And, Dr. Csaky, can you show us where that recommendation is.

A. Yes. Right there it says under the dosage and administration, the recommended dose of Yesafili is 2 milligrams administered by intravitreal injection every four weeks for the first five injections.

Q. Same question as the last time around. Which of those intravitreal injections every four weeks for the first five injections -- try that again. Which of those first five injections is the single initial dose?

A. The first one.

Q. Fair enough.

Can we check off the box, then, that Mylan or Biocon recommends doctors perform the second step of Claim 6 in the context of DME and DR?

A. Yes.

Q. Let's turn to PDX 28, which we have up on the screen.

Dr. Csaky, what are the next two limitations you'll

address in the context of DME and DR?

A. Right. The next two limitations are that there be one or more secondary doses of 2 milligrams and that the secondary doses be administered every four weeks following the immediate preceding dose.

Q. Does PTX 3097, the proposed labeling for Yesafili, recommend doctors perform these steps when treating DME and DR using Yesafili?

A. Yes.

Q. Let's bring back up the label.

Looking at page 1, Dr. Csaky, familiar question, where do you see that recommendation?

A. Right. It says here again that the dose is 2 milligrams by intravitreal injections every four weeks for the first five injections.

Q. Which of those first five injections, Dr. Csaky, correspond to the one or more secondary doses of 2 milligrams aflibercept in the claims?

A. The last four injections.

Q. Does Mylan's label recommend that those four secondary doses be administered approximately four weeks following the immediately preceding dose?

A. Yes.

Q. Where does it recommend that?

A. It says specifically that they should be administered

every four weeks.

Q. Is that a recommendation both for the treatment of DME and DR?

A. Yes, for both.

Q. So turning back to Slide 28, can we check off the boxes that Mylan or Biocon's label recommends the secondary doses limitations of Claim 6 in the context of DME and DR?

A. Yes.

Q. Let's turn to Slide 429.

What's the next limitation of Claim 6, Dr. Csaky?

A. So the next limitation is two-part. It says that it should be followed by one or more tertiary doses of 2 milligrams and that these tertiary doses be administered every eight weeks.

Q. Let's bring back up the label. That's PTX 3097 at page 1.

Dr. Csaky, this proposed labeling for Yesafili recommends that doctors administer, after that initial dose and the secondary doses, one or more tertiary doses of 2 milligrams aflibercept wherein each tertiary dose is administered approximately eight weeks following the immediately preceding dose.

A. Yes. It says exactly that these injections should be -- after five injections should be followed by 2 milligrams every eight weeks.

Q. And, Dr. Csaky, I noticed when you turned to face your screen, sometimes your microphone slips away from your face. It might be helpful to Madam Court Reporter if we try to keep that in front of you.

So sorry. Let me just -- I want to make sure I heard the answer to that last question.

Does the label recommend one or more tertiary doses of 2 milligrams aflibercept wherein each tertiary dose is administered approximately eight weeks following the preceding one?

A. Yes.

Q. Can you point that out to us, please.

A. Yes. It says, again, right under the dosage and administration, it's 2 milligrams via intravitreal injection once every eight weeks.

Q. Is that for both the treatment of DME and DR?

A. Yes.

Q. Can we check off those boxes, then? Does the label recommend doctors perform both of the tertiary dose steps?

A. Yes.

Q. Turning to the next slide then, that's PTX 430, are we -- will you perform any analysis of this limitation in the new DME, DR context?

A. No.

Q. And why is that?

A. So again if -- again, I've been told that this is a nonlimiting claim, and so it was not included in my analysis.

Q. Just to be clear, when you say a "nonlimiting claim," do you mean a nonlimiting portion of Claim 6 -- limitation of Claim 6?

A. Right.

Q. Let's move on to PDX 4.31.

Is it the same story, Dr. Csaky, for aflibercept formulated in isotonic solution as we talked about in AMD?

A. Correct. I did not include that as I am not a formulation expert.

Q. Okay. So I'm going to ask you to make the same assumption I did last time, which is for the remainder of your testimony about Claim 6, please assume that Dr. Trout will testify that the aflibercept recommended to be used by Mylan/Biocon's label is formulated as an isotonic solution.

Can you make that assumption?

A. Yes.

Q. Let's turn to PDX 4.32.

What's left, Dr. Csaky? Anything else in Claim 6 we need to cover?

A. Nothing.

Q. Have you hit all the limitations?

A. Yes.

Q. Turning back to your questions, PDX 433.

In view of what we just reviewed in PTX 3097, does the proposed labeling for Yesafili recommend that doctors perform the method of Claim 6 for the treatment of DR and DME?

A. Yes. My opinion was yes.

Q. Let's turn to Question Number 2. We talked about it in the context of AMD already, about whether doctors will actually follow the recommendations in Yesafili's label in the event Yesafili is marketed.

Is your opinion the same for DME and DR?

A. Yes.

Q. And what was the answer to Question Number 2? Sorry.

A. The answer was yes, that there will be some doctors who will perform these methods.

Q. Does your opinion, again, relate to the way that doctors currently use Eylea?

A. Correct.

Q. Let's bring back up PTX 917 on the left and PTX 3097 on the right.

Dr. Csaky, does Regeneron recommend that doctors use Eylea to treat DME and DR in the same way that Mylan or Biocon recommends that doctors use Yesafili to treat DME and DR?

A. Yes. I see no difference.

Q. In view of that and in view of your testimony reviewing Mylan's label regarding -- excuse me. Let me try that again.

In view of your testimony that the Mylan or Biocon label recommends that doctors perform every method of Claim 6 for the treatment of DME and DR, is it also the case that Regeneron's label recommends doctors perform every step of the method of Claim 6 for DME and DR?

A. Yes.

Q. Let me ask again. Do doctors follow this label recommendation for treatment of DME and treatment of DR when they use Eylea?

A. Yes. As I said, you know, in certain circumstances, in certain patients, there are reasons that some doctors will use this approach for the treatment of diabetic macular edema and diabetic retinopathy.

Q. Have you personally used this method for the treatment of DME and DR?

A. Yes.

Q. Have you personally used the method of Claim 6 for the treatment of DME and DR?

A. Yes. I have tried -- I have treated patients with diabetic macular edema and diabetic retinopathy using an approach like this in some patients.

Q. And what are the circumstances that lead you to do that?

A. Well, you know, again, as we talked about at the very beginning, what's critical in diabetic macular edema is that

there's more VEGF that's usually present. And so, again, this idea that we want to give multiple injections more than we do for the neovascular AMD has been well-supported.

And so again, in certain cases where you really want to be able to communicate here's going to be our approach, it's very common to say we're going to try five injections at the very beginning, especially for someone with diabetic macular edema; and then, of course, if they respond well, then you want to start extending them to a longer period, like eight weeks.

In terms of diabetic retinopathy -- so again these are patients sometimes with both, and we know that, again, the alternative for diabetic retinopathy can be laser photocoagulation. It's a destructive procedure. And so for certain patients, they would prefer and my colleagues now are extending -- they're going more and more to using this type of approach for treating diabetic retinopathy in particular.

Q. So you said the alternative can be laser. How does that work?

A. So laser is a destructive procedure. It's basically a light, and you shine it into the eyes with patients with more advanced diabetic retinopathy. And it was shown 50 years ago that, if you destroy the retina -- surprising, but if you destroy the retina in the periphery, that causes some of that retinopathy to regress.

And while it's still in many ways a very effective

treatment for a lot of patients, again, you want to be able to offer patients alternatives. And so this approach of using a proven way to regress the retinopathy by using this approach is becoming an attractive option for patients.

Q. And just to be very clear, Dr. Csaky, you have used the method of Claim 6 to treat patients with DME and DR?

A. Yes. So in the past I have treated patients who have DME and DR, and in using this approach, it's been very effective.

Q. And just referencing back to Dr. Do's declaration, did she also explain that she and others have used the method of Claim 6 to treat patients with DME and DR?

A. Yes. And so that was -- again, I know Dr. Do very well, and I respect her thoughts and opinions. And so I used that as well to kind of confirm in addition to, you know, other discussions with other doctors and hearing about what their approaches have been, it was just another step that I used to help confirm and form my opinion that, again, some doctors in certain patients under certain conditions will use this approach.

Q. And you mentioned conversations with other doctors.

Have you had a chance to understand how the retinal community uses Eylea to treat DME and DR?

A. Yeah. In certain situations I've been on, you know, committees where we actually had some very intense discussions

about the utility of Eylea, especially -- again, in the community, Eylea -- especially for diabetic macular edema and its adjoining entity, diabetic retinopathy, there's been some actual evidence that in certain severe cases, Eylea seems to have a better efficacy. And so there's a fair amount of, I think, thought in the community that Eylea, for these types of conditions, again, is the best anti-VEGF drug out there.

MS. LESKO: Objection, Your Honor. I've been trying to give some leeway, but these opinions are going very far afield of the opinions that are in his report. I think he has one sentence in his report about how the community or doctors would prescribe Eylea.

THE COURT: Understood. It's overruled. That opinion's been disclosed, and as we discussed earlier, Dr. Do's declaration and other information is information upon which this witness has relied in forming an expert opinion. Overruled.

MS. KAYALI: Thank you, Your Honor.

BY MS. KAYALI:

Q. So, Dr. Csaky, I think we've now covered your experience and we've covered your conversations with other doctors about their experience. We talked about Dr. Do's declaration.

I want to just briefly mention, we talked earlier about the Gallivan article, right? Is the Gallivan article

limited to AMD?

A. Yes.

Q. Let's set that aside, then, and turn back to Question Number 2 on PDX 4034.

In view of your own personal experience, your conversations with colleagues, Dr. Do's declaration, what is your opinion as to whether some doctors will use Eylea in accordance -- excuse me. Try that again.

In view of your own personal experience, your own conversations with colleagues, and Dr. Do's declaration and the recommendations in the proposed Yesafili labeling, what is your conclusion as to whether some doctors will use Yesafili in accordance with its label to treat DME and DR and perform the method of Claim 6 if Yesafili is on the market?

A. Yeah. My conclusion that some doctors under certain circumstances will use these infringing methods was yes.

Q. Then let's turn to PDX 4.35. And, again, let's take a step back.

In view of your opinion that Mylan or Biocon's label recommends that doctors perform the method of Claim 6 to treat DME, DR and in view of your opinion that some doctors will, in fact, perform the method of Claim 6 in order to treat DME or DR as a result of those recommendations in the label, what is your opinion as to whether or not Mylan or Biocon will induce infringement of Claim 6 if they sell Yesafili?

A. My conclusion was that they will infringe on Claim 6.

Q. And I just want to be clear for the record. When you say "they will infringe on Claim 6," do you know that Mylan or Biocon will induce the infringement of Claim 6?

A. Yes. Yes, Mylan and Biocon will induce the infringement of Claim 6.

Q. Okay. We're really done with Claim 6 now.

We're going to move on to Claim 25 of the '572 patent. We're one down, three to go, but it gets faster from here.

Let's turn to page 25 of PTX 3.

Dr. Csaky, what does Claim 25 of the '572 patent require?

A. Yes. The 25 method is a method of Claim 15 -- so it's dependent on 15 -- wherein four secondary doses are administered to the patient.

Q. And let's bring back up PDX 4.36. Bring back up your slides and look at Slide 36.

Just like you did for Claim 6, have you assisted in preparing a slide that shows how every limitation of Claim 5 feeds into Claim 25 when it's rewritten in independent form?

A. Yes.

Q. So do you understand that we need to review each of these limitations in order to assess infringement of Claim 25?

A. Yes.

Q. Let's focus on the language of the rewritten independent form of Claim 25. And that's on PDX 4.36. And let's turn to the checklist form on PDX 4.37 -- excuse me -- PDX 4.38.

Dr. Csaky, we're going to -- again, I'm going to ask you to address the first of your two questions regarding infringement, which is whether Mylan or Biocon's label encourages, recommends, or promotes infringement of Claim 25. Okay?

A. Yes.

Q. What is the first requirement of Claim 25?

A. The first requirement is that it be method for treating diabetic macular edema.

Q. Let's bring back up PTX 3097.

Let me ask a familiar question, Dr. Csaky. Does Mylan or Biocon's label recommend that doctors use Yesafili to treat diabetic macular edema?

A. Yes. It specifically indicates -- says that it's indicated for the treatment of patients with diabetic macular edema.

Q. Can we check off the first box in Claim 25 suggesting that Mylan or Biocon's label recommends that doctors perform the first limitation of Claim 25?

A. Yes.

Q. Dr. Csaky, let's turn, then, to PDX 4039. What is

the next limitation of Claim 25 you'll analyze?

A. The next limitation is that there are a single initial dose of 2-milligram aflibercept be given.

Q. Let's bring back up PTX 3097.

Does the Mylan Biocon label instruct sequentially administering to the patient a single initial dose of 2 milligrams of aflibercept?

A. Yes.

Q. Where is that recommendation?

A. It says the recommended dose for Yesafili is 2 milligrams administered by intravitreal injection every four weeks for the first five injections.

Q. Okay. Same question as before. Which of those first five injections is the single initial dose?

A. The first one.

Q. So can we check off the box that Mylan -- the proposed labeling for Yesafili recommends that doctors perform the method of sequentially administering to the patient a single initial dose of 2 milligrams of aflibercept?

A. Yes.

Q. Let's turn to the next set of limitations. It's on PDX 4.40.

What is the next set of limitations you'll analyze for infringement?

A. The next set of limitations are the secondary doses,

2 milligrams to be administered every four weeks, and these are four secondary doses.

Q. You mentioned four secondary doses. Is that the last limitation of Claim 25 there?

A. Yes.

Q. That's a difference from Claim 6, right?

A. Yes.

Q. So let's bring back up the label, PTX 3097. After that first initial dose proposed -- does the proposed labeling for Yesafili recommend that doctors administer to patients, after the first single initial dose, one or more secondary doses of 2 milligrams of aflibercept wherein each secondary dose is administered to the patient by intravitreal injection approximately four weeks following the immediately preceding dose and wherein four secondary doses are administered to the patient?

A. Yeah. It explicitly says that, again, every four weeks for the -- every four weeks for the first five injections.

Q. And you said every four weeks for the first five injections. Which of those five injections correspond to the secondary doses of the claims?

A. The last four.

Q. So then how many secondary doses does the proposed labeling for Yesafili recommend?

A. Four.

Q. How frequently -- how often does Yesafili's label recommend that doctors administer those four secondary doses?

A. Every four weeks.

Q. So can we check off the box that Mylan's label recommends the secondary dose requirements of Claim 25?

A. Yes.

Q. Let's do that, then, and turn to the tertiary dose limitations.

What does Claim 25 require in terms of tertiary doses?

A. Yes. There are two requirements: 2 milligrams be provided, one or more, and that those be administered every eight weeks.

Q. Let's bring back up the label, PTX 3097, at page 1.

After the single initial dose and after the four secondary doses, does the proposed labeling for Yesafili recommend that doctors administer one or more tertiary doses of 2 milligrams of aflibercept wherein each tertiary dose is administered to the patient by intravitreal injection approximately eight weeks following the immediately preceding dose?

A. Yes. It says again under the dosage and administration, "followed by 2 milligrams via intravitreal injection once every eight weeks."

Q. Which of those injections once every eight weeks corresponds to the tertiary doses of the claims?

A. All of them.

Q. Any of them that are given?

A. Yes.

Q. So then can we check off the box that Claim 25 recommends the tertiary dose steps of Claim 25?

A. Yes.

Q. Let me try that again.

Can we check off the box that Mylan or Biocon's label recommends the tertiary dose steps of Claim 25?

A. Yes.

Q. Thank you.

What else is missing -- are we missing anything from Claim 25? What else does it require?

A. We don't miss -- everything's there.

Q. So then turning back to your question on PDX 4.43, what's the answer to Question Number 1? Does Mylan or Biocon's label recommend that doctors perform every step of the method of Claim 25 of the '572 patent and thereby infringe Claim 25 of the '572 patent?

A. In my opinion, the Mylan and Biocon label does encourage, recommend, or promote doctors to perform a method that infringes.

Q. And that's Claim 25, right?

A. That's Claim 25.

Q. So can we check off that box?

A. Yes.

Q. All right. Let's turn, then, to Question Number 2. Thinking back to your earlier testimony, Dr. Csaky, if Yesafili is marketed, will some doctors actually use Yesafili as its label tells them to and thereby perform the method of Claim 25?

A. In my opinion, yes.

Q. How do you know?

A. Again, similar to the evidence or the basis for my opinions in the previous discussions, you know, these are an approach that I have used in a patient or some patients. And, again, in discussion with my colleagues, we've also had discussions about these types of approaches.

And, again, very similar to the discussion we had last time about diabetic macular edema and the need for a series of injections, five injections, and knowing that that has the evidence base to give the best outcomes in some patients, some doctors will use this approach.

Q. And you mentioned the first five injections monthly. Do you also use the method where you switch to eight-week dosing after that?

A. Yes. That's very common. If a patient does well after those injections, as we talked about, you want to start to extend that interval. And what -- this label, based off the

trial data, suggests that you can do that safely.

Q. And so I just want to be very clear, Dr. Csaky. Have you used Eylea in a -- according to the method of Claim 25 to treat DME and DR?

A. Yes. In the past I have definitely used this method.

Q. And are you -- through your conversations with colleagues, are you aware that other doctors also use the method of Claim 25 in order to treat DME and DR?

A. Yeah. In fact, like I said, we've been on various committees about approaches to DME and how best to treat, especially more severe, DME. And this is an approach that I've had doctors talk to me about as a method, again, in some cases with some patients they've used.

Q. And that's with Eylea, right?

A. Yes.

Q. And let's take a look at -- again, at how Regeneron recommends doctors use Eylea and how Mylan or Biocon recommends doctors use Yesafili in order to treat DME. Actually, let me try that again.

Have we already looked at how Regeneron recommends that doctors use Eylea and compared it to how Mylan or Biocon recommends doctors use Yesafili in the context of DME?

A. We haven't done the comparison, no. You haven't showed me that.

Q. Oh. Well, then, let's take a step back because I

thought we did that in Claim 6, but we can certainly do it.

A. We did that in Claim 6, yes.

Q. Let's just take a look. Give me one moment.

Can we pull up PTX 917 on the left. And can we call out the highlights of prescribing information for DME and DR. And then put up PTX 3097 on the right and call out the same information.

So, Dr. Csaky, just to be very short, is there any difference in how Regeneron recommends that doctors use Eylea to treat DME and DR shown in PTX 917 on the left when compared with how Mylan or Biocon would recommend doctors use Yesafili to treat DME and DR on the right?

A. No.

Q. No difference?

A. No difference.

Q. Okay. So in view of the fact that we've just walked through your opinion that Mylan or Biocon's label recommends doctors perform the method of Claim 25, if doctors used Eylea according to the label, have they also performed the method of Claim 25?

A. Yes.

Q. So in your opinion, if doctors use Eylea according to the method of Claim 25 and if doctors will use Yesafili in the same way, does that inform your opinion as to whether some doctors will perform the method of Claim 25 using Yesafili?

A. Yes.

Q. And in the context of Claim 25, we mentioned that that last limitation, the four secondary doses, is different than Claim 6. I just want to be clear.

When you say you have used Eylea to treat patients with DME and DR according to the method of Claim 25, have you also done that four secondary doses step?

A. Yes. In certain cases where there is severe DME, you need five injections, multiple injections. And, again, having, as I said before, that confidence that five injections gets us to a good place both anatomically and visually is a nice approach to take in some patients.

Q. So you've performed the method of Claim 25 using Eylea in patients with DME and DR?

A. Correct.

Q. And when you say your colleagues have used the method of Claim 25 to treat DME and DR, that's also including that four secondary doses step, right?

A. Right. Right. That's again a very common challenge we have in diabetic macular edema, that in certain cases you need these multiple injections to get the retina to really respond.

Q. So your colleagues have -- you're aware that your colleagues have performed the method in DME and DR, the method of Claim 25?

A. Correct. As I said, when we talk about this -- the connection and how we approach these diseases, we want to be able to get -- especially in diabetic disease, we want to get it as responsive as possible. And so we really want to be able to ensure that we get good regression of the diabetic retinopathy and good resolution of the diabetic macular edema.

Q. Let's head back to your slide PDX 4.45.

THE COURT: Counsel, before we do that, are we at a good spot to break or do you have a couple more on this particular issue?

MS. KAYALI: I think we could close out this claim, Your Honor. That might be advisable, and then we can break.

THE COURT: I would concur. Go right ahead.

BY MS. KAYALI:

Q. Let's head back to PDX 4.45. Am I right, then, that your answer is -- or what is your answer to Question Number 2?

A. Yeah. The answer -- the opinion that I formed after reviewing all of the evidence that I was able to take in my own approach to patients with diabetic macular edema in particular and also my colleagues and their now approaches to diabetic macular edema and diabetic retinopathy, the answer to this was yes.

Q. So taking a step back, then, in view of claim -- excuse me -- Claim 25, in view of your opinion that Mylan or Biocon's label recommends that doctors perform the method of

Claim 25 and in view of your opinion that some doctors will, in fact, perform the method of Claim 25 as a result, have you formed an opinion as to whether or not, if Mylan or Biocon markets Yesafili, they will induce infringement of Claim 25?

A. Yes.

Q. And what did you conclude?

A. My conclusion was that Mylan/Biocon will induce infringement on Claim 25.

MS. KAYALI: With that, Your Honor, we've reached the end of the claim.

THE COURT: Understood. I jumped the gun a little bit. My apologies, Counsel.

We'll go ahead and take our midday break at this point. Let's be ready to pick back up at 1:00. That will give everybody here 40 minutes or so. We can resume then.

As I mentioned, I think yesterday, we do have a proceeding that we need to take up during our break. So if I could ask lead counsel at the trial tables just to stack some things up out of the way. That shouldn't take all but a minute or two, but we do need the courtroom for that.

Doctor, you remain on your own. They're permitted to feed you, and I hope that they do. But, otherwise, you're still without a country. Thank you, sir.

We'll stand at ease until 1:00. Thank you all very much.

(A recess was taken from 12:22 p.m. to 1:08 p.m.)

THE COURT: Doctor, are you ready to resume, sir?

THE WITNESS: Yes.

THE COURT: Could I ask you to pull that mic back down. There you go. Perfect.

All right. Counsel?

MS. KAYALI: Thank you.

BY MS. KAYALI:

Q. Dr. Csaky, let's pick up where we left off. I think we ended with Claim 25. So I've got Slide 45 up here.

And am I right that you had answered yes to Question Number 2? In your opinions, at least some doctors will perform the method of Claim 25 in administering Yesafili to treat DME in accordance with Claim 25 as a result of Mylan's label?

A. Yes.

Q. As a result of that opinion, did you conclude that Mylan will, in fact, induce infringement of Claim 25?

A. Yes. My opinion was that Mylan will induce infringement on Claim 25.

Q. Okay. Let's turn to Claim 11. We're two down, two to go. And we're turning to the '601 patent.

Dr. Csaky, this is PTX 1. Do you recognize this document?

A. I do.

Q. And what is it?

A. This is the U.S. patent -- and we're going to call this the '601 patent -- for the use of VEGF antagonists to treat angiogenic eye disorders.

Q. In the course of your work on this case, have you reviewed the '601 patent in full?

A. I did.

Q. Let's go take a look at the first of the asserted claims in the '601 patent. That's Claim 11. This is page 21 of PTX 1.

What does Claim 11 of the '601 patent require?

A. Claim 11 again is a dependent claim. And it is dependent on the method of Claim 10, but in and of itself it has a limitation with an approximately every four weeks, comprising approximately every 28 days or approximately monthly.

Q. Let's bring up your slides again and compare this to PDX 4.46. Dr. Csaky, just like for the last two claims, do you understand that Claim 11, because it depends from Claim 10, therefore incorporates all the limitations of Claim 10?

A. Yes.

Q. And just like before, have you made a slide that attempts to rewrite Claim 11 in independent form?

A. Yes. Correct.

Q. So we're going to focus on the independent form of

Claim 11 in assessing infringement.

Let's turn to some familiar questions on PDX 4.47.

Dr. Csaky, in the context of Claim 11 we're going to march through the same two questions we have all day. And the first one of those is does Mylan or Biocon's label encourage, recommend, or promote doctors to perform methods that infringe Claim 11 of the '601 patent?

So let's jump in, PDX 4.48. Dr. Csaky, what is the first limitation of Claim 11 of the '601 patent that you analyzed?

A. The first limitation is a method for treating diabetic macular edema.

Q. Let's pull up PTX 3097.

Dr. Csaky, does Mylan's or Biocon's proposed labeling for Yesafili, PTX 3097, recommend that doctors use Yesafili in a method for treating diabetic macular edema in a patient in need thereof?

A. Yes.

Q. Where does it do that?

A. Yes. It says under indications and dosage you can clearly see that Yesafili is indicated for the treatment of patients with diabetic macular edema.

Q. We're looking at page 1 of PTX 3097. And, Dr. Csaky, I think I heard you say indications and dosage. Is that the title of this section?

A. Yes.

Q. Do you see the words "indication and usage"?

A. I'm sorry. Indications and usage, right.

Q. So the recommendation that Mylan -- or excuse me. The recommendation in PTX 3097 that doctors use Yesafili to treat a patient in need of treatment for diabetic macular edema, that's in the indications and uses section on PTX 3097, page 1, right?

A. Yes.

Q. Can we check off that box, then? Can we check off that Mylan's label or Biocon's label recommends that doctors perform the first step of the method of Claim 11?

A. Yes.

Q. Let's go to the second one. What are we looking at here?

A. Right. So there are now two limitations here. One is that there's an effective amount of aflibercept, which is 2 milligrams. And it's approximately every four weeks for the first five injections. And then there's a further stipulation that this approximately every four weeks comprises approximately every 28 days or approximately monthly.

Q. Let's pull PTX 3097 back up.

Dr. Csaky, does PTX 3097, proposed labeling for Yesafili, recommend that doctors administer Yesafili intravitreally in an effective amount of aflibercept, which is

2 milligrams approximately every four weeks, for the first five injections?

A. Yes.

Q. Where does it make that recommendation?

A. In the very first bullet point, the recommended dose is 2 milligrams administered by intravitreal injection every four weeks for the first five injections.

Q. The claim states an effective amount of aflibercept which is 2 milligrams. Do you see that?

A. Yes.

Q. Is that an effective amount -- is 2 milligrams an effective amount of aflibercept?

A. Yes.

Q. How do you know?

A. We know that from both multiple clinical trials as well as our own clinical experience.

Q. And the first five injections that are recommended in the proposed labeling for Yesafili, how frequently does Yesafili's label recommend that those be given?

A. Those -- on the label it's approximately every 28 days, or monthly, four weeks.

Q. So when Yesafili's label recommends that doctors administer Yesafili every four weeks (approximately every 28 days, monthly) for the first five injections, does Yesafili's proposed label recommend that doctors meet that final

limitation of Claim 11 wherein approximately every four weeks comprises approximately every 28 days or approximately monthly?

A. Yes.

Q. Let's turn back to PDX 450.

Excuse me, Dr. Csaky. I should have asked you.

Can we check off those boxes --

A. Yes.

Q. -- for the first five injections being administered approximately every four weeks, approximately every 28 days, or monthly?

A. Yes, we can check those off.

Q. All right. What's the next limitation you addressed?

A. The last limitation is that it be followed by 2 milligrams approximately once every eight weeks, or once every two months.

Q. Let's bring back up the label. That's PTX 3097.

Dr. Csaky, does the proposed labeling for Yesafili recommend that doctors, after those first five injections, administer Yesafili in 2-milligram doses approximately once every eight weeks, or once every two months?

A. Yes, it says that specifically under dosage and administration, followed by 2 milligrams via intravitreal injection once every eight weeks, or two months.

Q. So can we check off the method -- excuse me -- that the limitation requiring 2 milligrams approximately once every

eight weeks, or once every two months, is satisfied?

A. Yes.

Q. Looking at PDX 4051, Dr. Csaky, what else does Claim 11 require?

A. Nothing else.

Q. Have we caught all the limitations?

A. Yes.

Q. Does Mylan or Biocon's label recommend that doctors perform them all?

A. Yes.

Q. So turning back to your questions, let's look at PDX 4.52. What's the answer to Question Number 1? Does Mylan or Biocon's label encourage, recommend, or promote doctors to infringe Claim 11 of the '601 patent?

A. Again, in my opinion, the answer to that first question is yes.

Q. Let's talk about Question Number 2.

Dr. Csaky, you've spent quite a bit of time, I think, explaining in your opinion how -- how doctors use Eylea and how doctors will use Yesafili.

In your opinion, if Mylan or Biocon markets Yesafili with the label that's reflected in PTX 3097, will some doctors actually do what that label says and use Yesafili to perform the method of Claim 11?

A. Yes. In my opinion, there will be some doctors in

some situations who will perform that method.

Q. And is that substantially for the reasons which you've already explained?

A. Correct.

Q. Now, the final limitation of Claim 11 requires that the first -- wherein approximately every four weeks comprises approximately every 28 days or approximately monthly. When you were describing your practice and the practice of other physicians with whom you've spoken and explaining that they use methods of treating patients with DME using Eylea with five monthly injections followed by every-eight-week dosing, do you or do those doctors administer those five monthly doses approximately every 28 days, or approximately monthly?

A. Yes. I would say that we often do this approximately every 28 days.

Q. Or approximately monthly?

A. Or approximately monthly, correct.

Q. Let's take a look quickly at the Eylea label compared to the Yesafili label. And we're going to put PTX 3097 on the right here and PTX 917 on the left.

Does the Eylea label contain language regarding administering the first five injections approximately every 28 days, or approximately monthly?

A. Yes.

Q. And so if physicians follow the Eylea label, do they

administer the first five injections approximately every 28 days, or approximately monthly?

A. Yes. In some cases, they do.

Q. So when they follow the label, they do that. And in your opinion, do some people do that?

A. Yes.

Q. So does the Eylea label also recommend that doctors use Eylea to treat DME according to the method of Claim 11?

A. Yes.

Q. Well, then, let's see if we can turn to Question Number 2. That's Slide 54 -- let's back up one -- excuse me -- slide 53.

Dr. Csaky, you have your own experience with Eylea that you've described. In view of your conversations with colleagues about how they use Eylea, what is your opinion as to whether, if Yesafili is marketed, some doctors will administer Yesafili according to the recommendations in its label and thereby infringe Claim 11?

A. Yes, my opinion is that there will be, again, some doctors who will perform this method as described.

Q. Let's take a step back on Claim 11, then.

In view of your opinion that Mylan or Biocon's label recommends that doctors perform the method of Claim 11 and in view of your opinion that some doctors will, in fact, perform the method of Claim 11 as a result, have you formed an opinion

as to whether or not Mylan or Biocon will induce infringement of Claim 11 if they sell Yesafili?

A. Yes.

Q. What did you conclude?

A. Yes, in my opinion, Mylan/Biocon will infringe on Claim 11 by marketing Yesafili.

Q. And just so the record is clear, when you say infringe, do you mean induce infringement?

A. Induce infringement.

Q. Okay. Dr. Csaky, we are three claims down and one to go.

Let's turn to the final asserted claim. And that's Claim 19 of the '601 patent. What does Claim 19 of the '601 patent require?

A. So, again, we have this dependency on Claim 18. And in and of itself Claim 19 requires that these injections be given approximately every four weeks, comprising approximately every 28 days or approximately monthly.

Q. And just like the last three times, have you compiled all the limitations of Claim 19, including the incorporated limitations of Claim 18, into a single slide?

A. Yes.

Q. Let's take a look at that. That's PDX 455. Let's go straight to your questions now, PDX 4056.

Dr. Csaky, this is probably going to sound familiar,

but our first question is does Mylan or Biocon's label encourage, recommend, or promote that doctors perform methods that infringe Claim 19 of the '601 patent?

A. Yes. In my opinions, it does.

Q. Let's take a look at that. It's PDX 4057.

Dr. Csaky, what is the first limitation of Claim 19?

A. The first limitation is treating diabetic retinopathy.

Q. Is that an indication we've discussed already today?

A. Yes.

Q. So in your opinion, Dr. Csaky, does the proposed labeling for Yesafili, PTX 3097, recommend that doctors use Yesafili in a method for treating diabetic retinopathy in a patient in need thereof?

A. Yes.

Q. Let's take a look. PTX 3097, where is that recommendation?

A. It says specifically that Yesafili is indicated for the treatment of patients with diabetic retinopathy.

Q. And that's on page 1 under the indications and usage section?

A. That's on indications and usage section.

Q. So can we check off the box, then, that the proposed labeling for Yesafili recommends this first step of Claim 19?

A. Yes.

Q. What's the next step of Claim 19?

A. The next step is a two-part step, again where it says intravitreally administering aflibercept to patients every four weeks for the first five injections and that this four weeks comprise approximately every 28 days or approximately monthly.

Q. Let's pull back up PTX 3097.

Dr. Csaky, does the proposed labeling for Yesafili recommend doctors intravitreally administer to a patient an effective amount of aflibercept, which is 2 milligrams, approximately every four weeks for the first five injections to treat DR?

A. Yes. It explicitly states that Yesafili is to be administered intravitreally every four weeks, approximately between 28 days, monthly for the first five injections.

Q. That's on page 1 of PTX 3097 under "Dosage and Administration"?

A. That's under the "Dosage and Administration."

Q. And I just want to make sure we hit every point of that.

Does the recommendation recommend 2 milligrams?

A. 2 milligrams.

Q. And for the first five injections, are those recommended to be given every four weeks?

A. Yes, every four weeks, approximately every 28 days, monthly.

Q. Let's turn then -- pardon me. May we check off those boxes, then? Have you concluded that Mylan or Biocon's label recommends both of these steps of the steps shown on PDX 4058?

A. Yes.

Q. What's the last limitation you'll address today, Dr. Csaky, of Claim 19?

A. The last limitation is that the 2-milligram dose be given approximately once every eight weeks, or two months, following the first five injections.

Q. Well, let's pull back up PTX 3097.

Does the proposed labeling for Yesafili recommend that doctors treat patients with diabetic retinopathy using 2-milligram doses approximately once every eight weeks or two months after the first five injections?

A. Yes.

Q. Where does it make that recommendation?

A. Under "Dosage and Administration," it says followed by 2 milligrams via intravitreal injection once every eight weeks, two months.

Q. That's on PTX 3097, page 1, right?

A. Yes.

Q. So, Dr. Csaky, can we check off that last limitation shown on PDX 4059?

A. Yes.

Q. Dr. Csaky, what else does Claim 19 require?

A. Nothing. It does not require anything else.

Q. So let's head to PDX 461.

Turning back to your questions, can we answer Number 1? In your opinion, does Mylan or Biocon's label encourage, recommend, or promote doctors to infringe Claim 19 of the '601 patent?

A. Yes. In my opinion, Mylan/Biocon label does encourage, recommend, or promote these methods that will infringe.

Q. Now, let's turn to Question Number 2.

Dr. Csaky, this is about diabetic retinopathy, right? This claim?

A. Yes.

Q. And you testified earlier that you have personally and others have performed the method of Claim 19 in the context of treating diabetic retinopathy?

A. Yes. In the context, I've treated patients with diabetic macular edema and diabetic retinopathy.

Q. You've treated them in a method of Claim 19 where you administer intravitreal 2-milligram doses approximately every four weeks for the first five injections followed by 2 milligrams approximately once every eight weeks or two months wherein approximately every four weeks comprises every 28 days or approximately monthly?

A. Yes.

Q. Okay. And in conversations with other doctors, as you've testified earlier, do they also perform that method?

A. Yes. As I said, there's been more and more interest in using anti-VEGF in particular for diabetic retinopathy, especially if it's more severe, in certain cases where the alternative is laser photocoagulation. So there's more and more interest in using this approach, and so I've had physicians -- we've talked about the utility of this approach in treating these types of patients, and they claim that they are using this approach.

Q. And I know we spent a lot of time talking about those first five injections being administered monthly. I just want to make sure, when you're thinking back on that testimony when you spoke about those first five injections being administered monthly -- excuse me -- every four weeks, were those doses administered approximately every four weeks where that comprises approximately every 28 days or approximately monthly?

A. Yes.

Q. Let's pull up the comparison of the labels one more time here. That's PTX 917 on the left, PTX 3097 on the right.

Dr. Csaky, does Eylea's label also recommend that, when doctors administer intravitreal injections every four weeks for the first five injections, they do so approximately every 28 days or approximately monthly?

A. Yes.

Q. So when doctors administer Eylea according to the label for the treatment of diabetic retinopathy, do doctors perform the method of Claim 19?

A. Yes.

Q. And does that inform your opinion as to whether, if doctors -- if Yesafili is marketed with the label that we see at PTX 3097, some doctors will use Yesafili in exactly the same way?

A. Yes.

Q. So let's turn back to Question Number 2. That's on PDX 464 -- excuse me -- PDX 462.

Dr. Csaky, can we answer Question Number 2 at this point?

A. Yes.

Q. In your opinion, if Mylan or Biocon markets Yesafili with the label containing the recommendations in PTX 3097, will some doctors actually follow those recommendations and perform the method of Claim 19?

A. Yes, some doctors will follow that label and infringe on the methods.

Q. So then let's switch to PDX 463, and let's take a step back one last time.

In view of your opinion that Mylan or Biocon's label recommends that doctors perform the method of Claim 19 and in view of your opinion that some doctors will, in fact, perform

the method of Claim 19 if Yesafili is marketed, have you formed an opinion as to whether or not Mylan or Biocon will induce infringement of Claim 19 if they sell Yesafili?

A. Yes. My opinion is that Mylan or Biocon will induce infringement on Claim 19 if they market Yesafili.

Q. Okay. Dr. Csaky, we've made it through the claims, and we're nearly done. I want to touch on just two things briefly.

Thus far, your testimony about how Mylan or Biocon intends doctors to use Yesafili has been based on the proposed Yesafili labeling, right?

A. Yes.

Q. And was that proposed labeling enough for you to draw your conclusions about infringement?

A. Yes.

Q. Nevertheless, in the course of your work on this case, did you come across additional evidence of how Mylan or Biocon intends for doctors to use Yesafili?

A. Yes.

Q. Let's bring up PTX 331.

Dr. Csaky, what is this document?

A. So this is the first slide of a presentation that Dr. Susan Bressler at the American Academy of Ophthalmology where she is summarizing the INSIGHT study with Mylan 1701P, which we can now call Yesafili. And as you can see the title,

this is a proposed biosimilar to aflibercept, and she is outlining the outcomes from the Phase III study.

Q. Is this the document that also -- excuse me. Strike that.

I think you may have said this, but where did Dr. Bressler present this presentation?

A. At the very bottom it says AAO. The AAO is the American Academy of Ophthalmology.

Q. Who attends AAO?

A. It's the largest ophthalmology meeting in this country at least, and all general ophthalmologists, retina specialists will attend the American Academy of Ophthalmology meeting.

Q. So if a company wants to inform ophthalmologists about how to use a prospective drug, is this a place to do it?

A. This is the one place where you can disseminate information and share the results of data with the community.

Q. This is a Phase III study, right?

A. Correct.

Q. Did Mylan do any additional Phase III studies?

A. Not that I'm aware of.

Q. What indication is this about?

A. This indication is for diabetic macular edema.

Q. Let's take a look at page 5 of the slide deck.

What regimen did Mylan test and did Dr. Bressler

present in this study?

A. I think what you have to look under, you see at the very bottom -- I'm not trying to do this -- so here is the regimen that they're recommending -- not recommended -- they did for the trial. And you can see that, essentially, there was an injection -- all these needles being injections -- there's an injection at baseline, and then the injections are done every four weeks. So five injections monthly to begin with, and then there's a transition, you can see, from there to the 20 four-month injection going forward.

So the -- it's essentially a five loading doses and then transitioning to every eight weeks.

Q. So does this regimen reflect the regimen of at least Claims 6 and 25 of the '572 patent and Claim 11 of the '601 patent?

A. Yes.

Q. I see a note there at the end it says "with Q4w optional doses."

Do you see that yellow text?

A. Yes.

Q. What does that mean?

A. So this is not uncommon in a clinical trial. When you are assessing a drug and you want to make sure that there's safety, these patients are seen every month, and there's typically what's termed "rescue criteria," which means if they

are not doing well, they'll receive either an additional injection or some other modality.

So that's not a required injection. It's simply to indicate that these were times when patients were evaluated and, if they did not meet -- say the vision did not get better, they didn't get more swelling, they were not treated.

Q. So just to be clear, were those q4 optional doses given to every patient in the study?

A. No. So this was only those patients who met these criteria and needed, for example, another injection based on prespecified reasons.

Q. Did many patients in this study, in fact, receive the methods of Claim 6, 25, and 11 where they got five monthly loading doses followed by q8 dosing?

A. Yes. My understanding is that the vast majority of patients who went through that regimen.

Q. Let's turn to the last slide in Dr. Bressler's presentation. That's PTX 331, page 12.

Looking at the top of the slide, Dr. Csaky, what, if anything, is Dr. Bressler, on behalf of Mylan, telling doctors about how to use Yesafili?

A. Well, what Dr. Bressler is communicating -- there's the conclusions, and what she's demonstrating here is that the INSIGHT study demonstrated therapeutic equivalence. Again this is now -- we're going to call this Yesafili and aflibercept in

the treatment of diabetic macular edema. And then she goes on to say why, and she goes on to talk also about the bottom safety of the drug as well, and that was very similar to Eylea.

Q. And so just to make the record clear, MYL-1701P, I think you said that was Yesafili, right?

A. My understanding is that's Yesafili.

Q. And the reference to aflibercept there, is that a reference to Eylea?

A. That's my understanding.

Q. So if we look at the very bottom green box there, "Following regulatory approval, MYL-1701P is expected to be a new treatment option for patients with DME."

What, if anything, is Mylan telling doctors about what to do with Yesafili if and when it gets approved?

A. Well, I think here what's being communicated is that following approval, essentially, as we review her conclusions, the fact that there was therapeutic equivalence and safety equivalence, I think the ophthalmologists, in seeing this presentation, that their interpretation would be that I can use Yesafili essentially in an identical way that I'm using Eylea in the treatment of DME.

Q. And the regimen that Dr. Bressler recommended in this study -- or described in this study, that's the method of Claim 6, 25, and 11, right?

A. That's correct.

Q. Let's turn back one last time to PTX 3097.

I want to talk briefly, Dr. Csaky, about a portion of the Mylan or Biocon label we haven't looked at yet today. In the upper left-hand corner, I see some highlighted language right under the prospective approval date. It reads, "Yesafili (aflibercept-jbvf) is interchangeable with Eylea (aflibercept)."

Do you see that?

A. Yes.

Q. What does that mean to an ophthalmologist?

A. Again, for an ophthalmologist who's reading this, it's essentially telling us that the two drugs are the same.

Q. How is it telling doctors they can use Yesafili?

A. Well, it's essentially indicating that we would then, like you said, look at the label, and the label would then instruct us on how to use it. But even with this statement alone, the thinking of the ophthalmologist would be that I can essentially exchange and use Yesafili in the exact same fashion that I'm using Eylea in the clinic.

Q. And then finally, if we turn to some language in the bottom right of the highlights of the prescribing information -- so we're still on page 1 -- do you see the highlighted language stating that "There are no clinically meaningful differences between the products and it" -- Yesafili -- "can be expected to produce the same clinical

result as the referenced product" -- Eylea --

A. Yes.

Q. -- "in any given patient"?

A. Yes.

Q. What does that language alone tell you about how Mylan or Biocon intends for doctors to use Eylea?

A. Yeah. Again, this is communicating to ophthalmologists that the two drugs are the same.

Q. And how does it communicating to doctors that you can use those two drugs?

A. Because it's indicating it is expected to produce the same clinical result as the reference product. In this case the reference product was Eylea. So it's explicitly telling the ophthalmologist that, when you use it, you can expect the exact same clinical result.

Q. So is that an instruction that you can use Yesafili in the exact same way you can use Eylea?

A. Yes.

Q. Do you need to look at anything else in the label to know whether Mylan is -- Mylan or Biocon is telling you to use Yesafili in the exact same way as you use Eylea?

A. For the ophthalmologist who sees only this, I think the average ophthalmologist would read this and interpret it as saying these two drugs are essentially the same.

Q. And you can use them the same way?

A. And you can use them the same way.

Q. And just to close things off, does that new Biocon label we reviewed, PTX 3338, have you had an opportunity to confirm whether it contains the same language here?

A. Yes.

Q. And does it?

A. It does.

MS. KAYALI: One moment, please.

With that, Your Honor, we pass the witness.

THE COURT: Counsel, cross.

MS. LESKO: Your Honor, we have a couple of binders for cross. May we pass them up?

THE COURT: Permission granted. I'd be disappointed if there weren't binders.

MS. LESKO: May I proceed, Your Honor?

THE COURT: You may. Go right ahead, Counsel.

CROSS-EXAMINATION

BY MS. LESKO:

Q. Good afternoon, Dr. Csaky.

A. Good afternoon.

Q. I'm Ms. Lesko.

Dr. Csaky, you just offered a lot of opinions about my clients. But let's be clear, you do not contend that Mylan or Biocon directly infringed the asserted '572 or '601 patents, right?

A. Correct.

Q. Dr. Csaky, do you recall participating in a roundtable discussion at a Retina Society meeting in Washington, DC, on October 5th, 2012?

A. I do not recall that.

Q. Let me try to help refresh your recollection.

If you can please open your binder, there should be a document in the front pocket that is without a tab.

A. Uh-huh.

Q. It should be an article titled "Treating the Patient," dated January 1st, 2013. We'll put that up on the screen as well.

This article is described as highlighting a roundtable discussion during the Retina Society meeting.

Do you see your name there on the first page?

A. I do see my name.

Q. It indicates you were one of the participants?

A. Correct.

Q. Does this help you confirm that you were a participant in the roundtable discussion?

A. Yes, it does confirm that I was part of the roundtable discussion.

Q. Let's go to page 2 of this document. I'd like to direct your attention to the second full paragraph from the bottom.

Do you see the statement attributed to you that says, "Dr. Csaky: There is no set guideline that is applicable to a majority of patients with wet AMD. When is persistent fluid bad? I may tolerate a little subretinal fluid that remains despite several reinjections more than intraretinal fluid which has been shown in the CATT study to be associated with more severe vision loss. It is those variations that necessitate individualized decisions. I am finding there is no one-size-fits-all treatment."

Did you make that statement before your peers?

A. I did make that statement before my peers.

Q. Is it true for you today that, when it comes to treating your patients, there is no one-size-fits-all when treating patients with VEGF inhibitors?

A. That's correct. I mean, every patient requires -- as I mentioned earlier, that there is a whole range of decisions that you have to make in deciding what's the best treatment for that individual.

Q. Let's move to another statement attributed to you at the Retina Society roundtable, which appears at the top of this document, page 6. We'll put that up on the screen.

Do you have that?

A. Yes.

Q. Did you make the statement "That is what has surprised me the most, the number of patients who need

injections every six weeks or even every five weeks instead of every two months. We have seen very inconsistent results with that two-month window in our practice."

A. Yes, I made that statement.

Q. Okay. Let's talk about another time when you discussed the topic of settling on an anti-VEGF dosing regimen.

In around 2013 did you participate in a discussion about settling on an anti-VEGF discussion dosing regimen?

A. I'm sure you're going to tell me I did.

Q. If you want to flip to the back of your binder, there should be an article in the back pocket.

THE COURT: Feels like a safe assumption, Doctor. Go ahead. Feels like a safe assumption. Go ahead.

THE WITNESS: I'm starting to remember all these things. Yes. Go ahead.

BY MS. LESKO:

Q. So does that help refresh your recollection?

A. It does help refresh my recollection.

Q. And this is a review of *Ophthalmology* article titled "Settling on an Anti-VEGF Dosing Regimen" dated August 5th, 2013?

A. That's correct.

Q. It's directed to "Current options for anti-VEGF treatment, including continuous treatment at a fixed interval, prn treatment, and a treat-and-extend strategy."

Do you see that?

A. That's correct.

Q. Let's go to the third page of this exhibit.

A. Third page.

Q. Towards the middle of the page, do you see some quotes attributed to you?

A. Correct. The third paragraph is where I say some comments.

Q. I'd like to direct your attention to the first sentence, which states that "Karl Csaky, MD, PhD, of the Retina Foundation of the Southwest in Dallas, says, 'The challenge is that the three agents typically used all have very similar pharmacokinetics and durability, plus or minus a week or so.'"

Is that right?

A. Correct.

Q. You were also quoted in the second sentence of that paragraph as saying, "One confounding problem is that there appears to be an individualized durability interval that each patient demonstrates."

Correct?

A. Correct.

Q. In the third sentence, did you then explain, "It becomes a question of what strategy you use to dial in that sweet spot between injections and find out whether they are, for example, a five-weeker or a six-weeker."

Is that what you said?

A. Correct.

Q. Is it still true for you today that, when it comes to your patients, that you have to dial in that sweet spot between injections to find the correct dosing interval?

A. Yes. For a significant number of patients, it's important to try to figure out what's best for them. That's correct in the majority of patients.

Q. Let's move along in this third page of the article "Settling on an Anti-VEGF Dosing Regimen." We'll pull that up -- it up on the screen for you as well.

It's the one that starts with "he also notes that choosing a treatment strategy."

Do you see it in your paper exhibit?

A. Yes. "One confounding problem." Is that what we're talking about?

Q. There it is.

A. "He also notes." Perfect. "He also notes," yes.

Q. Were you quoted as saying that "So if it is the only good seeing eye, then you might want to be a little bit more aggressive with the interval. At the interval after which such an eye demonstrates recurrent fluid, we might want to have the patient come back even every four weeks just to be absolutely sure that we don't put them at risk for a bleed. That is the major catastrophic event that we want to avoid."

That's what you said, right?

A. Correct.

Q. And even today, do you believe that choosing a treatment strategy also depends somewhat on the status of the eye?

A. Yes, absolutely. So as we talked about, what we want in our armamentarium, right, is a host of approaches. There's some that we go to for sure and, depending on if it's the first eye or the second eye, what the vision in the first eye is versus the second eye, these are all various kind of considerations in making these treatment decisions.

Q. Let's turn back to the second page, if you will.

A. Sure.

Q. Towards the middle of the page it says, "Treat and extend is a more customized approach to treatment."

A. Yes.

Q. Do you agree with that?

A. It is a more customized approach to -- than other approaches, yes.

Q. Okay. We can pull that down.

Dr. Csaky, we can agree that you understand the Yesafili label instructs four alternative wet AMD regimens, one RVO regimen, and two alternative DME and DR regimens, right?

A. So we have one neovascular -- let me make sure. One neovascular AMD, one RVO, and one diabetic retinopathy and

diabetic macular edema protocol. That's what they recommend, correct.

Q. No, my question was slightly different.

Do you understand that the Yesafili label instructs four alternative wet AMD regimens?

A. My understanding is it doesn't recommend four alternatives; it recommends one.

Q. Right. But my question was asking about whether the label instructs for alternative regimens.

A. I think you said "recommend," and if it instructs, that's different.

Q. If I did, I apologize. So I'll ask it again just so it's clear.

We can agree that you understand the Yesafili label instructs four alternative wet AMD regimens, one RVO regimen, and two alternative DME and DR regimens, right?

A. Right. I guess I would use the term "describes," right? Instructs -- yeah, I mean, we can call it -- it tells how to do it.

Q. Okay. Just to make it easier, why don't we take a look at DTX 2028, exhibit page 24, in your binder?

A. 2028. Sure.

Q. Which is your March 30th, 2023, reply report.

A. Yes.

Q. I'd like to direct your attention to the top of this

page, and we're on page 24. It's also up on your screen, if that's easier.

A. Is it DTX 24? Are you using the bottom, not the actual page of the document?

Q. That's correct. DTX 24.

A. Okay. Yes, please.

Q. Looking at the top of this page, which is a part of your reply report, paragraph 43 -- and we have it up on the screen for you.

A. Yes.

Q. In your report did you give the opinion, "Far from offering 11 alternative dosage regimens for one indication, as Dr. Russell's language suggests, the labels instruct four alternative wet AMD regimens, one RVO regimen, and two alternative DME DR regimens"?

A. Right.

Q. Next let's pull up DTX 3311, the Eylea labeling.

A. DTX -- I'm sorry. Say that again.

Q. 3311.

A. 3311. Okay.

Q. Page 1. I'd like to take a look at a new indication that was recently put into the Eylea labeling under the dosage and administration section at the top in the right column that is titled "Retinopathy of prematurity, ROP."

A. Correct.

Q. Do you have that?

I would like to direct your attention to the recommended dose for retinopathy of prematurity which is 0.4 milligrams, 0.01 milliliters, or 10 microliters, administered by intravitreal injection.

Do you see that?

A. I do see that.

Q. Can you confirm that, for retinopathy of prematurity, the dosing regimen on the label calls for treatment that may be given bilaterally on the same day, injections may be repeated in each eye, that treatment interval between doses injected into the same eye should be at least ten days?

A. Yes.

Q. Next let's pull up PTX 3338. This is the proposed Yesafili labeling, 3338.

A. Have to get to the back of the binder here. Just a second.

Okay. All right. Very good.

Q. Do you have it?

A. I have it now.

Q. And, again, I would like to direct your attention to the dosage and administration section on the first page.

A. Yes.

Q. We also have it up on your screen.

A. Uh-huh.

Q. We can agree that the phrase "isotonic solution" is not in the dosage and administration section, right?

A. I didn't -- again, I did not opine on anything to do with isotonic solution; so I didn't review the label for that term.

Q. And on your direct examination, you did not opine that the phrase "isotonic solution" appears anywhere in the Yesafili label, correct?

A. I can't recall. But if I did, then I did not see it.

Q. Well, let's take a look at the text in the Yesafili label under the heading "Macular Edema Following Retinal Vein Occlusion, RVO."

A. Yes.

Q. For RVO it states that the recommended dose for Yesafili is 2 milligrams, 0.05 milliliters, administered by intravitreal injection once every four weeks, approximately every 25 days, monthly. Agree?

A. Yes.

Q. Can we agree that an only monthly dosing regimen here in the label is not any kind of eight-week dosing regimen?

A. Correct. For macular edema following retinal vein occlusion, there's no recommendation for extending the dose.

Q. Right. And a monthly dosing regimen is different from an eight-week dosing regimen, right?

A. Correct.

Q. Looking at the DME and DR heading that is titled "Diabetic Macular Edema, DME, and Diabetic Retinopathy, DR," do you have that?

A. I see that, yes.

Q. Let's look at the second bullet under DME/DR, last full sentence. We have it up on the screen as well. It says, "Some patients may need every-four-week, monthly, dosing after the first 20 weeks, five months," correct?

A. That's what it states, yes.

Q. Let's look at the AMD section. Are you there?

A. Yes. I see it right above it, yeah.

Q. And this is under the heading titled "Neovascular (wet) age-related macular degeneration, AMD." I would like to first direct your attention to the second bullet, last sentence. We can agree that it says, "Some patients may need every-four-week, monthly, dosing after the first 12 weeks, three months," yes?

A. Yes, we can agree.

Q. If we move to the third bullet under the AMD dosing and administration instructions in the Yesafili labeling, can you confirm it states, "Although not as effective, patients may be treated with one dose every 12 weeks"?

Correct?

A. Correct. After one year of -- after one year -- every 12 weeks after one year of effective therapy.

Q. And when we were talking about that 12-week dosing interval, we can agree that it is not the approximately eight-week dosing interval that is called for by Claim 6 of the '572 patent, right?

A. That's correct. That's not in the '572 patent.

Q. And we can agree that a four-week (monthly) dosing regimen is not an eight-week dosing regimen, right?

A. I'm sorry. Repeat that again. The four-week dosing schedule --

Q. The four-week (monthly) dosing regimen is not an eight-week dosing regimen?

A. That's true, yes.

Q. And we can also agree that an every-12-week regimen is not an eight-week regimen?

A. Yes.

Q. Dr. Csaky, can we agree that the various dosing regimens discussed in the Yesafili labeling that relates to dosing for CRVO, DME, DR, or AMD that is just monthly will not satisfy any of the asserted claims of the '601 and '572 patents?

A. So the monthly loading doses are within the claims, correct. And your question is if you go beyond the loading doses, correct?

Q. Correct.

A. So yes, if they go beyond the loading doses as

outlined -- now, it does say -- I'm not sure because it does say -- can you just refresh my memory on the -- you said the '572 patent?

Q. Yes. The asserted patent in this case.

A. Right. So can I just look at that real quickly?

Q. Can you answer this question first, and then we'll go back to that later.

A. Well, because I think you're asking does monthly dosing not apply to the '572. Is that what you asked?

Q. I'm just asking about the asserted claims of the '601 and '572 patents.

A. And I'm just trying to remember off the top of my head. And we can get to that. But I just want to make sure I understand because -- I may be wrong. I thought in the loading -- I thought in the -- it says one or more -- I just have to look at the '572 to be absolutely sure.

Q. Sure. Can we pull up the '572 patent, please.

A. I may be misremembering. I'm sorry. There's so many claims and such.

THE COURT: Agreed, Doctor.

THE WITNESS: Yeah, if you're confused, I'm confused. Okay.

BY MS. LESKO:

Q. And let's look at Claims 1 through 6 if we can pull that up. It should be in your binder as well, Dr. Csaky. It's

PTX 3, if you want to --

A. PTX? I'm sorry.

Q. 3.

A. 3. I'm sorry. I just want to make sure, if you don't mind. I apologize. I just want to make sure I don't misspeak.

So my understanding would be that in the '572, right, it has a method of treating an angiogenic eye disorder, correct, in a patient in need thereof, comprising sequentially administering to the patient by intravitreal injection a single initial dose followed by one or more secondary doses, which would imply that you can give more down the road, and then at some point down the road you follow that by one or more tertiary doses.

So there could be -- I guess you could interpret this that, for a period of time, you would be giving monthly doses, correct?

Q. So I just want to make sure we're understanding each other. For Claim 1, would a straight monthly regimen be within the scope of Claim 1?

A. Well, again, it would depend on -- you know, if I'm giving one or more loading doses and I am looking at that monthly regimen, it's kind of I'm having to just keep giving monthly injections. You know, as kind of an ophthalmologist reading this, I could interpret this as saying, well, I'm just

having to give monthly secondary doses, right? So for a while, depending on how long that went, I might have to give a series of secondary doses for a while and this claim would be still valid. Would that be a fair assessment?

Q. Well, the question is for you.

A. I'll ask myself. If I would ask myself, I guess that would be yes.

Q. You know what? Let's move on.

THE COURT: That's the beauty of being qualified as an expert, Doctor.

THE WITNESS: I'm sorry.

THE COURT: Ask yourself a question.

Go ahead, Counsel.

BY MS. LESKO:

Q. Let's talk about clinical judgment. Now, Dr. Csaky, a physician must exercise their clinical judgment to decide whether their patient needs dosing for the first three months followed by intravitreal injections once every eight weeks versus once every four weeks versus once every 12 weeks, yes?

A. Yes, absolutely.

Q. And, again, a physician must be the one who decides if their patient has had enough monthly doses or needs more monthly doses beyond five for DME or DR, right?

A. We make -- you know, yes, we make assessments. As we are treating patients, you know, we'll make assessments from

time to time to alter regimens depending on their response.

Q. And that comes down to the clinical judgment of the physician?

A. Yes. I mean, the -- as we see a patient, then yes, I can determine -- I'll give you an example. That if I'm treating a patient and I know that that patient, like I mentioned in my direct, that they have bad macular edema and I want to go ahead and say I'm going to go ahead and give five, I give five. And then I use my clinical judgment at that point to determine the next step.

Q. Could we also agree that the decision to use aflibercept in a fixed dosing regimen versus a prn regimen versus a treat-and-extend regimen is an issue left to the clinical judgment of physicians?

A. Yes. It's up to the clinician to determine what regimen is best for that patient. And that's -- like I told you, there's a whole series of decisions that we make deciding what our regimen is going to be for that patient.

Q. Okay. And you were aware that there are clinicians who exercise their clinical judgment to use Eylea in a treat-and-extend method, yes?

A. Oh, yes.

Q. And we can agree that there are some clinicians who exercise their clinical judgment to use Eylea in a prn dosing regimen?

A. Yeah, some. Most of my colleagues probably don't do that for macular degeneration. We tend to do it a little bit more for diabetic macular edema. But some people do.

Q. Right. My question was we can agree that there are some clinicians?

A. Clearly, yeah, there are some.

Q. And Claim 1 of the '572 patent does not cover treat-and-extend dosing regimens, correct?

A. So the -- I think in my deposition you asked me this question. And the term itself -- so we just want to make sure how we define treat and extend, right? So there are various terms for how we define treat and extend, correct. So at least among my colleagues, you can get variations on what the term "treat and extend" means, right? How -- and the term itself, from my perspective, is really that step when you are treating and extending, right? So that's a specific step of treatments, protocols, that I make as I go forward, right?

So that portion of treat and extend is very specific. And, again, each doctor, I can tell you, has -- we all have our own individual algorithms and paradigms and what eye and which patient, what our algorithm is for treat and extend.

So I'm not sure -- I'll give you an example. If I take a patient and I start with, let's say, three monthly dosing, right, and I switch to eight weeks, and I go for eight weeks, let's say, two or three injections, and then I start

extending, right. So that portion of the extension is definitely treat and extend, but the treat and extends can be very much about -- there can be variations.

So I think we have to understand that the term "treat and extend" is -- there's some variations in how we approach it. Every patient is different. That's really the bottom line.

Q. Well, Dr. Csaky, you were correct. You were asked this question at your deposition. So let's turn to your deposition transcript, which is at DTX 7224 --

A. Uh-huh.

Q. -- in your binder, Exhibit page 59.

A. Say that again.

Q. We'll put it up on the screen as well for you, but it's DTX 7224. Transcript page 232, lines 2 to 6. Do you see it up on the screen?

A. Sure do.

Q. Were you asked Claim 1 of the '572 patent also does not cover treat-and-extend dosing regimens, correct?

A. Yes.

Q. And the answer you gave was it does not appear to extend to incorporate the various aspects of treat-and-extend protocols?

A. That's correct.

Q. So I just asked you -- I just asked you about the

'572 patent. So now let's go to the '601 patent. Does the '601 patent cover treat-and-extend dosing regimens?

A. So, again, that portion of the treat and extend, it does not.

Q. And let me ask this just to be clear for the record.

Does Claim 1 of the '601 patent cover treat-and-extend dosing regimens?

A. So that portion that we talk about when we say treat and extend does not, right? It depends on the context in which you define -- so if we're talking about a true treat and extend when -- let's say right from the beginning I'm treating and extending, then it does not.

But if there's other regimens when I'm, let's say, doing a certain portion and then I start to treat and extend down the road at some point, then you might say that, well, at the beginning, I did something of the -- you know, in this case, '572. So the term "treat and extend" didn't apply. So as I said, it doesn't apply directly in that context because it's not that concept of treat and extend, right?

So it's important to understand what treat and extend is. It's truly what it means, right? It's -- you're treating and extending, treating and extending the interval, right?

Q. So, Dr. Csaky, I'm sure you're not surprised you were asked this question as well at your deposition.

A. Yeah.

Q. And the answer you gave then was a little bit with less commentary. So let's just look back at your deposition transcript and see what exactly you answered.

Were you asked the question, "Does Claim 1 of the '601 patent cover treat-and-extend dosing regimens?"

And the answer you gave was, "Of the -- Claim 1 of the '601 patent does not appear to extend to treat and extend."

Were you asked that question and you gave that answer?

A. Absolutely.

Q. So we just went through treat and extend. Let's now talk about prn dosing.

Is it your opinion that prn dosing regimens are not covered by the asserted claims here?

A. So that phase of the prn dosing regimen is not covered. By the '601 or the -- whatever the -- repeat -- the claims. That portion of what we would term prn is not covered.

Q. And you would agree that prn is significantly different than a dosing schedule that happens at fixed intervals?

A. Yes.

Q. Let's switch gears for a moment. Do you know Dr. Carl Regillo.

A. I know Carl.

Q. He's well-known and highly regarded in the

ophthalmology field?

A. Carl's a good friend and highly regarded.

Q. According to your CV, you have even published articles together?

A. Yes.

Q. So let's go to the "Settling on an Anti-VEGF Dosing Regimen" article that we previously looked at. It was one of the standalone documents.

A. Yes.

Q. Do you have that? We'll put it up on the screen as well.

A. Can you give me the -- do I need the PTX thing?

Q. This is one of the ones that was in the pocket.

A. Oh, okay.

Q. It's titled "Settling on an Anti-VEGF Dosing Regimen."

A. Okay. So there were two pocket articles. Right? They were these two, correct?

Q. Yes. And it's up on the screen.

A. Perfect. Okay. Thank you so much.

Q. Okay. So directing your attention to page 1 and specifically on the first page of that article, third paragraph, do you see Dr. Regillo's statement here that "You can do a continuous treatment at a fixed interval where you treat every month or every two months. That's the least

popular approach."

Do you see that?

A. Yes.

Q. Do you agree with Dr. Regillo that, even as early as 2013, fixed-interval dosing was the least popular anti-VEGF dosing regimen?

A. Yeah. I mean, it's hard to know back then, but I think it's fair to say that the term "popular" assumes that people didn't -- I think that it was -- there was only some indications in which people would use it. It clearly was in the minority. I would agree with that statement.

Q. Okay. We can take that down, please.

And do you see that the next sentence says, "Very few people do that because it may represent overtreatment in some people"? Do you see that?

A. Correct.

Q. The next is "Prn treatment, which is an approach to individualized therapy and minimize overtreatment."

A. Yes.

Q. Would you agree with that statement?

A. It definitely -- I just want to make sure we're clear because you heard you say about prn.

It's important -- and Carl said it correctly here. It definitely minimizes overtreatment, but it can minimize -- you can maximize undertreatment.

Q. And then the final line is "You treat monthly until the macula is dry, and then you monitor closely and treat recurrences."

A. Yes.

Q. And you agree with that?

A. That's Carl's approach to his description of what he's doing.

Q. And that's a prn approach?

A. Well, if you looked -- I mean, again, I think it's important to recognize that we all have our own -- you know, there's no set -- you know, these definitions -- prn, treat and extend -- are very much individually -- we all use our own kind of vocabulary, if you want to call it, right?

So our vocabularies that we use can be somewhat individual, right? You call it tomahto; I call it tomato. What you call prn, I call it something else. But this is Carl's -- his definition of prn.

Q. And let's look at Carl's -- Dr. Regillo's third statement here. "The third approach is the treat-and-extend strategy, which some believe may represent the best of both worlds in disease control and treatment burden."

Do you see that Dr. Regillo stated that?

A. Yes.

Q. And do you agree with Dr. Regillo's statement there?

A. You know, so again, I think -- I mean, we all use it.

We all do treat and extend. You know, the interesting thing about treat and extend is, you know, in many cases we end up with more injections, depending on the level of willingness to accept some degree of fluid, right?

So again, you know, some believe it's the best. Some believe it's the best; some don't believe it's the best.

Q. Let's put up on the screen DTX 2042.

And, Dr. Csaky, during your direct examination you testified that you are part of the American Society of Retina Specialists, correct?

A. Yes, I am.

Q. Can you confirm that DTX 2042 is the association of retinal specialists, 2017 PAT Survey?

A. I can.

Q. You've seen this before?

A. I have seen that.

Q. You have reviewed the PAT Surveys before?

A. I have reviewed the PAT Surveys.

Q. Do you typically review PAT Surveys?

A. I do -- again, I would say, you know, it just depends on kind of what mood I'm in, but yes.

MS. LESKO: And, Your Honor, we move to admit DTX 2042 into evidence.

THE COURT: Any objection?

MS. KAYALI: No objection, Your Honor.

THE COURT: Without objection, so admitted, DTX 2042.

(DTX 2042 was admitted.)

BY MS. LESKO:

Q. So let's look at DTX 2042 at exhibit page 17, which is Slide 7 of the 2017 PAT Survey.

A. Yes.

Q. It has the heading "In general, how do you treat wet AMD patients with active CNV"?

A. Yes.

Q. I'd like to direct your attention to Option 8, which reads, "Treat until dry on OCT, then as needed, prn."

A. Yes.

Q. Can we agree that Option A is a prn dosing regimen that was the preference of 9.8 percent of the physicians surveyed?

A. Yes. Again, I just want to make sure we're clear because I think it's these terminologies. When you say a prn, this is -- when doctors fill this out, there's choices --

Q. Sir, I'm just asking you to say what's on the screen, actually.

A. Oh, you want me to just repeat what's on the screen?

Q. I'm sorry. Go ahead. I didn't mean to cut you off. Do you want to finish your answer?

A. No. All I was saying was, when you asked does this represent prn, it represents to these individuals the choice of

whatever they chose as prn, correct.

Q. Okay. And that's 9.8 percent?

A. That's 9.8 percent.

Q. And Option B is described as a regimen of treat until dry on OCT, then extend -- treat and extend, correct?

A. Correct.

Q. That was the overwhelming preference of over 70.9 percent of physicians surveyed?

A. That is, again, this definition of "treat and extend until dry" and then how the physicians determined in their -- whatever regimen they're using for treat and extend, they would have chosen, you know, this category of -- on the survey.

Q. Let's look at Option C, which reads, "Treat until dry on OCT; then follow up every three or four months."

Do you see that?

A. Yes.

Q. Does the Option C regimen fall within the scope of the asserted claims here?

A. As written, this would not fall under the regimen as far as I can tell. So --

Q. Let's pull up Option D, which reads, "Inject monthly regardless of fluid or exam," yes?

A. Yes.

Q. Does the Option D regimen fall within the scope of the asserted claims here?

A. So again, as we talked about, could someone in the '572 be injecting monthly as a way to say I can inject on a -- with my secondary doses for a while, but I would say in general this would not fall under the '572 patent.

Q. We then have Option E, which encompasses Options A or B, and that was the stated practice of 60.3 percent of physicians responding to the survey, right?

A. Yes.

Q. That leaves Option F, other, at 1.2 percent in the PAT Survey, right?

A. Correct.

Q. We can pull that exhibit down.

In your opinions in this case, did you offer any data comparable to what we saw in the PAT Survey for physicians specific to treatment practices for diabetic retinopathy or diabetic macular edema?

A. I did not.

Q. In fact, you have not endeavored and did not attempt in your direct examination to quantify the number of ophthalmologists who currently employ the claimed methods with Eylea or the number who actually would follow the instructions to employ those methods with Yesafili, true?

A. I did not.

Q. Dr. Csaky, let's go back to PTX 586, which your counsel showed you in your direct exam. Let's start with

exhibit page 1. We'll put it up on the screen as well.

A. Yes.

Q. If we look at the background and objective section, this analysis of the IRIS Registry tried to see if they could emulate the VIEW randomized clinical trials, eligibility criteria, treatment protocol regimen, and primary end point, right?

A. That's what it states, correct.

Q. Let's take a look at the results section on the first page of PTX 586, bottom left-hand corner. It says that there were 90,900 patients who met the VIEW randomized clinical trial eligibility criteria, right?

A. Correct. I'm sorry. Say that again. I lost my train of thought. Say that last statement before. What did you say?

Q. In the results section, bottom left-hand corner, first sentence, it says that there were 90,900 patients who met VIEW RCT eligibility criteria?

A. That's correct.

Q. And that's the randomized clinical trial eligibility criteria?

A. That's correct.

Q. Let's go to the top paragraph in the upper right-hand column of exhibit page 1 of PTX 586, the conclusion section.

A. Yes.

Q. We can agree that in the conclusion section, they reported that a small percentage of real-world patients met the view randomized clinical trial study eligibility criteria and treatment protocol regimen, right?

A. Correct.

Q. Now let's go to the fourth page of this exhibit, Table 3, what is titled "Inclusion Criteria for Treatment Arms."

Do you have that on your screen?

A. Yes, I've got it. Thank you.

Q. If we look at the right-hand column, that is the one that is titled "IAI 2q8," right?

A. Yes. "IAI 2q8." Gotcha.

Q. That is the one you identified as the one covered by the claims here?

A. Correct.

Q. Let's look at the inclusion criteria of patient needed to meet that entry description of IAI 2q8.

Do you see that on the screen?

A. Yes. That's true. Yes, I see that.

Q. The first entry says, "Three consecutive monthly injections every 28 days plus or minus seven days," right?

A. Gotcha. Sorry. I was one page behind.

Yes. Go ahead. Yes, three monthly injections. Yes.

Q. So the first three loading doses could be spaced

anywhere from 21 days, three weeks, to 35 days, five weeks apart?

A. Correct. They can be plus or minus seven days.

Q. Now let's look at the last entry in this right-hand column titled "IAI 2q8." It states, "After the third monthly injection, injections needed to occur every 56 days, plus or minus seven days," right?

A. Correct.

Q. Every eight weeks would be every 56 days, true?

A. Correct.

Q. So their criteria included patients who were dosed every seven weeks as well as every nine weeks?

A. They could have been, plus or minus seven days, right. So it could have been eight weeks or nine weeks or seven weeks, correct.

Q. Let's sum this up, then. For a patient's medical record in the study to be put into the IAI 2q8 bucket, the term "monthly" was used to mean every three to five weeks and the extended interval afterwards was allowed to be seven to nine weeks. Is that correct?

A. Correct.

Q. Let's go to exhibit page 5 in PTX 586, right-hand column, near the bottom of the page, last full paragraph, please.

A. You're going a little faster than I can process. Say

that again.

Q. Exhibit page 5.

A. Exhibit page 5.

Q. Right-hand column.

A. Gotcha, gotcha, gotcha. Just a little faster than I am. Okay.

Q. I apologize. Last full paragraph.

A. Yes. I gotcha. The word "total." Yes, I gotcha.

Q. The one that starts off "there was a total of 606,971"?

A. Correct.

Q. It says in the first sentence that "For this publication, there was a total of 606,971 patients who had an anti-VEGF injection during our study period," right?

A. Correct.

Q. So that means in the patient records screened, the patient got at least one injection of aflibercept, bevacizumab, or ranibizumab or another VEGF inhibitor?

A. Those would be -- for this period of time, we don't have -- those are the three anti-VEGF agents we have right now.

Q. Let's go to the Table 5 you pointed to, which is at exhibit page 6 --

A. Yes.

Q. -- in PTX 586.

A. Yes.

Q. There were only 154 patients out of the over 90,000 screened that met the IAI 2q8 criteria, right?

A. So, again, you have to remember here that there was a restriction, right? I think you pointed out that restriction yourself, I think. And that is that there had to be -- maybe you didn't, but I will. So if you look on Table 2 -- and that's PTX 0003. Do you see that?

Q. Yep.

A. Okay. So the important thing here is to recognize that what they were trying to do is not identify everybody who was receiving this regimen, right? They were trying to identify the regimen that -- in people who met the VIEW 1-VIEW 2 inclusion criteria, right?

So there could have been people who didn't meet that inclusion criteria, right? They would not have been counted. They could be on this regimen.

So this is not a full survey. What they were trying to really do is emulate VIEW 1 and VIEW 2. So they didn't necessarily go -- say, hey, let's take everybody who received that regimen regardless of what -- how they fit into the VIEW 1-VIEW 2 eligibility criteria, right? So we have to understand that the purpose of this study was to really not just understand that we already excluded patients who didn't meet those inclusion --

Q. Dr. Csaky?

A. I'm sorry. Am I talking too much?

Q. No, I'm sorry. Go ahead. My question was slightly different, but I don't want to cut you off.

A. No, no. You were asking me -- because I think the question is this represents some number, and I wanted to make sure we're clear that there could have been other patients in the IRIS Registry who received this treatment protocol but would not have been included in this study.

Q. Okay. 20 times more patients in this chart were given monthly aflibercept injections as compared to patients in the IAI 2q8 group, right?

A. So 20 times more patients were given -- you're saying every four months -- four weeks. I'm sorry. I'm a little bit slow.

Q. 20 times more -- 15 times more patients in this chart were -- I apologize.

A. I miss --

THE COURT: It's math. That's all you, Counsel.

THE WITNESS: Okay. Yes.

MS. LESKO: Someone else drafted this particular question.

THE COURT: Noted.

THE WITNESS: Okay. Yes.

BY MS. LESKO:

Q. I believe it's 15 --

A. It's approximately 15.

Q. -- times more patients in this chart were given monthly aflibercept injections as compared to patients in the IAI 2q8 group; is that right?

A. On the patients -- again, you have to remember -- I just want to make sure we're clear for the record -- that this is in the groups of patients who met the eligibility criteria and then were allowed to be examined for when they got their treatment. So in this subset of patients, yes, your math is correct.

Q. And there were over ten times as many patients being treated with ranibizumab monthly as compared to patients in the IAI 2q8 group, right?

A. Yes. Again -- I'm not going to keep repeating the caveats, but yes.

Q. And, Dr. Csaky, let's take one more look at PTX 1527, which is Dr. Do's declaration.

A. Okay.

Q. In the front page do you see the title "Inter Partes Review Number 2021-0081"?

A. Yes.

Q. It says U.S. Patent Number 9,254,338 B2?

A. Yes.

Q. Are you aware that the '338 patent is in the same patent family as the '572 and the '601 patents here?

A. I'm not aware of any of those patents -- those patent issues.

Q. Are you aware that inter partes review proceedings are contested proceedings between Regeneron and Mylan in the PTO?

A. I'm not -- again, I hate to say this, but I'm -- when I can play down "I'm not a lawyer" card; and so I don't know all the details. I'm sorry.

Q. That's okay. Let's go to PTX 1527, the third page of Dr. Do's declaration.

A. Is it in my --

Q. We can pull it up on the screen.

A. So I don't have to find it through this -- go ahead.

Q. Can you confirm that Dr. Do stated in her declaration that she was retained by counsel for Regeneron when she made these statements?

A. Yes. She said, "I've been retained by counsel for Regeneron," correct.

Q. If we look at the bottom of exhibit page 3 in paragraph 2, did Dr. Do confirm that she was acting as a paid expert for Regeneron when she made the statements you relied on here?

A. Yes. She is being paid at an hourly rate, correct.

Q. Can you identify for me any of your published papers where you have relied on a paid litigation statement by an

expert witness as the basis for your scientific opinions?

A. No, I don't think I've ever relied on a -- I'm trying to remember because we do sit on scientific advisory boards, right? We all get paid to be on a scientific advisory board. And so in some of those cases, people are paid.

And so when people give opinions -- not to digress, but it is an important question because, as I think about it, right, in today's world, there's an interplay between industry and academics. And so, many times ideas are exchanged in the context of a scientific advisory board by a company, right?

And so I'd have -- I think -- I'd probably say I have used opinions in the context of somebody being paid from an advisory perspective from a company and used that in my thinking and how I write a paper or think about things for sure.

Q. So just to be clear, I wasn't just asking about any paid consulting relationship. I'm asking can you identify for me any of your published papers where you have relied on a paid litigation statement by an expert witness as the basis for your scientific opinion?

A. No, that's true. I don't think I've ever used a litigation document -- I mean statement for my scientific advisory.

Q. These conversations with doctors that you talked about in your direct examination, can you identify for me any

time when you talked about treatment guidelines and how to dose patients based on what was said in a statement they were paid to make in a litigation-type proceeding?

A. No. As I said, I don't think I've ever relied on a paid litigation context. But am I allowed to just say one other thing just because I know Dr. Do? Is that --

THE COURT: Is it in response to the question, sir?

THE WITNESS: Yeah. No, I just want to make sure because Diana Do is a good friend. She's an incredibly ethical person. And so I guess when I read this, for me it reflected Diana's opinions, right? And so from my perspective, because I know Diana -- I think you have seen my CV; Diana and I have published together -- I used -- my reliance was really on knowing Diana and knowing how ethical she is and what she's going to say reflects what she truly believes.

BY MS. LESKO:

Q. Can you identify for me any of your published scientific work before your peers where you have relied on assertions made in a declaration from legal proceedings?

A. I have not.

MS. LESKO: Your Honor, in view of this testimony, we renew our motion to exclude for noncompliance with Rule 703. We are happy to address it in posttrial submissions if you prefer.

THE COURT: The Court will hold that motion in

abeyance until the parties have a chance to brief in posttrial motions.

Any other questions on cross-examination, Counsel?

MS. LESKO: Nothing further at this time, Your Honor. Thank you.

Thank you, Dr. Csaky.

THE COURT: Redirect, Counsel?

MS. KAYALI: I do, Your Honor. If I could ask the Court's indulgence for a brief personal comfort break, I'd really appreciate it.

THE COURT: Certainly. Motion granted. We'll take ten minutes.

Doctor, you remain countryless, sir.

So we'll take ten primarily for counsel's benefit. I'll ask everyone else to let her head to the front of the line.

(A recess was taken from 2:36 p.m. to 2:52 p.m.)

THE COURT: Counsel, assuming an appropriate level of personal comfort has been restored, you may proceed.

MS. KAYALI: It has been, with sincere gratitude, Your Honor.

THE COURT: Outstanding. Go right ahead.

REDIRECT EXAMINATION

BY MS. KAYALI:

Q. Let's pull up PTX 3, if we could, and I want to look at Claim 6, please.

And, Dr. Csaky, I want to see if I can clarify the kinds of regimens that are in the scope of Claim 6. So I want you to imagine for me a regimen in which you gave three monthly loading doses followed by a switch to dosing once every eight weeks for at least one or two doses, and then you chose to extend the regimen from there in duration.

Have you performed the method of Claim 6?

A. If I did that, then I would have performed the method of Claim 6. Claim 1, actually.

Q. Claim 1 and then by virtue of assuming Dr. Trout testifies that Yesafili is isotonic, then you would have performed the method of Claim 6; is that right?

A. Correct.

Q. Let's turn, then, to DTX 2042, and I want to look at Slide Number 7. And so that's DTX 2042, page 17.

Do you see this?

A. Correct.

Q. And do you recall being asked about this slide and this document during cross-examination?

A. Yes.

Q. So I want you to imagine the very same regimen. A physician gives three monthly doses, followed by dosing once

every eight weeks for one or two doses, and then chose to extend the treatment interval from there.

Which of the options would the physician have selected in this survey?

A. So, again, this is what I was trying to explain was that the -- when I opined previously the treat-and-extend is a very specific regimen, right? It's -- and so it could very well be, and many times what we really are using treat and extend is for the extended maintenance period.

You have to remember that we don't cure a lot of these patients. We cure very few patients. And so we're trying to -- we struggle to get to that interval that's right for them.

The beginning stages are somewhat different, right? The beginning stages, as we've talked about, we want to control the disease, we want to give those almost three loading doses. Very common approach to give three loading doses. And then what this has taught us is we can go to eight weeks, right? And there's some people who would then go eight weeks for one or two just to make sure the disease is nice and quiet, and then they will start to extend.

So if I'm treating someone like that and I've been out a year or two, then I'm going to have picked B because they're on treat-and-extend regimen, right? But it could very well have been that at the beginning of my treatment regimen I

would have used a method that we just talked about where I'm giving three monthly loadings; I'm extending to eight weeks; I may give one or two eight-week injections, maybe even three; and transition to a treat-and-extend.

So that's what I was trying to explain, is that these treat-and-extend regimens are highly variable and there is no such thing as this is what treat and extend is because it all depends on the interval when you decide to choose, how aggressively you want to go to that treat-and-extend interval.

And so the beginning stages can be in some cases more like the claim; other cases you can go right into a treat-and-extend. So, for example, if I take -- see a patient, I inject, have them come back in four weeks, they're dry, I go right to six weeks, right to eight weeks, I'm treat-and-extending right from the beginning, then I'm not following the claim.

So there is -- you know, there's some complexity and tremendous amount of heterogeneity in this choice that physicians would have chosen in this PAT Survey.

Q. And, Dr. Csaky, I just have really one more set of questions. I believe you were asked on cross-examination about various ways doctors use Eylea that don't necessarily conform precisely to the label.

Does it remain your opinion that, if Yesafili is marketed, at least some doctors will do exactly what that label

says and perform the method of the claims?

A. Yeah. I mean, as we said, there would still be some doctors who will do, as we talked about, the methods of the claim.

MS. KAYALI: No further questions, Your Honor.

THE COURT: Recross, Counsel?

MS. LESKO: No, Your Honor. Thank you.

THE COURT: All right. Doctor, thank you very much, sir. You can step down. Yes, you're allowed to speak to other humans.

THE WITNESS: Thank you, Your Honor.

THE COURT: I don't know if that's good or bad.

THE WITNESS: They're all lawyers.

THE COURT: Trust me, I know.

That wasn't a personal comment on anyone here.

Counsel, I suspect I know what you're doing.

MS. KAYALI: Yes. Your Honor, I had wrote it on a sticky note and it went nowhere.

I would like to move the admission of the exhibits that we used in Dr. Csaky's direct examination.

I'm sorry, Ms. Lesko, to have you return.

THE COURT: All right, Counsel. Thank you. Do you have a list of those?

MS. KAYALI: I do.

THE COURT: If I could ask you to do that slowly,

please.

MS. KAYALI: Yes, Your Honor. Just for counsel's comfort, I do not intend to move the admission of Dr. Do's declaration; so I suspect we are otherwise in agreement.

The first was DTX 7053. The next is PTX 001, which I believe is already in evidence. The next is, again, PTX 003. I believe that's also already in evidence. The next is PTX 331. After that, PTX 586. And I have PTX 917, PTX 963, PTX 3097, and PTX 3338.

THE COURT: Any objection to any of those, Counsel?

MS. LESKO: No objection, Your Honor.

THE COURT: Without objection, those are hereby deemed admitted.

(PTX 331, 586, 917, 963, 3097, 3338 were admitted.)

MS. KAYALI: Thank you, Your Honor.

THE COURT: Thank you.

Musical chairs may resume. Thank you all.

Yes, Mr. Berl.

MR. BERL: Yes, Your Honor. Plaintiffs want to call Dr. Eric Furfine. I think opposing counsel has stated a request to note some objection before he takes the stand; so I'll yield so he can do that.

THE COURT: Counsel.

MR. SALMEN: Thank you, Your Honor. Heinz Salmen on

behalf of the defendant. I'll be very quick, Your Honor, but there was one issue that we wanted to bring to Your Honor's attention before Dr. Furfine took the stand.

Regeneron identified several dozen documents that Dr. Furfine is going to be testifying about today, and our objection to these documents -- to those exhibits is that the vast majority of them were not disclosed in response to our interrogatories regarding a prior invention and conception and reduction to practice.

Now, we anticipated this issue in our Motion in Limine Number 5. That's at Docket Number 449. And we are happy to defer argument on this to our posttrial briefing, but we wanted to make it clear that, in our view, plaintiff had an obligation to disclose these documents in response to our interrogatories. They did not, and they had an obligation to disclose them with particularity. They also did not do that.

THE COURT: Do you have these documents now, Counsel? Were they disclosed in discovery at some point?

MR. SALMEN: They were. They were produced, Your Honor. They were never disclosed in response to our interrogatories.

So we're not taking a position that Dr. Furfine cannot state his knowledge with respect to them, but in our view they should not be -- Regeneron should not be permitted to rely on these documents to establish that prior invention date.

THE COURT: Understood. The Court will continue to hold that issue in abeyance until posttrial briefing. For purposes of our trial record, the Court will presumably receive them as we go. They were produced in discovery, as counsel indicated. I realize there's a looming issue with respect to how specific those discovery responses may be. And we'll take that up I'm sure in posttrial briefing in the Court's ultimate order.

MR. BERL: In case it wasn't clear to Your Honor, we disagree with virtually everything that Mr. Salmen just said.

THE COURT: I assumed as much, Mr. Berl. I know what happens when you assume, but I feel safe doing that here.

With the -- I came to change of shift in a coal mine, but with that, Mr. Berl, plaintiff may now call its next witness.

MR. BERL: Thank you, Your Honor. Plaintiffs call Dr. Eric Furfine.

ERIC FURFINE, PhD, PLAINTIFF'S WITNESS, SWORN

MR. BERL: Your Honor, may I approach with exhibits and demonstratives?

THE COURT: You may.

Thank you, Counsel. You may proceed.

MR. BERL: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. BERL:

Q. Good afternoon, Dr. Furfine. And try to speak into the microphone and rather slowly. I'll try to do the same. I have a fear that Ms. Knecht is going to oppose my next pro hac vice application if we don't.

THE COURT: I'll take the fifth. Go ahead.

BY MR. BERL:

Q. Good afternoon, Dr. Furfine.

A. Good afternoon.

Q. Would you please introduce yourself to the Court.

A. My name is Eric Furfine.

Q. What do you do for a living, Dr. Furfine?

A. I'm a drug discovery and development scientist.

Q. How did you become interested in science?

A. My interest in science started many years ago when I was a child, and I guess I'm an example of the apple doesn't fall very far from the tree. My dad was a biochemist. And I remember when young, he would take my brother and I into the lab with him and, you know, we would help his graduate students and postdocs -- what we called washing the dishes, but was mostly really cleaning their glassware. And I just remember becoming fascinated with science and the work in the lab at a very early age.

Q. And what did you want to do when you grew up when you were a kid?

A. I was always headed towards some scientific endeavor. As I progressed through my schooling, college, and graduate school, it became clearer and clearer to me that I really wanted to work in making medicines, that that would be something I could get excited about on a regular basis and draw me into work.

Q. What do you do now?

A. I am the chief scientific and executive officer of a company called Mosaic Biosciences. We do drug discovery for other companies.

Q. Who are your clients for whom you help drug discovery?

A. Most of our clients are very small biotech companies that are looking to be able to build their company without actually hiring a lot of people and finding labs. We actually provide the service for them and a lot of strategic guidance.

Q. Can you briefly describe your education, Dr. Furfine.

A. I got an undergraduate degree from Washington University in St. Louis in chemistry. I got a graduate PhD degree at Brandeis University in biochemistry. And I did postdoctoral work at the University of California, San Francisco, in molecular parasitology. That's the study of the gory details of how parasites work.

Q. What did you do after that?

A. I went pretty much straight into industry at that

point, in fact, to pursue trying to learn how to be a drug hunter, which I've become. And that's why I went to Burroughs Wellcome to start. It was a fairly medium- to large-sized pharmaceutical company.

Q. How long did you stay there?

A. I was there about 13 years. And from there I went to Regeneron.

Q. And while you were at Burroughs Wellcome did you do any work on formulation research?

A. Yes, I did.

Q. Why did you decide to go to Regeneron at that point?

A. There were three big reasons for me. One is an opportunity to work with a graduate student colleague of mine who I had a lot of respect for, Neil Stahl, and to have an opportunity to work with him again was an exciting thing for me.

It was exciting that Regeneron was a smaller company and was a biotechnology company working in protein therapeutics and an opportunity to expand my understanding of new types of drugs, proteins instead of small molecules that I was doing earlier. So that was a good opportunity.

And there was also a major opportunity to expand my understanding of the later stages of drug development and discovery and to really work in more of the development end. So that was also enticing to me.

Q. What year did you join Regeneron?

A. 2002.

Q. How long did you stay?

A. I was there till summer of 2006.

Q. And you said it was a relatively small company. Can you describe what Regeneron was like during the years that you worked there?

A. Yes. You know, there was several hundred people there, probably 5 or 600 people, I would guess, but -- which is much smaller than Burroughs Wellcome which is a major pharmaceutical company. And I just was always interested in the fact that there was just so much discussion of science at Regeneron and how strong a force it was in driving decision-making there. It was a great place in that regard.

Q. Since 2006, have you had any professional relationship or association with Regeneron?

A. Nothing professional. I maintained friendships and collegial interactions with people I know there, but nothing other than that.

Q. Dr. Furfine, I'd like to discuss with you today your role on the project with the aflibercept molecule.

What was your role at Regeneron during that time?

A. I was the head of preclinical development, it was called. Preclinical development involves -- a big part of what it involves is to do formulation development for the proteins

that we were working on.

A second, similar sized part was to really understand what happens in animals, in humans, and to be able to measure those things and prepare drugs to get ready to move into the clinic.

Q. When did you begin working on the VEGF Trap or a VEGF Trap?

A. I would say approximately a year after I was there, maybe 2003.

Q. And what was the result of that project?

A. The biggest thing that came out of it was Eylea.

Q. Now, I'm going to place on the screen what's been marked as PTX 2 in this case.

Dr. Furfine, is this the patent that describes and claims your inventions working on the project on aflibercept?

A. Yes, it is.

Q. We've highlighted various people who are listed as inventors. The first one, Eric Furfine, we know.

Who is Daniel Dix?

A. Daniel Dix was the head of the formulation group that reported to me.

Q. How about Kenneth Graham? Who is he?

A. Kenneth was a scientist in the formulation group, and he reported to Dan.

Q. And Kelly Frye, who is that?

A. Kelly Frye was also a formulation scientist that reported to Dan.

Q. Dr. Yancopoulos, from whom the Court heard yesterday, is not listed as an inventor on the patent.

What was his role vis-a-vis the project that you were working on with aflibercept?

A. Yeah. I mean, as a senior leader in the company, George was very intimately involved in all the things that were required to move a drug into the clinic and follow it throughout the clinic. And he stayed abreast of the work that we were doing to prepare drugs to be ready to go into clinical trials and to be able to maintain them in clinical trials.

Q. Did you meet with Dr. Yancopoulos during this period?

A. Absolutely. Yes, on a regular basis.

Q. Now, we've highlighted under Number 73 there "Assignee: Regeneron Pharmaceuticals."

What is your understanding about how Regeneron Pharmaceuticals is the assignee of the patent that you helped invent?

A. All employees of Regeneron were required to assign their inventions to the company. That was a condition of your employment.

Q. Was that true throughout the time that you were at Regeneron?

A. Yes, it was, absolutely.

Q. Now, we've been talking in this case about aflibercept. What is aflibercept?

A. Aflibercept is a man-made, humanly devised protein where you take two receptors that are normally on the surface of the cell and you genetically engineer them to be on an antibody part. We call that the FC domain.

So you make this construct of receptor domains fused to an antibody part, and that creates a drug.

Q. And when you say they're fused, does that make them what we've heard of called as a fusion protein?

A. Correct. It's referred to commonly as a fusion protein.

Q. And was aflibercept the only VEGF blocker known at the time that you were working on the project?

A. No, it was not.

Q. Were there any prominent VEGF blockers that you were knowing about and following at the time?

A. Two of the most prominent VEGF blockers were Avastin, or bevacizumab is the genetic name, and Lucentis, or it was ranibizumab at that time because it wasn't approved when we first started working on it.

Q. Who was developing those molecules?

A. Genentech was the company that was doing that.

Q. And at the time you were working on your project, who was Genentech in the field of biotechnology and in the field of

VEGF?

A. Genentech were really leaders in both of those spaces. They were probably the premier company in protein therapeutics, and they were arguably the premier company in understanding VEGF biology and pursuing drugs that modulate or inhibit VEGF.

Q. Who did you understand to be leading their VEGF development?

A. A lot of the scientific leadership came from a man named Napoleon Ferrara, who is arguably the father of VEGF and Avastin.

Q. How did Regeneron compare to Genentech at the time?

A. Analogous to us being David in the David and Goliath.

Q. Was aflibercept initially being pursued by Regeneron to treat eye diseases?

A. Not originally, no. It was treating cancer.

Q. Did you participate in that work?

A. I did, yes.

Q. Did there come time when Regeneron considered using aflibercept to treat eye diseases?

A. Yes, we did.

Q. And at the time you began the project, did you consider the project of formulating aflibercept to treat eye diseases easy or hard?

A. We considered that it would be a challenging,

difficult problem.

Q. Why is that?

A. First of all, aflibercept itself being a fusion protein was a challenge because there just wasn't that much knowledge on how to formulate and what the behaviors of those types of molecules, of fusion proteins general.

And the second reason was there just wasn't a lot of experience in the industry in developing formulations that were going to be injected intravitreally.

Q. Did the fact that aflibercept Trap VEGF mean that it could be used to treat diseases in the retina?

A. No. It had to reach the retina in order to be able to do that, both block VEGF and reach the site of action.

Q. Now, you mentioned ranibizumab, which was one of the two molecules that Genentech was developing.

What was your understanding about for what diseases Genentech was pursuing ranibizumab?

A. My understanding was they were only pursuing retinal diseases with ranibizumab.

Q. Did you consider aflibercept to be like ranibizumab for purposes of treating eye diseases?

A. It was similar in a very high-level sense in that they're both protein therapeutics, but the chemical nature of these two drugs was very, very different, and they were different classes of proteins.

Q. Did they have any other differences that you considered to be important for purposes of your project?

A. Yes. Aflibercept was considerably larger than ranibizumab was.

Q. What do you mean by larger or smaller in the context of molecules or proteins?

A. So what we mean by larger is molecular weight, kind of the space a molecule takes up. And the ranibizumab molecule was about a third the size of a full antibody. So it's an antibody part. It's in some ways considered an antibody, but it's really a part of an antibody, the FAB domain. And that's about a third of the size of a total antibody.

And the VEGF Trap or aflibercept is much more similar in size to an antibody than it is to ranibizumab.

Q. Was a molecular weight or the weight the only thing you considered in terms of the size?

A. No. So the molecular weight of aflibercept was a little bit smaller than an antibody, but we felt like it behaved more like the size of an antibody. It's kind of like if you -- could make a football analogy where you get somebody who's a fullback might be or a running back might be, this relatively heavy, relatively dense, small, compact person; and then you have a wide receiver who might weigh even maybe a little bit less but be much bigger, might have more trouble fitting in an airplane seat because of their -- they just take

up more space.

Q. And so was aflibercept more like the wide receiver or like the fullback?

A. More like the wide receiver and, therefore, more similar to an antibody in size, despite its actual weight being somewhat less.

Q. And was aflibercept in the same class of molecules as ranibizumab?

A. No. As I mentioned, ranibizumab was an antibody or considered an antibody as it was part of an antibody, and aflibercept was a receptor fusion protein. It had receptor domains on it that were previously in a normal setting on the surface of a cell and bore no resemblance to the structures of an antibody.

Q. Based on your understanding at the time, does a formulation that works to stabilize one protein in a class work to stabilize a separate protein in a class?

A. No, not necessarily.

Q. Why not?

A. The chemical nature of even two antibodies can be very different, and it's the chemical nature of those antibodies, how charged they are, hydrophobic they are -- hydrophobic meaning kind of a dislike of water, if you will. Depending on the nature, they could be very different things that are required to maintain their stability in solution.

Q. Did you understand that a formulation that stabilizes an antibody could be used to stabilize a fusion protein?

A. Definitely not. The differences between a fusion protein's chemical nature is even more different than an antibody to an antibody.

Q. And I should have asked you this before. When you came to Regeneron in 2002, did you start working on protein formulations immediately?

A. Yes.

Q. Was it your understanding, Dr. Furfine, that you could take an existing antibody formulation, take out the antibody, and put in a different molecule such as a fusion protein?

A. No. That's not how we do formulation discovery. We have a path where we do things that are fit for purpose. You decide what's going to be used for, you decide the nature of the molecule you're formulating, and you design the formulation for that.

Q. Would it even be allowed to make that kind of substitution to make your product that way?

A. Absolutely not. It's a cardinal rule of formulation science and drug discovery generally that you only put things in that you need. You have to actually go through the process of showing that you need something and figuring out exactly not only that you need it but how much to put in, and that includes

the drug itself.

Q. Now, you said a moment ago that you had to get into the proper areas of the eye. I just want to put up a figure on the screen from Exhibit 579. That's PTX 579.

When you were working on the project on aflibercept, what was your understanding about where the molecule had to go to treat the diseases you were targeting?

A. It would help if I had --

MR. BERL: May I approach, Your Honor?

THE COURT: You may.

THE WITNESS: So you see the word "choroid" here. This is the -- roughly the place in the eyeball where you would stick the needle, and it would go through the sclera here and into this kind of like peach-colored area. That's called the vitreous. So you would directly inject the drug right into the vitreous.

Now, the drug will freely over time, maybe about a day, diffuse throughout the vitreous, but the key is you see this lighter yellow-colored part that abuts the vitreous here, that goes here, that's the retina. So it has to be able to get out of the vitreous and into the retina.

It also needs to be able to get past the retina into this next darker red color next to the light yellow. That's called the choroid. Those are the two places where the disease happens, the choroid and the retina. So the drug needs to get

out of the vitreous, needs to penetrate these two tissues in order to work.

BY MR. BERL:

Q. And what was your understanding at the time about what kind of molecules would be most likely to get in significant amounts into the retina and choroid?

A. So there was evidence from our colleagues, competitors at Genentech that said that larger molecules, antibody-sized molecules, essentially stayed mostly in the vitreous and did not penetrate the retina; but smaller molecules, like ranibizumab, which is a third of the size of an antibody, was able to actually get into those tissues where the disease biology happens.

Q. Let's take a look -- it's in your binder as well -- at Exhibit 1848. Can you identify this document for the Court?

A. Yes. This is the paper that I was referring to from Genentech that compared the antibody to the ranibizumab.

Q. And did you read this article when you were working on your aflibercept project at Regeneron?

A. Yes, I did.

Q. And you mentioned Dr. Ferrara earlier. Is he one of the authors of this article?

A. Yes, he is, right here.

Q. Let's take a look at the abstract, and we've highlighted part of the abstract on the first page.

Can you explain what Genentech was conveying and what you understood about it when you were working on your project?

A. Right. So you can see right here they point out the difference in molecular weight or the size. So you can see it's 150 versus about 50. So it's a third the size; so that's essentially consistent with what I was saying. And that the antibody, the bigger molecule, did not penetrate the retinal tissues whereas the ranibizumab, or the FAB fragment of the antibody, was able to penetrate the tissues in this study.

Q. What was the principle of this -- what was the relevance of this principle to your work on aflibercept at the time?

A. Well, as I mentioned before, because aflibercept was more similar in size to an antibody, we were concerned that we could see the same thing and that, if we gave an intravitreal injection of aflibercept, it might not get to the place where we needed it to go to affect the disease. So we were concerned about that.

Q. Did you understand this issue of size to be relevant to Genentech's development of ranibizumab?

A. Absolutely. I think that's partly why they published this paper too. And they clearly thought that this smaller molecule was the better way to go, and that's what they pushed forward with.

Q. When you read this when you were working at

Regeneron, were you certain that Genentech was correct about what it was saying?

A. I wasn't. I was skeptical of this article. As a scientist, we're often skeptical of articles and not that they think of everything. And I didn't -- I wasn't sure that this was right.

Q. What did you do in view of your skepticism?

A. Usually what scientists do when they're skeptical is they do their own experiment, and we did a study in rabbits.

Q. We'll get to that in a moment.

This issue of getting into the retina and the choroid, is it all or none like a light switch, Dr. Furfine?

A. No. I think there are degrees of penetration, and there can be examples sometimes where there is a sharp cutoff, but I don't think that was the case here. This is a gradient, if you will.

Q. Did Regeneron only have aflibercept to block VEGF, or did it have smaller molecules too?

A. We had small molecules. Well, we had something called a Mini-Trap. Kind of like what the FAB or the ranibizumab was a part of the antibody, we had the Mini-Trap that was a part of aflibercept that, in case I was wrong, then we would have the smaller molecule to move forward with as well.

Q. Just so it's clear, why did Regeneron create the

Mini-Trap?

A. Really in response to this report and other reports that suggested that smaller things do penetrate the retina better than larger things do.

Q. Let's take a look at one of your internal documents at the time. We'll call up PTX 83.

And, Dr. Furfine, is this an internal clinical program strategy meeting from the 14th of June 2003?

A. Yes, it is.

Q. And if we look on the first page, there's a number 4, formulation issues, Eric.

Who is that referring to?

A. That's this Eric.

Q. That's you?

A. Yes.

Q. Let's take a look at page 3 of the document, Dr. Furfine.

THE COURT: For the record, I'm fascinated by this time travel with documents and such. It looks like they were doing MSP. Very excited about this. Go ahead.

MR. BERL: It's probably the dot matrix printer or something.

THE COURT: As an aspiring boomer, I have greatly enjoyed this trip down memory lane.

MR. BERL: I'm with you.

BY MR. BERL:

Q. So looking at page 3, Dr. Furfine, it says "Systemic IV Administration, single-dose escalation IV with full-length VEGF Trap."

Can you explain what that means.

A. So this was -- IV stands for intravenous or the abbreviation for intravenous. So the idea here was to inject the VEGF Trap directly into the vein so you get what we call systemic exposure, and then with that systemic exposure you can penetrate the ocular tissue to treat the disease. And then these are the doses that were tested. You start low, and you go up higher.

Q. What is the full-length VEGF Trap referring to there?

A. That's aflibercept, full-size aflibercept.

Q. Why were you considering intravenous systemic administration to treat AMD with aflibercept?

A. There was evidence preclinically and clinically that the aflibercept -- that drugs could penetrate the retina and aflibercept preclinically could penetrate the retina after a systemic exposure. And so this was a good way to test the hypothesis in humans.

Q. And at this time did you know that you could get aflibercept into the retina by injection into the eye?

A. We did not. And part of the reason for doing the systemic study is that we maintained concern for that.

MR. BERL: I apologize, Your Honor. I think I said this is Exhibit 83. It's actually Exhibit 82.

THE COURT: Understood. Thank you.

MR. BERL: Sorry.

BY MR. BERL:

Q. Now, you had mentioned the Mini-Trap before. Were you considering the Mini-Trap for systemic intravenous administration?

A. No, only intravitreal.

Q. Let's take a look at the two bullets on page 2 of Exhibit 82. It says "Local administration - Full-Length Trap" and "Local administration - Mini-Trap."

What is that referencing?

A. Local administration here refers to an intravitreal injection, so a direct injection to the eye where that needle, as I was pointing out in that eye figure, it goes directly into the vitreous. So this is the possibility of doing both of these treatments using both of these drugs, it being administered intravitreally.

Q. Both of these drugs being aflibercept and the Mini-Trap?

A. Correct.

Q. Let's take a look in that section under "Issues & Risks." And in that section under "Local administration - Full-Length Trap," we've highlighted "intravitreal PK."

What does that mean?

A. So PK stands for pharmacokinetics. That's the science of seeing where a drug goes after you inject it or administer it, could be oral too. In this case we were injecting it. You see where it goes and how long it stays there. So you want to see does it penetrate certain tissues? Does it stay in the place you went? And how long is it in those places?

Q. Why is that listed as a risk or issue?

A. As we discussed a little earlier, we weren't sure that the drug was going to penetrate the retina after we shot it into the vitreous. And so we wanted to do our own study to see whether it did or didn't.

Q. Had Regeneron, at the time you were working on the project, compared the efficacy of aflibercept injected intravitreally in a mouse compared to systemically in a mouse?

A. Yes. There was a study done in the Campochiaro Lab where those things were compared directly.

Q. And if we turn to Exhibit 1785 in your binder -- and we'll put the first page of that on the screen -- is this the publication that you're referencing?

A. Yes, it is.

Q. And is the first author Saishin from 2013?

A. That's correct. And here's the Campochiaro that I referred to.

Q. Just at a high level, what was the result of this study?

A. The high-level result was that, if you inject the drug in the mice to give systemic exposure -- this was not intravenous, it was subcutaneous, but that still gives a big blood level and allows it to go into the retina from the blood. We compared that with an intravitreal injection to see if it could reduce the effects and the disease model that happened in the retina.

Q. What did better, the systemic administration or the intravitreal administration of aflibercept?

A. The subcutaneous injection. So the systemic exposure suppressed the disease model in the retina much more than the intravitreal did.

Q. You mentioned a moment ago a pharmacokinetic study in rabbits.

Was that an important experiment in the course of your project in developing Eylea?

A. Yes, it was a critical experiment.

Q. Let's take a look at Exhibit 1079.

Can you identify this 2005 document?

A. Yeah. This is a clinical investigator's brochure.

Q. And if we move to page 4 of the document, in the table of contents, under "Pharmacokinetics of VEGF Trap," what's Section 8.2 about?

A. That's the study that we did where we administered the Trap in rabbit eyes intravitreally and we measured how long it was there -- as I measured, pharmacokinetics is how long it's there -- and what tissue did it distribute it to. So did it get in the vitreous? Did it get in the retina? Did it get in the choroid? The two tissues, retina and choroid, where the disease would happen.

Q. Let's go to page 46 now, Section 8.2 of the same document, Exhibit 1079. And we've highlighted some language on the screen.

Can you explain, first of all, what is being measured in this study, Dr. Furfine?

A. Yeah. So we developed assays to measure the drug, the VEGF Trap, in the vitreous, in the choroid, and in the retina. And we collected those tissues after we injected the drug, and we measured the drug levels in those drugs. And here, as we say, the bottom-line result is, in fact, the VEGF Trap did penetrate the retina and the choroid.

Q. Let me just back up a moment ago. I want to break that down a little.

You said you developed assays. Is that another word for tests?

A. Yes. Sorry.

Q. No problem. That's okay.

You said you measured in the vitreous, the retina,

and the choroid. Did I get that right?

A. Correct.

Q. Where is it easier to measure how much aflibercept is present, in the vitreous or in the retina and choroid?

A. It's easiest to measure the drug in the vitreous.

Q. Why did you measure in the retina and choroid also?

A. The retina and choroid, as I mentioned, are the sites where the disease biology happens. It's where the VEGF is produced; it's where it needs to get blocked. If the drug does not get to the site of action of the biology, you can't block the biology.

Q. We looked at general results here. I want to look at the more detailed results.

If we could turn to Exhibit PTX 3257. Is this a report about the rabbit pharmacokinetics study?

A. Yes, it is.

Q. Let's turn to page 5 of this report.

When was this study conducted?

A. In July of 2004.

Q. Did you receive the results soon after that?

A. Yes, I did.

Q. And was -- were these data kept confidentially when they received it at Regeneron or was it published when they received it?

A. They were confidential to Regeneron.

Q. Let's take a look at page 100 with the results. And we've highlighted the sentence that begins "despite the differences described above."

What does this sentence convey?

A. The idea here is a comparison of a relatively large molecule, the full-length Trap, to the Mini-Trap, a smaller molecule; and that despite those size differences, both drugs got into the retina and the choroid at respectable and reasonable levels.

Q. What did you call the retina or related structure in this document?

A. The desired site of action. That's the place where the disease biology happens, and you need to get your drug there.

Q. Did you think it was enough for aflibercept just to get into the vitreous?

A. Absolutely not.

Q. Did you think that having aflibercept in the vitreous would somehow get rid of the VEGF in the vitreous and then suck VEGF out of the retina and thereby treat retinal diseases?

A. I can't imagine a way that would work.

Q. Was that finding that we show here in the rabbit pharmacokinetic study, that aflibercept will get to the desired site of action in the retina and related structure, good news or bad news?

A. This was very encouraging to us. It meant that we actually had a potential path forward to move forward with a program where we did an intravitreal injection and could expect that the drug would get to the site of action that we desired and have good effects on the biology of blocking VEGF.

Q. Dr. Furfine, without this information, would you have decided to move forward with intravitreal injection of aflibercept?

A. No, we would not have.

Q. If not enough aflibercept had reached what you call here the desired site of action, what would you have done?

A. We would have probably switched to the Mini-Trap, which would have -- you know, based on this study and on the analogy to ranibizumab, would have worked better to penetrate that tissue.

Q. Now, Doctor, I'd like to move to a different topic now, which is the dose or concentration that was used in your aflibercept project.

What dose did you understand Genentech to be pursuing for ranibizumab?

A. It's a 10 mg/mL solution that results in a 500-microgram dose because you take 50 microliters of that solution and inject it. So 10 mg/mL equals 500 micrograms.

Q. How did you understand that 10 milligrams per milliliter of ranibizumab that Genentech was using to map onto

the aflibercept that you were studying at the time?

A. We were looking at 40 mg/mL solution.

Q. How did you try to -- how did you map -- how would 10 milliliters of ranibizumab correspond or map onto aflibercept?

A. So they would be similar doses in that regard, but because the aflibercept was a more potent molecule, you would expect it might work even better even at the same levels or even slightly lower levels.

Q. If you wanted to make a similar or a me-too version of ranibizumab that had aflibercept instead, what kind of concentration would you have used in the formulation?

A. By the same analogy, given that the drug was somewhat more potent, you would not have to go any higher than 10 and you could potentially go lower, but you would have to prove that in the clinic.

Q. Now, did you follow Genentech's literature regarding ranibizumab when you were working on your project?

A. Yes.

Q. And let's put up on the screen Exhibit PTX 1839, the Gaudreault article from 2005.

Did you read this article when it was published?

A. Yes, around that time, somewhat after.

Q. While you were still working on the project?

A. Yes, near the time when it was published.

Q. Turning to page 2 of the article, can you explain this experiment and how you understood it at the time?

A. Yes. So this was a study where the drug was injected into the animal eyes and they were assessing the pharmacokinetics; so what the tissue distribution was and how long it was staying.

And during that assessment they also looked at if there were any adverse effects of these injections into the eye, and you could see that at the lower dose, the 10 mg/mL solution, there was relatively small amounts of inflammation; it was here absent to moderate.

But at the higher dose the 40 mg/mL formulation or 2 micrograms, that high dose, four times higher now, had substantial and concerning inflammation after this single injection.

Q. Is that the moderate to severe information?

A. Correct, yes.

Q. It says in the next sentence that it had been completely resolved by day eight.

Was that comforting?

A. Not really. I mean, I guess better than being there the whole time, but not good.

Q. How often would you administer a drug like this approximately?

A. So as we know now, these drugs are administered

roughly monthly. And, you know, so to have this happen every time you administer the drug would not be an acceptable tolerability profile.

Q. Now, just so the record's clear, what drug is being administered in this Gaudreault study?

A. It's ranibizumab.

Q. You said it was a pharmacokinetic study. Was there a long discussion of the health findings of the toxicity or was it more of a shorter, minor discussion?

A. It was a more minor discussion, but still it pointed to an issue that we were concerned about.

Q. Was this encouraging or discouraging at the time that you read it for purposes of potentially using a higher concentration?

A. This was quite discouraging for using a higher dose. I mean, we clearly see a lot of inflammation here, an unacceptable amount of inflammation. Apparently Genentech found it to be unacceptable as well because they moved forward with the 10.

Q. We'll look at that in a moment.

Let me just understand, though, Doctor, if you're trying to treat a disease, why wouldn't you just use as much as possible, the highest concentration you could?

A. I think this is the classic example of why you don't do that, is that you can get adverse effects. In drug

discovery almost everything we do is a yin and a yang. There's a benefit to be gotten from having a lot of something, and there's also a downside to be had of those things. And you have to find that balance of safety versus risk, efficacy versus adverse effects. And, you know, the higher you go, the higher the chances you're going to get an adverse effect that may dampen the benefit that you get.

Q. What about stability in formulation?

A. Higher concentration formulations with proteins in particular are much more challenging to do.

Q. What happens when it's challenging? What happens with high concentrations sometimes?

A. High-concentration formulations of proteins often aggregate and precipitate out of solution and cause particles.

Q. Is that a problem?

A. That's a big problem, and it's probably more of a problem for an eye drug than it is for a regular drug.

Q. Why is that a problem for an eye drug?

A. So there's three big reasons why particles are a problem for an eye drug. These are probably somewhat obvious, but one is, if you put particles in the eye, you can imagine obscuring your vision. And, in fact, that can happen.

The other thing is you can induce inflammation, which, in fact, we see inflammation here. We don't know that it was particles, but it very well could have been.

And the third thing is you can stimulate an immune response to the drug that you've injected. And if you get an immune response to the drug, you can end up neutralizing the drug so it doesn't work anymore.

Q. And when you said we --

THE COURT: I'm sorry. What do you mean when you say "immune response," Doctor?

THE WITNESS: So what happens -- immune response can be a number of things; so it's a good question. So a lot of times you get an antibody response, like to COVID. And if you make antibodies to COVID, you clear the COVID. If you make antibodies to your drug, you clear your drug.

THE COURT: Understood.

Sorry, Mr. Berl.

MR. BERL: Thank you. We're all here to help you understand. Doesn't matter if anyone else does.

BY MR. BERL:

Q. You said in your answer we see inflammation here. I just want the record to be clear. When you said there's inflammation here, were you referring to the Gaudreault reference on the screen, Exhibit 1839?

A. Yes.

Q. Now, let's go back with that in mind to the rabbit PK study that you had mentioned, which is PTX 3257, and the results at page 100. We looked at this paragraph before. I'd

now like to ask you about the language further down in this paragraph about how long the protein can be present in the tissue.

Can you explain what result you obtained in your study?

A. Yes. So as you can see here, the drug was present in the tissue for at least through 28 days. And, again, this is a yin and a yang situation. If you have a lot of drug around for a long time, there's a chance it could have an adverse effect. But if you have a drug around for a long time, it could be having efficacy for that time.

I was a little bit more on the optimist side of things in this case, but nonetheless one has a concern that you can have a problem with it, and you need to do further testing to sort that out.

Q. To be clear, Dr. Furfine, did you expect to obtain this result in the pharmacokinetic study in the rabbits of the protein being present in the tissue for up to 672 hours?

A. No, we did not expect this.

Q. Is that a high number or a low number?

A. It's a high number. This was, roughly speaking, about twice as good as ranibizumab, and that was encouraging to us.

Q. And just again so the record's clear, was this public at the time?

A. It was not.

Q. Now, given all the concerns that you've mentioned, why did you end up using a higher concentration?

A. So when you see one advantage -- in this case, it was how long it was staying in the eye; it was staying in the eye longer than ranibizumab -- you can actually leverage that to your advantage in another way by adding more.

So if you add more of something that's longer-lived, you kind of double down on the longer-lived. So every time you double the concentration that you inject, you get an extra half-life. If your half-life is already longer than ranibizumab and now you're getting more of them, this was an exciting possibility to reduce the number of injections a patient would have to get. And so we were excited about that possibility.

Q. Did you still have all those concerns you mentioned about toxicity and stability?

A. Absolutely.

Q. So what did you do in view of those concerns?

A. We did a lot of experiments to figure out whether we could make a stable formulation and whether we were going to have toxicology that was associated with higher concentrations.

Q. I'd like to discuss some of those experiments with you. Let's turn to Exhibit PTX 81.

What is this document, Dr. Furfine?

A. This is a summary of a lot of the nonclinical work that we did, including the formulation development to support clinical studies.

Q. You've been using the term "nonclinical" or "preclinical." Is that experimentation done before you actually administer something to human beings?

A. Yes.

Q. Now, let's turn to the Bates number ending in 262 which is on page 10 of the document. And this is under -- at the top of the page we can see here 1.3. It's a little faded, but it says "Summary of Formulation Development." And then there's a Table 3.

Can you explain what's shown in Table 3.

A. Yes. This shows four formulations. Two of them are intravitreal formulations, and then the other two are what was used in the cancer programs for systemic, either IV or subcutaneous is SC.

The intravitreal formulation 1 there was the first formulation that we moved forward with into clinical studies.

Q. Why did you start with this formulation, labeled ITV-1?

A. So as I mentioned, you don't want to have anything in your formulation that is, you know, more than what you need or have a reason for having it there. So this was a minimalist approach that we took to this formulation. And we wanted to

make sure that we were using things that we thought had a high probability of success in the eye because there wasn't a lot of experience with eye formulations.

And so we focused on mostly excipients that we knew actually were there already. Sodium phosphate, of course, is in the eye; sodium chloride, saline, same thing is in the eye. So we used ingredients here that we thought would be reasonably well-tolerated. It was kind of a minimalist approach, if you will.

Q. Didn't you already have formulations of aflibercept that had been developed for systemic treatment of cancer?

A. Yes. The two furthest to the right, IV and SC, were already developed.

Q. Did you consider starting with those in your research on an ophthalmic formulation?

A. That didn't occur to us. That's not how you do science.

When you make a formulation, when you make a drug or a drug product, there's this idea of fit for purpose. You have to decide what you're going to do with the drug, what's it going to be used for, and what are you stabilizing.

And so you don't start with something that was made for something else to use it for something completely different. You have to start over again and ask your question: What's the right thing to do in this situation?

And so that's what we did. We started over.

Q. Are there considerations that are relevant for intravitreal formulations that are less important for intravenous or subcutaneous formulations?

A. Absolutely. One big one, and maybe one of the biggest ones, was that there's a stress that happens in intravitreal formulations that wouldn't happen in systemic formulations.

So when you do an injection in the eye, you can imagine you want to use the smallest needle you can because who wants a big needle in their eye?

THE COURT: That is well established.

THE WITNESS: See, I don't have to do too many more studies on that. It's already known.

So what you do is you use these really narrow-bore needles. It's a very thin hull. What happens is, when you force solutions, protein solutions especially, through a narrow-bore needle, you create what's called shear stress. It's like a pressure, and that creates a stress that can cause a protein to come out of solution.

So you need to add agents into your formulation, ingredients that stabilize the solution and keep the drug in solution under these kinds of stressful situations. That would not happen for IV and SC.

THE COURT: When you say "in solution," I assume you

mean still floating in the carrying liquid, for lack of any scientific term.

THE WITNESS: That's exactly right. That's perfectly scientific.

And what happens here, in fact, is if you don't survive shear stress, you see particles that are clearly -- by definition, a particle is not in solution. So, in fact, it's black and white. They're either in solution or they're not.

THE COURT: And in this form, again, because we're using a needle and a syringe, particles might be attached to the syringe itself or --

THE WITNESS: No. The manufacturer of syringe needles and the like has them clear of, really, any detectable particles. And so if you saw particles after shooting the drug through it, it would be solely the result of the protein coming out of the solution.

MR. BERL: I think what Your Honor -- what the Court may have been asking is do the particles get stuck in the needle? Is what you're asking, Your Honor?

THE COURT: Yeah. You're talking about shear stress which I'm envisioning sort of three lanes of traffic merging as one, right?

THE WITNESS: That's right. That's right. That's right.

THE COURT: You have all that there. So when that

occurs and that buildup occurs, if the protein falls out of solution, where does it go? Where do the particles exist?

THE WITNESS: So most -- it's a great question. So most of the time they actually don't clog the needle, but they could. If you had a severe enough response, you could actually clog the needle.

What usually happens is you shoot them into the eye, and that's where you get your trouble.

THE COURT: Okay.

BY MR. BERL:

Q. Do you ever want to shoot a particle into the eye, Doctor?

A. No, no, you don't.

THE COURT: Again, I believe that also has been well established.

BY MR. BERL:

Q. Now, let's take a look at the same page further down, 262 in Exhibit 81.

Was the ITV-1 formulation that you said you started with, was that ultimately a formulation that met your needs for intravitreal administration?

A. No. In fact, it was problematic in this very stability test that we were just referring to. It did not withstand shear stress to the degree that we wanted it to and had a second problem that it didn't stand up -- withstand heat

stress as well.

Q. But let's take a closer look at those data. If you could turn to Exhibit PTX 2223 for a moment.

Are you familiar with this document, Dr. Furfine?

A. Yes.

Q. Is this a protocol for stability study?

A. It is.

Q. And we're looking at the first page here and it talks about data from stability studies indicate that there's a problem with the physical stability of VEGF Trap in the current ITV formulation above 10 milligrams per milliliter VEGF Trap. Do you see that?

A. Yes.

Q. So first of all, when we say current ITV formulation, was this referring to what you've been calling ITV-1 in your testimony?

A. Yes. It was the first clinical formulation we used.

Q. When do you start to have problems with ITV-1, at what concentrations?

A. Concentrations that were above the 10 mg/mL. So if we wanted to go to 20 or 40 or whatever, that's where we started to have issues where it was not surviving this syringe needle test that we do. We have to -- you actually put it through tests that mimic what's going to happen in real life. So we say is it going to make it through without making

particle? We actually do the experiment before we stick it in someone's eye.

THE COURT: Comforting.

MR. BERL: For all of us.

BY MR. BERL:

Q. Doctor, is that consistent with the principle you articulated earlier that you get more instability and aggregation at higher protein levels compared to lower?

A. Yes, it is.

Q. And let's take a look -- let me ask this: Before you did this manipulation where you did the syringe, was all of the aflibercept in the solution?

A. It started in the solution, yes.

Q. Let's go further down this page on 2223. The "in addition" paragraph, if we could pull that up.

Is this another test that you conducted on your ITV-1 formulation?

A. Yes. This is an agitation stress study that we did, and it's kind of analogous to a shear stress. Basically what you do is you whip the solution around for long periods of time and see whether it comes out of solution. It's like an extreme agitation.

Q. Went you say you whip it around, is that referenced on the document on the page as "vortexed"?

A. Vortexed, that's right. That's what we call it.

"Vortex" is another word for whipping around.

THE COURT: Thank you.

BY MR. BERL:

Q. This document says -- Exhibit 2223 -- that the ITV-1 formulation has been shown to be prone to precipitate when vortexed.

What does that mean?

A. That means the protein was coming out of solution. It was precipitating when we stressed it by -- this is exactly what it does, is it goes around in circles at a really high rate. So it's like shaking it up as hard as you can, or even more than that, for two hours.

Q. Before you shook it, was all of the aflibercept in solution?

A. Yes.

Q. And then when you shook it, was it still all in solution?

A. No. It came out as a result of being stressed by the shaking.

Q. Now, is this condition of vortexing or whipping it around, as you've been calling it, is that relevant as to how the drug's actually going to be used?

A. Absolutely. All the tests we do along this line are called accelerated stability studies. The idea is you want to, in a short time, mimic what happens in real life that might

include something that happens over a long time.

So there's a lot of shaking that can happen over the course of time in preparing the drug in the manufacturing, distributing it, bouncing around in the clinic, and so on and so forth. And so you need to -- if you shake it up a lot in a short period of time, you can mimic what happens for longer times.

Q. Did you have any experience while you were at Regeneron with things coming out of solution in actual use?

A. Yes. So with another program that preceded the VEGF Trap was called the IL1 Trap. So we had a formulation that we developed there, and we used a shorter vortex time. We only did 30 minutes, not the two hours. And we thought that was good enough at the time; we didn't know any better.

And what happened, disappointingly and kind of interestingly, is that during a clinical study a few months down the road when the manufacturing facility does its check on how's the drug supply doing, they saw particulates coming out. And we didn't anticipate that because we had never seen it happen. And we, even in the stressful situation, didn't see it happen.

So we instituted a new test in response to that, which was essentially to vortex not for 30 minutes but now for two hours because we didn't want this to happen to us again.

Q. Doctor, it says later on in the same paragraph on 22,

23, "VEGF Trap no longer precipitated upon vortex when the clinical DP was spiked with .03 percent polysorbate 20."

Can you explain what that means?

A. So basically we had to find an ingredient that we could put in the formulation that would make it soluble under the conditions of vortexing. And so one of the ones that we tested is this organic cosolvent, polysorbate. We had prior to that a cosolvent called PEG. We thought this one might be better, and we tested it. And, in fact, it did work superiorly to PEG.

Q. When you said keep it soluble under the conditions of vortexing, are those conditions also relevant to actual use of the product?

A. Yes. Everything we do in an accelerated stability study is intended to mimic what happens in real life over sometimes the same and sometimes over longer periods of time.

Q. So was this ITV-1 formulation that came out of solution upon the needle test and being vortexed, is that something you wanted to move forward with as a product?

A. No. It would have been unacceptable. It would have been very high risk and probably would have failed.

Q. What did you do as a result of that?

A. We started examining new formulations where we put in different ingredients that we thought would make it more stable to this agitation and shear stress and also the thermal tests

that we do.

Q. Dr. Furfine, let's turn to Exhibits 97 and 98 and show them together because they're associated. They're also in your binder, but we'll put them on the screen.

Can you explain what Exhibit 97 and 98 are.

A. Yeah. So these are the stability tests with the new formulations that had excipients or ingredients that we thought would better stabilize the two problem areas, thermal stability, heat, which also translates to shelf life. If you can tolerate heat better, you're more likely to even last longer in cold. There's kind of a correlation there. And then also the agitation stability.

Q. So we'll get to the data in a moment. Is Exhibit 97 an email from November 2005 from Kelly Frye to various people that you received?

A. Yes.

Q. Okay. And it says, "I've attached a chart with the new formulations so that it's clear what the new formulations consist of."

Do you see that?

A. Yes.

Q. And if we turn to Exhibit 98, PTX 98, its says, "New ITV Formulations."

Is that the chart that Kelly Frye attached in the email?

A. Yes, it is.

Q. And I want to take a look at this chart in Exhibit 98. What is this showing?

A. This is showing what formulations we tested. They're listed 1 through 8. Number 1, it says old. That's IVT-1. It's the original one that we drove into the clinic that was insufficient long term.

And then the others, if you look at the top row, the columns show the ingredients we tested and in what concentrations we tested them to see if we could make superior formulations.

Q. So, for example, ITV-1, did that have any sucrose or mannitol?

A. It did not.

Q. And then did you test at least one formulation with sucrose, Formulation Number 41?

A. Yes. 4 was sucrose.

Q. Now, we see all these formulations with ingredients and amounts. How did the formulations actually get made?

A. Laboratory scientists who are easily skilled to do this. It's not a major problem.

Q. What kind of training or expertise or degrees did the people who made these formulations require?

A. Nothing more than a bachelor's degree would be required.

Q. And how much training in making formulations in order to take this information and turn it into something that has a formulation?

A. I think if someone came in fresh out of school, a matter of a week or two would probably be sufficient to get them to know this.

Q. Now, I'd like to go through a couple of the ingredients with you. It says "10mM" -- is that millimolar?

A. Millimolar yes.

Q. -- "phosphate." Was that in all of the formulations?

A. Yes, it was.

Q. And what is that?

A. That's a phosphate buffer. It's -- a buffer is used to maintain the pH of the solution in a narrow range.

Q. And did you understand that other buffers could do that too?

A. Yes, they could, of course.

Q. We have sucrose listed here. What did you understand sucrose to be doing?

A. Sucrose in this case we were using primarily as a thermal stabilizer, so basically make the protein more -- less susceptible to heat and increase the shelf life.

Q. What was your understanding as to whether other stabilizing agents other than sucrose could do that too?

A. They could potentially work. In fact, we tested

mannitol, which is a very similar chemical; it's the same class of molecule. And, in fact, it did work to some degree.

Q. Now, if these ingredients are useful to maintain the pH and to keep the solution -- keep the protein in solution under stress like thermal conditions, why wouldn't you have just included them in the first place?

A. Well, as I mentioned, you know, we take as strategy a fit for purpose, first of all; and, second of all, you can't add things that you don't know you need and you can't add more of them than you need. And so you really need to do an experiment to test what's my problem? And now what am I going to add to solve that problem? And what's the least amount I can add of it to solve the problem? You don't want to give anything in a drug that you don't need to give.

Q. I see PS 20 listed here. Is that polysorbate 20?

A. Yes, it is.

Q. What did you understand that to be doing in the formulations?

A. We refer to it as an organic cosolvent. It helps stabilize and keep the drug in solution under stresses like agitation and shear.

Q. What was your understanding about whether other organic cosolvents other than polysorbate 20 could do that?

A. They can. In fact, PEG is right next to it and was serving a similar purpose.

Q. Let's take a look at PTX 86, Dr. Furfine. Can you identify this document for the Court?

A. Yes. This is a meeting between -- our partner at this time was Aventis, the pharmaceutical company partner. Was a joint meeting between our teams to discuss the development of the VEGF Trap.

Q. Just so the overall story's clear, is Aventis a predecessor of Sanofi?

A. Yes.

Q. And if we go to page 11, did you attend this meeting?

A. I did.

Q. And did you present to Aventis about intravitreal formulation issues relating to aflibercept in 2004?

A. Yes, I did.

Q. Let's take a look at what you said on page 5.

What did you say at the beginning of this paragraph?

A. Basically sort of what the data that we've shown so far is that we needed an organic cosolvent to stabilize the protein against agitation or shear stress induced coming out of solution. We call it aggregation, but it's a forcing a precipitation, not a solution.

Q. And what examples did you provide of organic cosolvents in your 2004 presentation to Aventis?

A. As you can see there, there are PEG and polysorbate, the same two that were on that table that we just were looking

at.

Q. How did you understand organic cosolvents like polysorbate to work?

A. So proteins have a surface, and on that surface there can be patches of different sort of chemical nature. And sometimes there's a patch that we call a hydrophobic patch. Hydrophobic, as I mentioned, means don't like water.

If you have two hydrophobic patches one on one protein, one on the other one, they like to come together because neither of them wants to be in water but they prefer -- hydrophobic likes hydrophobic, doesn't like water.

So when you have two hydrophobic patches, you can get an aggregation that happens, and that's when the protein can come out of solution.

If you have an organic cosolvent in there, that can kind of coat or associate with that hydrophobic patch because there are parts of polysorbate that are hydrophobic as well. So the hydrophobic likes the hydrophobic, and they kind of associate. And that blocks the protein from doing that because it's already got polysorbate there. So, basically, it stabilized it to hydrophobic against intermolecular, what we call molecule-to-molecule, hydrophobic aggregation.

Q. Let's take a look at your testing of the various formulations, Dr. Furfine. If we could go to 2223 in the first instance, and I'm now on page 2. We looked at page 1 a moment

ago.

In the bottom of the page, which is shown here on the left, what conditions are you studying in this test?

A. Yes. These are a classic subset of the accelerated stability that we do. The agitation, which is essentially vortexing that we discussed before, and the thermal stability. So you incubate the tubes of drug formulation at elevated temperatures.

Q. And let's take a look at some of the results of the testing.

If we could go to 2224 and look at page 1. If we could go down just a little more, Mr. Schliesske, and look at the 45-degree data.

Can you explain what these data shown in PTX 2224 reflect?

A. Yes. As you can see, if you look at the yellow lines on the bottom there, the formulations that contain a thermal stabilizer, in this case it's sucrose, are doing pretty well. They're not aggregating, and they're not coming out of solution. But you see the number is higher in Formulation 5 that does not have the sucrose in; it only has the sodium chloride in it. There's some other excipients but no thermal stabilizer, and so the number is higher.

So when numbers go up higher, those are the results of particles forming and light scattering, and the more light

scatters, the higher the number goes. So particle, light scattering both go up, and that's how you know you're getting precipitation and particle formation.

Q. Let's break that down just a little. The test you're running at the top of it says OD 405. What is that?

A. That's the absorbance at 405. That's a measurement of the scattering of the light in the solution. So when you send a light beam through the solution, if you have particles, it scatters them and then it doesn't make it through the detector. And that's how you measure the 405.

Q. So in laymen's terms, are you measuring how clear or how cloudy the solution is?

A. Essentially, yes.

Q. And the numbers at the bottom that you're showing that are in yellow under 14 day 45 degrees, did I get it right that the higher numbers are worse than the lower numbers?

A. Higher number is worse, like golf, as you say.

Q. Now, what did that teach you with respect to whether you wanted to use a thermal stabilizer?

A. This was an indicator that, in fact, we needed a thermal stabilizer. We needed something more than just the salt that was in IVT-1.

Q. And let's now go to additional data in this test. If we could go -- and we're still in 2224. On the left it says VTX.

A. VTX is going -- it's an abbreviation for vortex. So we're back to this agitation stress. And you can see the times. We started with 30 minutes of vortexing, which was our old way, and then we moved to up to see how much it could do. And we went up the way up to two hours, 120 minutes, two hours of vortexing. And you can see the numbers are not going up at the OD 405.

Q. And just to be clear, did you have organic cosolvents in these formulations?

A. Yes.

Q. And so what did you think about these results?

A. These indicated that the more recent organic cosolvent of polysorbate was going to be necessary and that it was superior to the PEG. The PEG was in the IVT-1. We didn't have polysorbate there.

Q. If we look at the next test or another test also on page 1, there's something a little higher up.

We did that one already, I think, Mr. Schliesske. I think this is 1.9.

There's something called F/T there. Can you explain for the Court what that test is?

A. Yeah. F/T stands for freeze/thaw. So when you manufacture a drug, there are lots of times when you have to freeze it, usually in bulk, to store it until you're going to fill it or modify it in some way to get it towards its final

form.

And so you may several times thaw the drug out to transfer it into whatever its new manufacturing state is and then refreeze it because maybe you don't use it all; you just take part of it. And so you need to be able to make your drug stable to freeze/thaw.

And polysorbate is actually pretty good at stabilizing drugs to freeze/thaw. And as you can see here, it did a nice job both through four or even eight freeze/thaws.

Q. In your testing, Dr. Furfine, out of all of these formulations, which one performed best?

A. The 5 percent sucrose, .03 percent polysorbate. So that's Number 2 there.

Q. What is this formulation called?

A. That formulation is now called Eylea.

Q. Did you also study the ability of your formulations to withstand the shear stress of a narrow needle?

A. Yes, we did.

Q. And what did that testing show with respect to whether your 40 milligram per milliliter formulations you created was able to withstand shear stress of a 30-gauge needle?

A. We required the polysorbate to withstand the shear stress in addition to the agitation stress.

Q. Did the 40-milligram-per-milliliter formulations you

created with polysorbate withstand shear stress of a narrow needle or did they fail?

A. They passed that test.

Q. If your 40-milligram-per-milliliter formulations had not passed that test of getting through a 30-gauge needle, would you have developed it for intravitreal formulation?

A. No, we would not have.

Q. Did you perform additional testing, Dr. Furfine, that we haven't discussed or shown here?

A. Yes. There's a lot of testing needed before you can move a drug into the clinic.

Q. Did you think those tests were important in terms of determining whether you could have a successful 40-milligram-per-milliliter intravitreal formulation with aflibercept?

A. We only do tests that we consider important.

Q. Let's bring your patent up.

THE COURT: You asked, Counsel.

MR. BERL: I deserved that. Sorry.

THE COURT: I tell you what, though, since I've interrupted and my personal comfort schedule usual regimen was disrupted earlier, let's take five and take a personal comfort break and we can come back.

Doctor, we're going to take a few minutes. You're not allowed to talk to anybody. They're not allowed to talk to

you. So don't mean to be discourteous.

THE WITNESS: Can I sit here?

THE COURT: You're welcome to, but you're free to not aggregate as a particle.

See, I'm learning. How about that?

You do not have to remain there, Doctor. If you need to use the restroom, whatever, feel free. But no one can talk to you.

THE WITNESS: Thank you.

(A recess was taken from 4:16 p.m. to 4:23 p.m.)

THE COURT: Counsel, you may proceed, sir.

MR. BERL: Thank you, Your Honor.

BY MR. BERL:

Q. If we could put up PTX 2 again. That's your patent.

Dr. Furfine, what did you think you and your coinventors had invented when you filed the patent application?

A. We thought we'd invented two things. One is Eylea, the drug that's on the market now; and the second thing is a set of principles and guidelines on how to formulate aflibercept into an intravitreal formulation.

Q. As you look back on your career, Dr. Furfine, how long have you worked as a scientist in the pharmaceutical field?

A. Since 1989. I'm sorry. I can't do that math.

Q. In that time that you've been working in this field since 1989, how does the invention described and claimed in this product patent, the '865 patent, fit in?

A. This is something that I remain very proud of. I guess maybe just to give a little context, you know, I've always wanted to make medicines, and that's what kind of gets me up in the morning, is knowing that everything we do in the lab or in designing strategies for experiments is with the goal of making a medicine that's going to make somebody feel better. And that's what motivates me; it's what gets me excited about going to work.

And to know that we actually created something here that became a drug that transformed the way age-related wet AMD is treated and -- it's like night and day, right? I mean, these drugs are amazing. They stop people from going blind. And to have contributed to that with my colleagues is something I'm very proud of.

MR. BERL: Thank you very much, Dr. Furfine.

THE COURT: Cross?

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

THE COURT: You may.

MR. RAKOCZY: Good afternoon, Your Honor. William Rakoczy for Mylan and Biocon. May I proceed?

THE COURT: You may. Sorry. Go ahead.

CROSS-EXAMINATION

BY MR. RAKOCZY:

Q. Good afternoon, Dr. Furfine.

A. Good afternoon.

Q. I represent Mylan and Biocon. I have just a few questions for you.

Now, you testified quite a bit at the beginning of your direct testimony about the aflibercept molecule, correct?

A. Correct.

Q. Now, you don't purport to have invented the aflibercept molecule, correct?

A. That's correct. It was before my time at Regeneron that that molecule was invented.

Q. And your patent doesn't purport to invent the molecule aflibercept, correct?

A. Correct.

Q. The patent is about a formulation of the aflibercept molecule, correct?

A. Correct.

Q. So the molecule was known before your patent, correct?

A. Yes, it was.

Q. Now, you talked a lot about aflibercept penetrating the retina.

Do you recall that testimony?

A. Yes.

Q. There are no studies or tests in your patent about aflibercept and whether it will penetrate the retina or not, correct?

A. That's correct.

Q. There are no PK studies on aflibercept of any kind in your patent, correct?

A. That's correct.

Q. There are no tox studies on aflibercept in your patent, right?

A. That's right.

Q. No rabbit studies, no monkey studies, correct?

A. That's correct.

Q. As a matter of fact, there's no human studies of any kind on the formulations in your patent, correct?

A. That's correct.

Q. Your patent -- the only tests it has are you made formulations, you put them on stability, and then you tested them for native conformation and turbidity, correct?

A. That's correct.

Q. Now, you mentioned some skepticism about 40 mg/mL concentration. Do you recall that?

A. Yes.

Q. Now, your patent doesn't contain any statements about skepticism or insights about 40 mg/mL, correct?

A. It doesn't contain anything about skepticism. That's correct.

Q. As a matter of fact -- I'm sorry. I didn't mean to interrupt.

A. There is data on 40 mg/mL in there, though, but no statements of skepticism.

Q. Correct. Let me rephrase it. I'll make it clear.

Your patent doesn't say anything in there that skilled persons didn't think you could make a 40 mg/mL concentration formulation, correct?

A. Correct. It does not say you can't do that.

Q. In fact, your patent covers any concentration of aflibercept, correct?

A. I don't know what -- whether the claims would be -- cover -- what the range of coverage is. That's kind of out of my field.

Q. Let's pull up PTX 2. It's in your counsel's binder he gave you.

If we could have PTX 2 on the screen, Claim 1, please.

THE COURT: Do you have that, Doctor?

THE WITNESS: I do.

THE COURT: Okay. Go ahead, Counsel.

MR. RAKOCZY: Could we have Claim 1, please. If we could blow up Claim 1, please. Thank you, Mr. Gibson.

BY MR. RAKOCZY:

Q. You see this is Claim 1 of your '865 patent, Dr. Furfine?

A. Yeah. Hang on just a minute here. Yep, go ahead.

Q. You see Claim 1 is directed to a vial that comprises, and the first ingredient is a vascular endothelial growth factor, VEGF antagonist, correct?

A. Correct.

Q. It doesn't specify any concentration there, right?

A. That's correct.

Q. So it could be below 40 mg, well above 40 mg. That would cover any concentration of aflibercept, correct?

A. You're kind of getting into this space of legal interpretation, I think, of claims, and that's out of my field.

Q. My question is simple. When it says "VEGF antagonist," it doesn't specify a concentration, correct?

A. It's true that it does not specify a concentration.

Q. And if we look at the other ingredients, the buffer, for example, it doesn't specify a buffer either, right?

A. It does not specify a buffer, correct.

Q. So that could be any buffer?

A. I don't think it could be any buffer, but in this case it does not specify the buffer.

Q. And it doesn't specify the stabilizing agent either, correct?

A. It does not specify it in this specific claim, no.

Q. Let's talk about the formulation. And I want to start with polysorbate 20, as you can imagine. That's a nonionic surfactant, correct?

A. Correct.

Q. And in your formulation development work at Regeneron, you and your colleagues described polysorbate 20 as a stabilizer or stabilizing agent, correct?

A. Yes.

Q. Let's look at some of your formulation work. Let's start at DTX 722. It's in your binder, and I'll also pull it up on the screen for you.

A. This is your binder now?

Q. Yes, sir. My apologies.

So you have my binder, and then I'll always pull the document up on the screen for you as well.

A. 722 you said?

Q. Yes, at page 1. I want to look at the first email.

A. Hang on a second. Okay.

Q. Look at the first email you see. It's from Amy Galluccio to you, coinventor Kelly Frye and others, dated November 8th, 2005, with an attachment entitled "Sucrose VGT formulation help." Correct?

A. Yes.

Q. Now, I want to move to page 2 of this email, and

there's an attachment entitled "Product Composition." Do you see that?

A. Yes.

Q. And below that we see a formulation, right?

A. Correct.

Q. And we see 10 millimolar phosphate, 40 millimolar NaCl, 0.03 percent polysorbate 20, and 5 percent sucrose.

Is that the formulation?

A. Correct.

Q. Now, I want to focus on --

A. The formulation is 40 mg/mL VEGF Trap too and pH .5, but I assumed you were inferring that, but I just want to make sure.

Q. Absolutely. And I want to go to the paragraph above that and look at the first sentence. You see it says, "This is an unstable formulation for VEGF Trap since there are minimal excipients for intravitreal delivery and the formulation contains a high concentration of VEGF Trap."

Do you see that?

A. Yes.

Q. And then it goes on to say that "The drug substance, formulated drug substance, or drug product is held or stored at 25C and should be kept to a minimum during the manufacturing process."

Do you see that?

A. Yes.
Q. And that "Temperatures above 25C must be avoided," right?
A. Yes.
Q. And that it "should be held or stored at less than minus 20C," correct?
A. Yes.
Q. So this was an unstable formulation as of the date of this email, November 8, 2005, correct?
A. I would have to look at this a little more closely to make sure I understood the context at which this was being stated.
Q. We can agree your formulation group attached this product composition memo, and they said this is an unstable formulation, correct?
A. I think that what you stated in the text is absolutely correct, but I think there are -- stable to what? And so you have to take it within the context, and I'd have to think back to things that I don't have the information on here as to what the situation was that we're talking about being stable to, you know.
So it's possible that it could be stated as being unstable in this situation, does not necessarily mean it's unstable to become a marketed product and used in the clinic as we want.

Q. We can at least agree that as of November 8, 2005, this formulation, someone wrote, is unstable, correct? Can we agree with that?

A. It is stated as such in the text, yes, absolutely.

Q. Now, let's look at the table on that same page, and here we have the ingredients of the formulation. And we can see that the solvent in this formulation is the WFI, or the water for injection, correct?

A. That's correct.

Q. And that's used to dissolve the aflibercept, correct?

A. Yes.

Q. And the buffer is phosphate, correct?

A. Yes, it's a mixture of two different salt forms, but yes.

Q. And then the sucrose is identified as a stabilizer, correct?

A. Correct.

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

A. Yes, it is.

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

A. It is in this document not identified as a solvent.

Q. And polysorbate 20 is not used to dissolve aflibercept, correct?

A. It is not used to dissolve aflibercept.

Q. And this document also does not identify polysorbate 20 as a cosolvent, correct?

A. In this document it does not.

Q. And, in fact, in your development of the Eylea formulation, you did not use polysorbate to remove or dissolve aggregates, correct?

A. That's correct. We did not use it to remove or dissolve aggregates.

Q. And it doesn't do that, right? Once there's an aggregate in the formulation, you don't put polysorbate in there to dissolve it, right?

A. That is typically correct, yes.

Q. Now, let's go to another one of the formulation development memos. I believe even after 2005 we'll see representations of polysorbate as a stabilizer.

So let's look at DTX 736 in your binder, and it's also on screen. And you see this is an email dated April 21st, 2006, now, with attachments from coinventor Dr. Graham and copied to you and coinventor Dr. Dix, correct?

A. Correct.

Q. And if we go to page 3 of this exhibit, we see a memo from coinventor Dr. Graham that he signed and actually dated April 21, 2006, correct?

A. Yes, I see -- you said page --

Q. Page 3 of the exhibit. So it would be --

A. I have -- it's weird. It says page 1 of 1, 1 of 2, 2 of 2.

Q. I apologize. I'm referring to the exhibit number. So DTX 736.0003.

THE COURT: The bottom right-hand corner in bold typeface, Doctor.

THE WITNESS: Okay. Yeah, 0003. Got it now.

BY MR. RAKOCZY:

Q. So just for the record, on page 3 of DTX 736, we have Dr. Graham signing and dating this memo, April 21, 2006, correct?

A. Yes.

Q. It's entitled "Revised pH for 40 mg/mL VEGF Trap for ITV in a 0.03 percent polysorbate-containing formulation," correct?

A. Yes.

Q. And the first sentence, obviously, identifies this as a formulation of VEGF Trap for intravitreal delivery, correct?

A. Yes.

Q. And if we look at the formulation here, we can see a formulation identified as 10 millimolar phosphate, 135 millimolar NaCl, 0.03 percent polysorbate 20, 40 mg/mL of VEGF Trap pH 6.3, correct?

A. Correct.

Q. Now, I notice there's no sucrose stabilizer in this

formulation, correct?

A. That's correct.

Q. So let's look at the table below that and let's see what folks said about these ingredients. And, again, water is the solvent, correct?

A. Yes, it is.

Q. That's what's dissolving the aflibercept in this formulation, correct?

A. It's not dissolving the aflibercept because the aflibercept is already in a solution prior to adding the WFI.

Q. So aflibercept is already in solution. Then you add the water?

A. Yes.

Q. And then we have the other ingredients. We see the phosphate buffer again, correct?

A. Yes.

Q. We have the NaCl, salt, correct?

A. Yes.

Q. We have no sucrose stabilizer this time, right?

A. Correct.

Q. So this formulation as of April 2006 does not have the sucrose stabilizer, right?

A. This specific memo quotes a formulation that does not have the sucrose in it, correct.

Q. And this memo identifies the function of

polysorbate 20 as stabilizer, correct?

A. Yes, it does.

Q. It doesn't say solvent; it doesn't say cosolvent. Correct?

A. It does not say solvent or cosolvent.

Q. All right. Now, let's jump back to the formulation on DTX 722, if we could very quickly.

THE COURT: That's on page 2, Counsel?

MR. RAKOCZY: Yes. And, Your Honor, I apologize.

THE WITNESS: This is .0002? Is that the right one?

MR. RAKOCZY: Yes.

Your Honor, I neglected to move to admit DTX 722 into evidence.

THE COURT: Any objection?

MR. BERL: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 722 was admitted.)

MR. RAKOCZY: And I also neglected to move to admit DTX 736 as well, please.

THE COURT: Any objection to 736?

MR. BERL: No objection.

THE COURT: Without objection, DTX 736 is hereby admitted.

(DTX 736 was admitted.)

BY MR. RAKOCZY:

Q. Now, this formulation does have the 5 percent sucrose, correct?

A. Yes, it does.

Q. So this is similar to the Eylea formulation, right?

A. Yes, it is.

Q. So let's take a look at that. I'd like to go to PTX 1519, pull it up on screen for you.

A. Is this now back in my --

Q. This is in the same binder I gave you.

A. I thought you said -- there are Ps here. Sorry.

Q. There should be PTX 1519 in the binder I gave you.

A. I got it now.

Q. Or my colleague. I apologize.

A. I got it now.

Q. And this is the drug product section from the Eylea BLA, and I'd like to focus on components of Eylea, which are on page 5 of PTX 1519.

A. This is your 1519.0005?

Q. Yes, sir.

A. Okay.

Q. We can see on screen we have a Table 1.

A. Yes.

Q. And you see it is entitled "Nominal Composition of VEGF Trap-Eye DP Formulation," correct?

A. Yes, it is.
Q. And this identifies the ingredients of Eylea and the functions, correct?
A. Yes, it identifies the ingredients and the functions.
Q. So we have aflibercept, the active ingredient, correct?
A. Yes.
Q. We see the buffering agents, the phosphate again, correct?
A. Correct.
Q. We see the sucrose stabilizing agent, correct?
A. Yes.
Q. And the BLA then identifies polysorbate 20 as stabilizing agent, correct?
A. Yes.
Q. It does not say solvent or cosolvent, correct?
A. It does not.
Q. And you know what a BLA is, don't you?
A. Yes.
Q. So a BLA, they're supposed to be truthful and accurate, correct?
A. They must be truthful and accurate, yes.
Q. Because you're making representations to the FDA to seek approval for your drug, correct?
A. That's correct.

Q. So in this BLA identifies the ingredients and the function. It represents to the FDA the polysorbate 20 functions as a stabilizing agent, correct?

A. Yes, it does.

Q. Now, let's look at the same exhibit, page 5. I'm sorry. Let's go to the same exhibit, page 6, sir. My apologies.

Here we have another table and this one is Table 2 from the BLA, and it says, "Role of Excipients in the VEGF Trap-Eye Formulation," correct?

A. Yes.

Q. And the role of polysorbate 20 here is identified again as "stabilizing agent," correct?

A. Correct.

Q. Not solvent?

A. Correct.

Q. Not cosolvent?

A. Correct.

Q. And it goes on to provide additional description. Do you see there it says for polysorbate 20, "The addition of polysorbate 20 reduces the rate of aggregation and precipitation when the protein is handled and agitated as a liquid," correct?

A. Correct.

Q. And you agree with that, correct?

A. I do.

Q. Now, it says "reduces the rate of aggregation and precipitation." I think we just established polysorbate 20, it doesn't dissolve aflibercept, right?

A. That's correct.

Q. And it doesn't dissolve or get rid of aggregates, correct?

A. That's correct.

Q. And just to be clear, there are no solvents identified in this formulation to the FDA other than water for injection, correct?

A. That's correct.

Q. All right. I'd like to talk a little bit about some of the information that you were tracking from your competitors like Genentech.

Do you recall testifying about that?

A. I do.

Q. Let's look at a couple documents. Let's pull up the first one, DTX 710.

MR. RAKOCZY: I apologize, Your Honor. I need someone to pass me some notes.

Move to admit PTX 1519, Your Honor.

THE COURT: Any objection to 1519?

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(PTX 1519 was admitted.)

MR. RAKOCZY: Let the record reflect Mr. Salmen did not hand me the note he was supposed to hand me.

THE COURT: You may now ask for notes, Counsel, and I suspect you shall receive.

BY MR. RAKOCZY:

Q. All right. Apologize, Dr. Furfine. So we have DTX 710. Are you with me?

A. I am.

Q. On page 1 you see this is an email from Jesse Cedarbaum, dated March 1, 2004, to you and others including cofounder Dr. Yancopoulos, correct?

A. Correct.

Q. Here Mr. Cedarbaum is circulating an abstract that Genentech had published for Lucentis, correct?

A. Let's see. Just give me a second to read it.

Q. Absolutely.

A. Yes, it is a pharmacokinetic study for ranibizumab.

Q. Yes. The abstract title was "Pharmacokinetic Study of Ranibizumab (Lucentis) Following Subconjunctival" --

A. Conjunctival, yes.

Q. -- "Intracameral and Intravitreal Administration in Rabbits."

A. Yes.

Q. So this is consistent with your testimony you were

following Genentech and what they were doing with intravitreal delivery of that molecule, correct?

A. Yes.

Q. This is March 2004. Let's look at January 2005 and see what else you got your hands on.

MR. RAKOCZY: That time, I did get a note.

THE COURT: Noted for the record.

Good job, Counsel.

MR. RAKOCZY: Move to admit DTX 710, Your Honor.

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 710 was admitted.)

BY MR. RAKOCZY:

Q. Dr. Furfine, on screen should be DTX 714.

A. 714. Yes.

Q. This is an email dated January 27, 2005, to you and others at Regeneron, again including cofounder Dr. Yancopoulos, correct?

A. Yes, it is.

Q. And the subject is "Lucentis ITV PK," correct?

A. Correct. Yes.

Q. And if we go to page 2 of the document, this email was forwarding the Gaudreault paper entitled "Preclinical Pharmacokinetics of Ranibizumab (rhuFabV2) After a Single Intravitreal Administration." Correct?

A. Yes.

Q. And this is the Gaudreault paper you mentioned earlier, right?

A. Yes, it is.

MR. RAKOCZY: And, Your Honor, we will get you and Madam Court Reporter a list of all of these terms. I realize we're ripping them off pretty quickly.

THE COURT: Much appreciated.

MR. RAKOCZY: Move to admit DTX 714, Your Honor.

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 714 was admitted.)

BY MR. RAKOCZY:

Q. Now, in this paper, in addition to the part you cited or testified about, you also got your hands on the actual formulation of ranibizumab in this paper, correct?

A. I believe it is in here somewhere, though I don't remember exactly where right this second.

Q. Let's go to page 3 of DTX 714, left-hand column below the table, the fourth line.

A. Got it, yep.

Q. Here we see that ranibizumab was "formulated as 10 millimolar sodium succinate, 10 percent trehalose, and 0.5 [sic] percent Tween 20 (pH 5)," correct?

A. Correct.

Q. I'll read it again. I apologize.

Again, we're in DTX 714 on page 3. And here we see that ranibizumab "was formulated as 10 millimolar sodium succinate, 10 percent trehalose, and 0.05 percent Tween 20 (pH 5)," correct?

A. Yes.

Q. And Tween 20 is another name for polysorbate 20, correct?

A. Correct.

Q. And trehalose here is the stabilizer, correct?

A. Trehalose is known as a stabilizing agent. It can be used that way. Because I did not develop this formulation and were not aware of the testing they did, I can't say for sure that that's what it was used for here.

Q. So you wouldn't know what the function of that ingredient is unless you actually had test data on it, correct?

A. That's correct.

Q. And sodium succinate, would it be the same answer? That might be a buffer, but you would actually have to see testing data to know. Am I right?

A. I don't know for a buffer -- I guess in a perfect world, yes, you would want a pH test done.

Q. Now, same answer for the Tween 20, the 0.05 percent. You would need to see test data to know exactly how that was behaving and how it was functioning in the formulation,

correct?

A. You would, though these would be relatively easy tests to perform.

Q. Okay. That's fair. But you would want to do that test to know what it was doing, correct?

A. I think it's slightly different than that. If you don't mind my -- so science is done a little bit differently than that. Basically, you have a challenge that you're trying to solve, and you add things to try and solve those problems.

And so it's really kind of -- you're kind of putting the cart before the horse a little bit in the way you're describing it. So, really, like, you decide what you want to test because you're trying to solve a problem. Then you run that test.

Q. My question is much simpler. We're looking at a formulation of ranibizumab. You don't have any data on it. To know the functions of those ingredients, you would want to see test data on them, correct?

A. I would.

Q. Okay. And this article is what ran the PK study on -- can you pronounce it for me? Is it cynomolgus monkeys?

A. Cynomolgus monkeys, correct. You pronounced it correctly.

Q. Now, this publication, would it advance the skilled person's knowledge, at least to some degree, regarding the

tolerability of polysorbate in an intravitreal injection? Correct?

A. It would have advanced the knowledge and would have actually been potentially concerning, given their information results.

Q. We'll get to that. But my question is it would have advanced the skilled person's knowledge at least to some degree?

A. That's correct.

Q. Now, in fact, Genentech here had beat you to the punch, right, in measuring or attempting to evaluate tolerability of polysorbate in a formulation? Is that right?

A. I don't know that we were in a race with Genentech to test polysorbate. That wasn't really a competition that was going on. So I would say no to that.

Q. Well, you were tracking Genentech's work, at least. That's fair, right?

A. We were.

Q. Now, Genentech was proposing to use five times the amount of polysorbate 20 in this formulation than you were proposing at around this time; is that right?

A. I think we tested .1 to .03; so this is not five times those.

Q. At the time of this article, isn't it true that you were proposing to limit the amount of polysorbate 20 in the

formulation to 0.01 percent?

A. Oh, yeah. That's a function of a manufacturing process where we had to add a little bit to stabilize it to the stringencies that happened during manufacturing.

And the idea there was that, if we didn't want polysorbate in there, we would have to be able to state what the minimum that was in there was.

So we were first making formulations that didn't have polysorbate. As you saw, IVT-1 did not have polysorbate in it. But, in fact, it had a small amount because that got carried through in the manufacturing.

So that's what that was about. We didn't go with polysorbate until later when we required it because it worked better than PEG.

Q. Let's take a look at DTX 711. And I want to look at the first email on the page.

You see this is an email dated December 8, 2004, around the same time as you received that Gaudreault paper. And this is from named coinventor Dr. Graham on the subject of "Specification for intravitreal VEGF Trap," correct?

A. Yes.

MR. RAKOCZY: Move to admit DTX 711, Your Honor.

THE COURT: Any objection?

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 711 was admitted.)

BY MR. RAKOCZY:

Q. All I want to do is confirm here lower in the email at the end of the second -- or the last paragraph, you see here that Dr. Graham is proposing a limit for the polysorbate as not to exceed 0.01 percent in the specification, correct?

A. Yes, that's what it states.

Q. So the ranibizumab formulation you saw in Gaudreault was using five times that amount of polysorbate 20, correct?

A. Yes, it was five times the amount -- well, five times the maximum amount that could have been in the solution, yes.

Q. Correct. Thank you.

So in April 2005 I believe you received information on Genentech's Avastin formulation.

Do you recall that?

A. Not off the top of my head, but --

Q. Let's take a look. DTX 714 on screen. It's also in your binder.

A. So this is still the -- the Gaudreault paper is 14.

Q. I'm sorry. DTX 716. My apologies.

Do you see this?

A. Yes.

Q. This is an email dated April 12, 2005, from you to your coinventors, Dr. Dix and Dr. Graham, correct?

A. Correct, yes.

Q. And the subject is "Avastin EMEA discussion," correct?

A. Correct.

Q. Now, Avastin was the name of Genentech's bevacizumab; isn't that right?

A. Yes.

Q. Now, if we look at who forwarded this, you see there's a forward from the CEO, Leonard Schleifer, correct?

A. Yes, that's correct.

Q. And you see he says, "This is single-most comprehensive discussion of Avastin all in one place. The European approval discussion document!" Correct?

A. That's what it says.

Q. Now, you then forwarded this to your formulation team?

A. Yes.

Q. Dr. Dix, Dr. Graham, and Kelly Frye. And you instructed them to take a close look at the protein characterization, manufacturing, and stability part of this document, correct?

A. Yes, I did.

Q. And you pointed out that there may be some other things Regeneron should consider based on what Genentech had done, correct?

A. Correct.

Q. Now, the attachment, the EMEA report, actually discloses the Avastin formulation, correct?

A. Yes, it must. I haven't read it in a long time; so --

Q. Let's --

A. -- I'll trust you on that.

Q. Let's go to page 9 of DTX 716, under the drug product section. Do you see that?

A. Yes.

Q. And if we go to lines 4 to 5, you see the bevacizumab or the Avastin formulation there, correct?

A. Yes. 10 mg/mL.

Q. It's a formulation containing 51 millimolar sodium phosphate, 60 mg/mL trehalose dihydrate, and 0.04 percent polysorbate 20, correct?

A. Maybe I'm looking at a different one. I'm sorry. Say it again just to make sure I'm in the right place.

Q. It's highlighted on screen as well; so...

A. I'm sorry. I was looking at the one above that. Yeah. Okay. 51 millimolar.

Q. The Avastin formulation had phosphate --

A. Yes.

Q. -- trehalose, and 0.0 [sic] percent polysorbate 20?

A. Correct.

Q. So four times the amount of polysorbate that your

specification topped out at, correct?

A. Correct, though this is for cancer treatment, systemic exposure, not eye.

Q. Now, you understand this formulation was used in the eye, though, correct?

A. At later points in time, there were people who administered off-label -- unapproved, off-label -- bevacizumab to the eye, yes.

Q. A lot of off-label use, right?

A. A lot, yes.

Q. Now, I want to ask you about this formulation and the functions, and I don't need to spend a lot of time on it. I just want to confirm your answer would be the same.

Looking at the formulation, you don't know the function of those ingredients unless you had test data on it, correct?

A. I wouldn't know for sure. I could suspect, but I wouldn't know for sure.

Q. Now, let's look at page 4 of this document, DTX 716.

MR. RAKOCZY: And I apologize if I neglected to move to admit -- move to admit DTX 716.

THE COURT: Any objection?

MR. BERL: No objection.

THE COURT: Without objection, motion, in note form, granted.

MR. BERL: I have no objection to him just doing it at the end too.

BY MR. RAKOCZY:

Q. All right. If we look under the introduction, I want to look at the size --

A. Which tab are we on now?

Q. So we are on the same exhibit.

A. Okay.

Q. DTX 716 at page 4.

A. Oh, page 4.

Q. It's the first two lines right under the introduction.

And Avastin is a big molecule, isn't it?

A. It has a molecular weight of 150,000, like most antibodies, yes.

Q. It's bigger than aflibercept, correct?

A. Depends how you want to measure it. If you measure it in absolute molecular weight, yes, it's a little bit bigger. If you measure it kind of like we talked about before and its function, it's more similar in size.

Q. We want to look at kilodaltons, at kDa's. Aflibercept is, I think, 115 you mentioned?

A. That's correct.

Q. And bevacizumab, or Avastin, is 149 kilodaltons, correct?

A. That's correct.

Q. So bigger. And used in the eye successfully, correct?

A. It has at later points, than I think when this document came out, been used in the eye successfully.

Q. Now, let's look at -- I want to go back to your instructions to your team in the email. You told them to take a close look at the stability part of the document?

A. Yes.

Q. And let's go to the stability part of the Avastin report, which I believe is page 10 of DTX 716. And if we look at the third-to-last line --

A. Third-to-last line.

Q. -- we can see that the Avastin report concluded that "The submitted stability data support the proposed shelf life of 24 months when stored at 5 degrees C plus or minus 3 degrees C," correct?

A. Yes.

Q. So this formulation containing the trehalose, the polysorbate 20, and the buffer was stable for 24 months at 5 degrees C, correct?

A. Yes, it was.

Q. Now, the EMEA discussion document for Avastin was not the last information that you obtained on Genentech's Avastin, correct?

A. No, I doubt it. I don't remember everything I received, you know, 20 years ago on this topic, but probably not.

Q. Let's look at DTX 718.

A. Okay.

Q. And this is an email from Kelly Frye on your team to you and others dated April 18, 2005, with the subject line "Avastin and Macugen formulations," correct?

A. Yes.

Q. And if you look at the bottom half of the email, she provides the formulation for Avastin?

A. Yes.

Q. Apologize. We need to go down further in the email. There it is.

A. I see it.

Q. And so we see the Avastin formulation again -- the phosphate, the trehalose, and the polysorbate 20, correct?

A. Yes.

Q. And then the Macugen formulation there as well, correct?

A. Correct.

Q. And below that she says, "Both of these formulations would be iso-osmolar," correct?

A. Yes, she says that.

Q. That's the same thing as isotonic, correct?

A. Yeah, they're synonymous.

Q. So the Avastin formulation, even though it was for cancer at 10 millimolar phosphate, 6 percent trehalose, and 0.04 percent polysorbate 20, was isotonic, correct?

A. Yes.

Q. Now, by July of 2005 it was also known that Avastin, or bevacizumab, a much larger molecule than aflibercept, had actually been used in the eye, correct?

A. So, first of all, it's not a much larger molecule. It's actually functionally about the same. So I would disagree with that assessment.

And I don't know when the Avastin was started to be used off-label in people's eyes instead of ranibizumab. I don't remember when that started. I started tracking it more when it was after the ranibizumab approval, so after Lucentis was approved, when it became an issue and more in the news because Genentech was not happy about it.

Q. We'll take a look.

MR. RAKOCZY: Before we do, move to admit DTX 718, Your Honor.

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 718 was admitted.)

BY MR. RAKOCZY:

Q. Let's pull up DTX 3058 on Avastin.

A. Sorry. Say the number again.

Q. DTX 3058. And you see this is a paper dated July-August 2005 entitled "Optical Coherence Tomography Findings After an Intravitreal Injection."

Do you see that?

A. Yes.

Q. Does this refresh your recollection that Avastin, or bevacizumab, had been used by intravitreal injection?

A. Yes. This is a publication on the topic, yes.

Q. So by July or the summer of 2005, someone had used bevacizumab, or Avastin, off-label in the eye, correct?

A. That's correct, yes.

Q. All right. I want to talk briefly about this ITV-1 formulation, the PEG formulation.

Do you recall that?

A. Yes.

Q. And just to clear up, some of the documents say ITV and some say IVT. Can I assume that's the same thing?

A. Yes.

Q. Okay. So the IVT-1 was the PEG formulation, and that was the first one that you put into the clinic at Regeneron, correct?

A. That's correct.

Q. And so that did not use polysorbate, correct?

A. That's correct. That did not use polysorbate.

Q. Let's pull up DTX 719 and look at page 1.

And you see this is a memo. It's copied to you, dated August 16th, 2005, from --

A. Yes.

Q. It's from coinventors Dr. Dix and Kelly Frye, correct?

A. Yes.

Q. And the subject is "VEGF Trap intravitreal formulation storage and shipping conditions," correct?

A. Yes.

MR. RAKOCZY: Move to admit DTX 719, Your Honor.

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 719 was admitted.)

MR. RAKOCZY: I apologize. Also move to admit DTX-3058.

THE COURT: Any objection to 3058?

MR. BERL: No objection.

THE COURT: Without objection, that is also admitted.

(DTX 3058 was admitted.)

BY MR. RAKOCZY:

Q. Let's look at the formulation identified on DTX 719. And we can see this is a 10-millimolar sodium phosphate, 135-millimolar sodium chloride, and 0.1 percent PEG 350, correct?

A. Yes, that's correct.

Q. Now, I think you mentioned that this formulation, in your view, was somehow inferior, but this is the one that was actually moved into the clinic first in Phase I and Phase II trials, correct?

A. It was moved into the clinic first, but we didn't know, when we moved it into the clinic, that it was inferior.

Q. But it was actually used in Phase I and Phase II clinical trials, correct?

A. Yes, it was.

Q. I'd like to look at another study on this IVT-1 PEG formulation, and it's at DTX 723.

A. Organic cosolvent. Got it.

Q. This is a memo from Laura Pologe copying you --

A. Pologe, yes.

Q. I apologize.

This is a memo from Laura Pologe copying you to coinventors Dr. Graham and Dr. Dix, dated March 10, 2006, entitled "Syringe compatibility of 10 mg/mL and 40 mg/mL VEGF Trap," correct?

A. Correct.

Q. And this study actually tested the PEG formulations, correct?

A. Give me a second to look. Yes, it appears to be the PEG.

Q. If we look at the first paragraph, last two lines on page 1 of this exhibit, we see the formulation. 0.1 percent PEG, correct?

A. Correct.

Q. And so this test was using the same amount of PEG, 0.1 percent, but testing it in 10 mg/mL and 40 mg/mL, correct?

A. Yes.

Q. So you don't have to add more PEG to dissolve aflibercept or the other ingredients in here, correct?

A. When we make a formulation, the aflibercept is already in solution; so we don't use the PEG to dissolve it.

Q. Thank you, sir.

MR. RAKOCZY: Move to admit DTX 723, Your Honor.

THE COURT: Any objection?

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 723 was admitted.)

BY MR. RAKOCZY:

Q. Now I'd like to move on to the polysorbate formulation, or, I believe, IVT-2, correct?

A. Hang on a second. Say which one you are again.

Q. The IVT-2 formulation was the polysorbate formulation.

A. Yeah, but which page are you on?

Q. Oh, I'm moving to a new exhibit now.

A. Okay. Can you just restate the number?

Q. I just had a quick question to confirm. IVT-2, that denoted the polysorbate formulation without PEG?

A. Sorry. Yes. Correct.

Q. Okay. So let's go to DTX 725. And this is an email you're copied on from coinventor Dr. Graham?

A. Yes.

Q. Dated May 8, 2006, with the subject "VEGF Trap formulations for ITV," correct?

A. Yes, correct.

Q. And in the email below on this page, you are asking Dr. Graham to provide the formulations moving into the tox study, correct?

A. Yes.

Q. And this email is dated May 8, 2006, correct?

A. Yes, correct.

Q. And let's look at the formulations above that very quickly. We see that he sent along a lead formulation and a backup formulation, correct?

A. Correct.

Q. And the lead formulation had phosphate, NaCl, polysorbate 20, and 5 percent sucrose, and 5 to 40 mg/mL VEGF Trap, correct?

A. Correct.

Q. And the backup formulation had phosphate, NaCl,

polysorbate 20, and also 5 to 40 mg/mL VEGF Trap, correct?

A. Correct.

Q. Now, this email does not contain any tox data, correct?

A. It says we're going to use it in a tox study, but it does not show the data from that study, correct.

Q. So you didn't have that tox data yet. You were moving these into the study, correct?

A. That's correct.

Q. And this email does not provide any stability data on these formulations either, correct?

A. It does not, no.

Q. And you agree that the purpose or the role of the 0.03 percent polysorbate in this lead formulation and the backup formulation was as an agitation stabilizer, correct?

A. It does serve that purpose, yes.

MR. RAKOCZY: Move to admit DTX 725, Your Honor.

MR. BERL: No objection.

THE COURT: Without objection, 725 admitted.

(DTX 725 was admitted.)

Counsel, may I inquire? Where are we in the grand scheme of things?

MR. RAKOCZY: Your Honor, I'm terrible at time, but I may have a decent amount. If you want me to break, I'm happy to break.

THE COURT: Are we at a good spot in that to do so?

MR. RAKOCZY: Yes, we are. We're moving to a new module.

THE COURT: Why don't we do that then, given the hour.

MR. RAKOCZY: Did I move to admit DTX 725? I did, right?

THE COURT: Yes. Based on affirmative head nod from Madam Clerk, yes.

MR. RAKOCZY: Thank you.

THE COURT: Doctor, this may come as good or bad news to you. In the back of the room to the right, just you and I hear that. You're midstream on your testimony. So my admonition about being a man without a country applies to you this evening as well. So have dinner on your own and perhaps decompress a little bit. But formally, for the record again, because you are midstream, so to speak, on your testimony, you're not permitted to interact with anyone. They're not allowed to talk to you, vice versa. So I'll offer that as protection for you or an excuse as to why folks may run from you during this evening.

But you're free to step down, sir. Go right ahead. You can leave those materials right there.

THE WITNESS: Thank you.

THE COURT: No, thank you. And have a pleasant

evening in solitude.

THE WITNESS: Still okay to, like, get a ride back to the hotel?

THE COURT: I will give you special dispensation. Someone will give you a ride. Turn the radio up really loud.

Good question, though, Doctor. Good question. You don't have to stay in the courthouse. That's reserved for other people.

We'll pick up with the doctor's testimony tomorrow morning at 9:30, unless there's anything else we need to take up at this point.

MR. RAKOCZY: Nothing from Mylan.

MR. BERL: Nothing from us.

THE COURT: Any additional exhibits plaintiffs expect to seek to introduce for Dr. Furfine?

MR. BERL: We have a list from what happened on direct. I can just do that at the end of the redirect.

THE COURT: That's fine. Just make sure that's kept in updated condition, and we'll do that.

MR. RAKOCZY: That's fine with us, Your Honor.

THE COURT: Great.

With that, everyone have a pleasant evening, and we'll resume tomorrow morning. Thank you all very much.

(Proceedings concluded at 5:16 p.m.)

CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 13, 2023, as reported by me in stenotypy.

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

Given under my hand this 13th day of June 2023.

/s/Cindy L. Knecht

_____

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

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 3

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 14, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

APPEARANCES:

On behalf of the Plaintiff:

David I. Berl
Arthur J. Argall, III
Andrew V. Trask
Williams & Connolly, LLP
680 Maine Avenue, SW
Washington, D.C. 20024
202.434.5000

APPEARANCES CONTINUED ON NEXT PAGE

On behalf of the Plaintiff, continued:

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

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

On behalf of the Defendant:

Deanne M. Mazzochi
William A. Rakoczy
Heinz J. Salmen
Eric R. Hunt
Lauren M. Lesko
Neil B. McLaughlin
Rakoczy, Molino, Mazzochi & Siwik, LLP
6 W. Hubbard Street, Suite 500
Chicago, IL 60654
312.527.2157

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

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

Wednesday Morning Session,
June 14, 2023, 9:30 a.m.

- - -

THE COURT: We all reconvene for day three of trial. Happy Flag Day to everyone.

A couple things to start with. I will remind everyone, counsel and spectators, local rule 85.01 of the Northern District of West Virginia absolutely prohibits any recording or photographs of the courtroom or in the areas immediately adjacent to the courtroom. There was a report yesterday that there had been photographs being taken. If that gets confirmed, if that happens again, violators will be dealt with accordingly. But everyone is hereby reminded of that local rule as an FYI.

I'm aware there's been a flurry of filings this morning. Regeneron's motion to exclude. And there was also a letter emailed to Ms. Marcum this morning on Steptoe & Johnson letterhead. The Court will order that filed and made part of the record as well. We have not had a chance to read that; so we'll take that up after we do.

If we're ready to resume with our current pending witness, we can proceed.

Yes, Doctor, there you are. I'm sorry. Good morning, sir. Go ahead and resume the stand. I'll remind you you remain under oath. Good morning. I hope you enjoyed your

evening of solitude.

THE WITNESS: I did.

THE COURT: Good.

(Witness resumes stand.)

THE COURT: You're welcome.

Counsel, go right ahead.

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

CROSS-EXAMINATION

BY MR. RAKOCZY:

Q. Good morning, Dr. Furfine.

A. Good morning.

Q. Let's jump back to your '865 patent, if we could, go over just a few items. It is PTX 2 in your binder. If we could go to page 7, please.

Go to the beginning of the examples. I believe if you start on page 7, Dr. Furfine, you'll see that your patent has eight examples. Do you see that?

A. I see the examples list.

Q. And if you look through the next couple pages, you'll see it runs through eight total examples, correct?

A. Yes.

Q. Now, let's look at Examples 1 and 2 quickly, please, on page 7. And you see both of those examples are directed to a formulation containing 50 mg/mL VEGF Trap, correct?

A. Correct.

Q. So those examples would not be covered by a claim that required 40 mg/mL of VEGF Trap, correct?

A. I don't think I'm qualified to decide what claims cover what.

Q. You agree 50 is different from 40 mg/mL, right?

A. I would indeed.

Q. Now, if you could quickly look at Examples 7 and 8 on page 9 of the exhibit, and you see both of those examples are directed to 20 mg/mL VEGF Trap, correct?

A. Correct.

Q. So, obviously, not 40 mg/mL VEGF Trap, correct?

A. Correct.

Q. And if you look at Examples 4 and 6, do you see those are liquid formulations in a refilled syringe, not a vial, correct?

A. Correct.

Q. Now, Examples 5, 6, and 8, can you confirm for me those do not contain a sugar stabilizer? Is that right?

A. 5. What were the other ones?

Q. Excuse me. 5, 6, and 8 do not contain a sugar stabilizer; is that correct?

A. Correct.

Q. Now, you did not invent any new or novel excipients in your '865 patent, correct?

A. No, there were not novel excipients.
Q. The excipients used in your patent were known and available before the patent, correct?
A. Yes, that's correct.
Q. Can we look at Example 3, please, on page 9. And you see that's a liquid formulation in a vial, correct?
A. Sorry. Example 3 on page 9?
Q. Yes, sir.
A. My page 9 has Examples 7 and 8.
Q. I'm sorry. Page 8. My fault. Example 3 on page 8 is directed to a liquid formulation in a vial, correct?
A. Correct.
Q. And liquid protein formulations in a vial, they were known before your '865 patent, correct?
A. Generally speaking. Is that what you're asking, liquid formulations?
Q. Yes.
A. Yes.
Q. And we saw yesterday, we discussed the Lucentis and the Avastin formulations were liquid formulations known, correct?
A. Yes, they were liquid formulations known.
Q. And your Example 3 also contains 10 millimolar phosphate, correct?
A. That's correct.

Q. You didn't invent a phosphate buffer for a protein formulation, correct?

A. I'm not sure exactly how to answer that. I didn't invent a phosphate --

Q. Let me back up.

A. I invented the use of a phosphate buffer in this formulation to stabilize aflibercept.

Q. But phosphate buffers were known before your patent, correct?

A. That's correct. Phosphate buffers were known.

Q. Now, your Example 3 also contains 5 percent sucrose, correct?

A. Yes, that's correct.

Q. And sucrose stabilizers were known before your '865 patent, correct?

A. They were known generally as a class of molecules that could stabilize proteins, yes.

Q. And Example 3 also contains 0.03 percent polysorbate 20, correct?

A. Yes.

Q. And polysorbate 20, I believe you said yesterday, was a known excipient before your patent, correct?

A. That's correct.

Q. Now, we discussed yesterday, I believe, Lucentis formulation we looked at was for intravitreal administration

and that had used sodium succinate, trehalose, and polysorbate 20, correct?

A. That's my recollection.

Q. So you would agree those excipients would be suitable for intravitreal administration, correct?

A. So depends whether you mean at the time that I was inventing this or what eventually became true.

Q. Before your patent, you would agree it was known that excipients used in Lucentis would be suitable for use in an intravitreal injection, correct?

A. I don't know that there was enough data to make that claim at that point.

Q. So you would have needed more test data at the time to know that?

A. I think so, yes.

Q. And would the same answer be true for the excipients in the Avastin formulation for your patent? You would have needed more test data to know whether those would have been suitable for intravitreal administration?

A. Yes, probably.

Q. And that's true even though Avastin had been used in the eye by intravitreal administration, correct?

A. One patient and also animal studies suggesting that it could be problematic.

Q. So you wouldn't have known before your patent whether

you could use the Avastin excipients in the eye?

A. Not for sure. No, you wouldn't.

Q. Now, let's talk about buffers. Can you confirm for me, sir, that every example in your patent, 1 through 8, they all use a phosphate buffer, correct?

A. Correct, they all use a phosphate buffer.

Q. And you didn't personally develop a histidine buffer aflibercept formulation when you were at Regeneron, correct?

A. I'm not sure the timing of when the histidine buffer was developed, whether it overlapped with my time or not. I don't recall working on it. I think I stated that previously in deposition. But I can't tell you for sure that it didn't happen and I'm just not remembering.

Q. I think you testified at your deposition you couldn't recall seeing a histidine buffer formulation during your time at Regeneron. Is that right?

A. I did not recall it, that's correct.

Q. Now, I'd like to switch gears -- yesterday you talked about the Gaudreault reference from Genentech.

Do you recall that?

A. Yes.

Q. And I believe you testified that there was -- the results from Gaudreault, the transient ocular inflammation, I believe you used the words, were concerning or discouraging at the time to you.

Do you recall that?

A. I do recall that, yes.

Q. Now, to be clear, there was nothing discouraging about those results to Genentech, correct?

A. Actually, I think there probably was, but it would be me inferring things. The fact is that they didn't go with a 40 mg/mL formulation and they could have, and perhaps that was part of the reason why they didn't.

Q. They continued to develop their Lucentis formulation despite the Gaudreault results, correct?

A. The 10 and lower, not the 40.

Q. But they continued to develop despite the results, right?

A. They continued to develop the lower concentrations despite the results, yes.

Q. Now, Regeneron wasn't discouraged by those results from pursuing Eylea either, correct?

A. We thought that it was possible that there could be something specific to Eylea -- excuse me -- specific to ranibizumab and it could be possible for us to find something better, yes.

Q. And you actually continued developing Eylea even after seeing the Gaudreault results, correct?

A. Yes, we did.

Q. And, in fact, you saw similar results of transient

ocular inflammation in your own monkey studies, correct?

A. It's been a while since I've looked at that data, but I believe that's correct.

Q. Let's pull up PTX 3255. Should be in your binder. And let's look at page 4.

A. Say the number. 5 --

Q. Yes, sir. PTX 3255.

THE COURT: 3255, Counsel?

MR. RAKOCZY: Yes.

THE COURT: Thank you.

THE WITNESS: 3255, yes.

BY MR. RAKOCZY:

Q. You see this is the nonclinical overview from the BLA, correct?

A. I do.

Q. If you look at page 4, there's a reference in that sentence to a comprehensive toxicology program, including a treatment schedule of every two to six weeks.

Do you see that?

A. This is page 4?

Q. Yes. It's on your screen as well.

A. Yes, I see the paragraph now.

Q. So if we go to page 19 of this exhibit, you see a reference to a repeat-dose toxicity study, correct?

A. I do.

Q. And we see there that the chronic toxicity of VEGF Trap was evaluated in the -- I'm going to mispronounce it again -- cynomolgus monkey, correct?

A. That's correct.

Q. Let's look at -- a little further down in that paragraph we see the results. We see Regeneron told the FDA that the "ocular findings were consistent across all GLP IVT studies and consisted primarily of mild and transient ocular inflammation."

A. Correct.

Q. Is that correct?

A. Yes, that's what it states here.

Q. And then if you go a couple sentences down, Regeneron concluded that "these ocular findings were mostly or completely reversible before the next dose or during the recovery periods." Correct?

A. I'm just trying to find where you're reading this.

Q. It's in that same paragraph, fifth line down.

A. Yes.

Q. Now, these results did not discourage Eylea's development, correct?

A. They did not.

Q. And when you said the results from Gaudreault were concerning, you're not suggesting that moderate to severe inflammation would somehow outweigh vision loss, are you?

A. Moderate to severe inflammation -- repeated moderate to severe inflammation might cause vision loss.

Q. So your view is that moderate to severe vision loss that could resolve in a week would be enough to stop development of a drug that can prevent vision loss. That's your testimony?

A. My testimony is not exactly that. It's that a repeated moderate to severe inflammation could have consequences that might result in vision loss. You would have to do the experiments.

Q. But that inflammation, that transient inflammation that resolved in a week or two, was not enough to prevent Lucentis development or Eylea development, correct?

A. It prevented -- well, by inference, because they did not develop the 40 mg/mL formulation, it would suggest that they were concerned about the same thing because they stuck with 10, which didn't have that finding in that study.

Q. The Gaudreault paper concluded that all the doses they tested had transient inflammation that resolved.

A. The degree. It's a severity. You have to include the severity when you make your judgment of what you want to do.

Q. All right. Let's actually -- I forgot to mention something in your patent. Let's toggle back to your patent.

A. Okay. Remind me.

Q. PTX 2. If we go to page 2. And I'm going to focus -- and I'll put it on the screen -- on the application number and date.

A. Yes.

Q. And you see that the --

If we could go down, Mr. Gibson, to the application number in the middle.

You see this patent issued from Application Number 16 --

A. -- 739 --

Q. -- 739,559, filed January 20 -- let me back up. Let me strike that. I'll start over.

Your '865 patent issued from Application Number 16/739,559 filed January 10, 2020; is that right?

A. That's correct.

Q. I want to look further down on this same page to the related U.S. application data.

A. Yes.

Q. You see that section?

A. I do.

Q. And I want to focus on paragraph 60 where it says "Provisional Application."

Do you see that?

A. I do.

Q. And so the provisional application, number 60/814,484

was filed on January 16, 2006, correct?

A. Say that number again, which one you were...

Q. Yes. So it's highlighted on the screen.

A. Sorry.

Q. The U.S. Provisional Application Number 60/814 --

A. Right.

Q. -- 484 was filed on June 16, 2006, correct?

A. That's correct, yes.

Q. Are you okay if I refer to that as the provisional application just for short?

A. Yes.

Q. Now, let's look at PTX 8. I'm sorry. Strike that.

Let's look at PTX 3249, which is in the small binder right in front of you.

A. Sorry. It's not another tab on here?

Q. No. The small binder right there. Go to PTX 3249. If we go to page 8, please.

A. Okay.

Q. You see this is the provisional application for patent. Do you see that?

A. I do.

Q. And you're listed as an inventor right there. Do you see that?

A. Yes, I do.

Q. And you see the title is "VEGF Antagonist Formulation

Suitable for Intravitreal Administration," correct?

A. Yes, I do.

Q. And if you go to the bottom of this page, you see dated June 16, 2006, correct?

A. Yes.

Q. Did you review this provisional application before it was filed on June 16, 2006?

A. I presume that I did, but, honestly, I don't remember that far ago. That was, like, 20 years ago or something.

Q. How about before your testimony yesterday? Did you review this provisional application before yesterday?

A. I reviewed the patent application, but I'm trying to remember if I reviewed the first -- I think I might have reviewed the provisional, but I can't remember for certain.

Q. So do you remember doing a side-by-side comparison of this provisional application with your issued '865 patent before your testimony yesterday?

A. I don't recall doing a side-by-side comparison, no.

Q. Let's look at page 11 of your provisional application. So that's PTX 32 --

A. It doesn't mean that I didn't. I just don't recall.

Q. I'm asking, before your testimony yesterday, did you do a line-by-line comparison?

A. No, not that I remember, no.

Q. So let's look at page 11 of your provisional

application. And I've got it on screen, PTX 3249.

A. Yes.

Q. And I'd like to focus on paragraph 8 and the sentence that starts "more specifically, the ophthalmic formulations comprise."

Do you see that?

A. I see in paragraph 8 is "in several embodiments," right, "more specifically," yes.

Q. So you see that sentence that starts "more specifically, the ophthalmic formulation comprises," and then it continues on, correct?

A. Yes.

Q. So I want to toggle back to your issued '865 patent, which is PTX 2 --

A. Right.

Q. -- at page 4. And we'll put it on the screen. And I want to focus on Column 2, lines 53 to 57. And we'll put it on screen.

A. Okay.

Q. You see here in your '865 patent, it says, "more specifically, stable liquid ophthalmic formulation." So you see the words "stable liquid" have been added.

Do you see that?

A. I see this "stable liquid" in this one. I haven't looked to see if it's not in the other one.

MR. RAKOCZY: Mr. Gibson, can we please pull up that paragraph 8 from the provisional. If we put it next to the paragraph from PTX 2, please.

BY MR. RAKOCZY:

Q. All right. So you see on screen in the provisional paragraph 8, you see it says "the ophthalmic formulation."

Do you see that?

A. Correct, the top one.

Q. Yes, that's the provisional. And in your '865 patent, it says, "the stable liquid ophthalmic formulation," correct?

A. Yes.

Q. Did you add "stable liquid" to the '865 patent specification?

A. I don't recall personally doing that. I don't write the applications.

Q. Did you authorize someone to add the words "stable liquid" to your '865 patent specification?

A. I do not believe I -- I didn't -- I didn't authorize or not authorize. I wasn't involved in that, to my recollection.

Q. Your '865 patent claims are all directed to stable liquid formulations, correct?

A. Yes.

Q. Now, I'd like to put up a demonstrative for you of

your PTX 2, and we'll call up DDX 5 at page 5.

What I've done here is I've highlighted in yellow parts of Columns 3 and 4 from your issued '865 patent at PTX 2 at page 5.

Do you see that on your screen?

A. I see it here. It's easier for me to look at the book here, but yes.

Q. Are you aware that everything that is highlighted on this demonstrative in Columns 3 and 4 of your '865 patent -- so it's Columns 3, line 11, extending through Column 4, line 10, of PTX 2 -- is not found in your original provisional application? Are you aware of that?

A. I'm not aware of that. I've not done the head-to-head comparison, as you suggested.

Q. So at no time before your testimony today or yesterday did you do the comparison to see that this is all new matter added to your '865 patent, correct?

A. I did not -- I did not do the comparison to be able to detect that that was the case.

Q. Did you authorize anyone to add all this new material to your '865 patent?

A. Again, I didn't authorize or not authorize. I don't recall being involved in that process.

Q. Let's stay on DDX 5, page 5, and I'd like to look at Column 3, lines 36 to 40. If we could blow that up. And I'd

like to focus on -- I apologize. I'm pointing to the wrong -- I'm sorry.

Column 3, lines 36 to 40. And do you see here in the third line it says "about 0.013 to about 0.1 percent polysorbate"? Do you see that?

A. Can you just tell me -- I'm having trouble finding this. Is this in the Column 3?

Q. Yes. Column 3, lines 36 to 40.

A. I see it now.

Q. And do you see there is a range there for the polysorbate? It says, "about 0.3 to about 0.1 percent polysorbate." Do you see that?

A. I do see that, yes.

Q. Do you know whether that exact range is found in your provisional application?

A. I do not recall if it is or isn't.

Q. I would like to look at one more portion of this highlighted document. If we could look at Column 4, lines 36 to 44.

A. Yes.

Q. And you see this is a paragraph directed to a lyophilizable ophthalmic formulation. Do you see that?

A. I do.

Q. Are you aware of whether this paragraph in this formulation appears in your provisional application?

A. I don't recall it being in there or not. I don't remember everything that's in that provisional application.

Q. And assuming it wasn't in your provisional, did you authorize anyone to add this paragraph to your issued '865 patent?

A. I didn't authorize or not authorize that.

Q. All right. Thank you, sir.

MR. RAKOCZY: I believe I have a couple exhibits to move in, Your Honor.

Move to admit PTX 1519, PTX 3255, and PTX 3249.

THE COURT: Any objection to those three exhibits?

THE WITNESS: I'm sorry. Can you say that --

THE COURT: We're just tidying up, Doctor. I'm sorry, sir. That wasn't a question for you.

Any objection to any of those exhibits?

MR. BERL: Oh, sorry. No. That was a question for me?

THE COURT: That was a question for you.

MR. BERL: We're all confused. I can be better at this. I've been here before.

No, I have no objection, Your Honor.

THE COURT: Without objection, so admitted.

I'll repeat something that I shared at home. For those of you unfamiliar with the sports calendar of West Virginia middle school and high school sports, we're in what we

call three-week period, which means school, even though it's out, the various teams will have workouts and play in tournaments and the rest. The time-old adage from when I was younger, Wednesday of camp week is always the hardest day of basketball camp. That applies to trial as well.

So with that, those exhibits, so admitted with no objection and pass the witness.

(PTX 1519, PTX 3255, and PTX 3249 were admitted.)

MR. RAKOCZY: Pass the witness.

THE COURT: Understood.

Mr. Berl, recognize it's Wednesday of basketball camp week, sir. You're up, redirect.

MR. BERL: It's been a great basketball week for me, Your Honor. I've waited 40 years for my favorite team to win a championship, and it finally happened.

THE COURT: Congratulations, sir. Congratulations.

MR. BERL: Thank you.

REDIRECT EXAMINATION

BY MR. BERL:

Q. Dr. Furfine, I'd like to start with where Mr. Rakoczy left off with your provisional application, which is PTX 3249.

Can we put page 11 on the screen, the same page that Mr. Rakoczy just asked Dr. Furfine about.

And Mr. Rakoczy asked you various questions about

paragraph 8.

Can we blow that up.

And do you recall questions in which Mr. Rakoczy was suggesting that the provisional application does not include a disclosure of the words "stable liquid" before formulation.

Do you recall that?

A. I do.

Q. Now, let's take a look at paragraph 7, same page, higher up. Did Mr. Rakoczy show you this paragraph, Dr. Furfine?

A. He did not.

Q. And can you read the first four words of that paragraph.

A. "The stable liquid ophthalmic formulation of the invention."

Q. Now, Mr. Rakoczy also showed you PTX 3255.

Let's pull that up on page 19.

Do you recall he asked you some questions about toxicology studies that were conducted at Regeneron?

A. Yes.

Q. And he asked you various questions about the particular data, including evidence of inflammation. Do you remember that?

A. I do.

Q. Just to be clear, was this information public as of

the time of your invention?

A. I don't believe it was, no.

Q. And is this information the same information that Genentech published in Gaudreault or is it more detailed and additional information?

A. This is much more detailed and a much more detailed and extensive study of animals than their study was.

Q. And, now, if we go back to the Gaudreault reference, which he was asking you about in purported comparison to this exhibit -- this is Exhibit 1839.

And if we could go to the portion that we talked about on direct examination about the toxicity of the 40 versus 10 mg/mL ranibizumab injections into the eye.

Now, Doctor, were the results that you obtained with your Eylea formulation the same as the results that Genentech obtained with their 40 mg/mL ranibizumab formulation?

A. No. These results seem less severe than what's stated here.

Q. Sorry. "These" and "these" won't come up on the transcript?

A. I'm sorry. You're right. I'm sorry.

The aflibercept data appears to be less severe than what is noted here in the ranibizumab paper.

Q. And in the ranibizumab paper they found inflammation that was from absent to moderate at 500 micrograms per eye; is

that right?

A. That's correct.

Q. Is that the same as the 10 mg/mL?

A. That's correct.

Q. And then it was moderate to severe for 40 mg/mL?

A. That's correct.

Q. And what was your understanding about whether Genentech continued to develop this 40 mg/mL that was indicated publicly to cause moderate to severe inflammation?

A. They did not progress anything beyond the 10 mg/mL formulation.

Q. Is that surprising to you in view of the data that they published?

A. It's not.

Q. Now, I'd like to go back and discuss a few things that Mr. Rakoczy talked about yesterday.

He asked you various questions about whether polysorbate dissolves aflibercept. When you formulate proteins, Dr. Furfine, do they start out as a solid, like a powder, or are they in liquid?

A. They're liquid at all times unless they become lyophilized at some point.

Q. So when you're doing a liquid formulation, do you dissolve the active ingredient like aflibercept like someone would dissolve sugar in their coffee?

A. No, you do not.

Q. You were asked various questions about whether polysorbate dissolves protein aggregates. Do solvents dissolve protein aggregates?

A. No.

Q. What do they do instead with respect to aggregates?

A. They protect against degradation and precipitation and falling out of solution.

Q. So does water dissolve protein aggregates?

A. No.

Q. Does water remove protein aggregates?

A. No.

Q. Do solvents remove protein aggregates generally?

A. No.

Q. Okay. Now, you were shown documents yesterday by Mr. Rakoczy in which you called polysorbate a stabilizing agent, including in the BLA. Do you recall that?

A. I do recall that, yes.

Q. When you call something a stabilizer, is that an indication that it's not increasing solubility?

A. No. They're two separate things, and it can do both.

Q. Did you also call polysorbate an organic cosolvent in your documents at the time?

A. Yes.

Q. Let's pull up PTX 86 again.

If we go to the front, is this again a document that you -- that reflects meeting minutes from February 2004?

A. Yes.

Q. And if we go to page 5. And if we put up -- you said here in 2004, "VEGF Trap" -- is that referring to aflibercept?

A. It is, yes.

Q. -- "requires the presence of an organic cosolvent to stabilize the protein against agitation-induced aggregation."

Do you see that?

A. Yes, I do.

Q. And you see further down in the paragraph, what organic cosolvents are you providing as examples in 2004?

A. PEG and polysorbate.

Q. Are you saying that those aren't stabilizers because you called them organic cosolvents?

A. No. We're saying they are. They serve both purposes.

Q. There was some suggestion yesterday, when Mr. Rakoczy was showing you a lot of Genentech articles from the 2005 time frame, that you got the idea of using an organic cosolvent like polysorbate from Genentech. Was this written before 2005 or during or after 2005?

A. This was written in -- before.

Q. Now, you answered some questions yesterday about whether various ingredients like trehalose were being used, how

they were being used in Genentech's program. Do you remember?

A. I do recall, yes.

Q. Do you recall your testimony that you couldn't be sure what they were doing in Genentech's formulations without seeing data?

A. That's correct.

Q. What if someone who was participating in Genentech's program told you how they were functioning in Genentech's formulations? Then would you know?

A. Yes, you would, absolutely.

Q. In your patent do you tell the public what trehalose and other sugar stabilizers are doing?

A. We do.

Q. Now, a few more points.

There was a suggestion yesterday that bevacizumab, the active ingredient in Avastin, is much bigger than aflibercept. Do you recall those questions?

A. Yes.

Q. In terms of how much space aflibercept occupies compared to bevacizumab, is bevacizumab bigger?

A. Not substantially, if at all.

Q. Now, you were asked at the beginning of the cross-examination about whether you invented aflibercept. Do you remember that?

A. I do.

Q. Can aflibercept be administered by itself with nothing else?

A. No.

Q. How is it administered?

A. It's administered as the formulation called Eylea.

Q. And did you help invent that?

A. I did.

Q. Thank you. No further questions, Dr. Furfine.

MR. BERL: I do have some exhibits to read in, though.

THE COURT: At a measured pace.

MR. BERL: I absolutely will. I didn't need a reminder, but thank you.

PTX 2, PTX 579, PTX 1848, PTX 82, PTX 1785, PTX 1079, PTX 3257, PTX 1839, PTX 81, PTX 2223, PTX 97, PTX 98, PTX 86, and PTX 2224.

THE COURT: Any objection to any of those, Counsel?

MR. RAKOCZY: One moment, Your Honor. It's a long list.

THE COURT: Certainly.

MR. RAKOCZY: No objection, Your Honor.

THE COURT: Without objection, Mr. Berl's lists are all deemed hereby admitted.

(PTX 2, PTX 579, PTX 1848, PTX 82, PTX 1785, PTX 1079, PTX 3257, PTX 1839, PTX 81, PTX

2223, PTX 97, PTX 98, PTX 86, PTX 2224 were admitted.)

THE COURT: Recross?

MR. RAKOCZY: Nothing from us, Your Honor.

THE COURT: Nothing.

Doctor, you may step down, sir. And, unfortunately, I now must lift my ban of anyone speaking to you; so you're fair game. Thank you very much. You can leave all that there. Someone will tidy up. Thank you very much.

If I could ask counsel to clean up and get whatever Madam Clerk requires to her, please. Thank you.

Call your next witness.

MR. BERL: Thank you, Your Honor. Plaintiffs call Dr. Bernhardt Trout.

THE COURT: Doctor, good morning.

BERNHARDT TROUT, PLAINTIFF'S WITNESS, SWORN

THE COURT: Thank you so much, Doctor. Once you're seated and comfortable, if you wouldn't mind adjusting that mic so everyone can hear you. Take a pause for a few seconds while we distribute binders. Thank you, sir.

Counsel, you may proceed whenever you're ready.

MR. BERL: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. BERL:

Q. Good morning, Dr. Trout.

A. Good morning, Mr. Berl.
Q. Could you please introduce yourself to the Court.
A. Yes. My name is Bernhardt Trout.
Q. And what do you do, Dr. Trout?
A. I'm a professor of chemical engineering at MIT in the Boston area.
Q. And can you briefly describe your educational background.
A. Yes. I was an undergraduate at MIT, also got a master's degree both in chemical engineering. And then I went to University of California at Berkeley also for my PhD in chemical engineering. And then I did a postdoctoral engagement at the Max Planck Institute in --
THE COURT: Could you spell that for us.
THE WITNESS: Yes. M-A-X P-L-A-N-C-K.
THE COURT: Thank you very much.
THE WITNESS: Yes, sir.
An institute in Stuttgart, Germany.
BY MR. BERL:
Q. What did you do after that?
A. After that, I returned to MIT but this time on the faculty at the beginning of 1998 also in chemical engineering.
Q. And have you been there since?
A. Yes, I have been.
Q. Can you briefly describe the research you conduct at

MIT.

A. Yes. In a word, I describe it as pharmaceutical development and manufacturing research.

Q. And does your research include both small molecules and proteins?

A. Yes, it does.

Q. And what are you doing with formulation research generally?

A. Well, that's a major aspect of what I've been doing since I started in 1998. So I do research in order to advance the field in formulation -- excuse me -- in formulation, better understand formulations and formulizing, and also developing algorithms to try to make predictions.

Q. Have you worked on any biologic therapeutics?

A. Yes, I have. I've worked on quite a few biologics, again, starting in 1998 when I began as an independent researcher.

Q. Approximately how many biologic therapeutics have you worked on?

A. Probably roughly around 50.

Q. Have you worked on any molecules administered to the eye?

A. Yes. I have worked on bevacizumab, which we've been talking about in this case.

Q. Do you teach?

A. Yes, I do.

Q. And who do you teach?

A. Well, I teach primarily at MIT. I teach undergraduates, graduate students, classes, fundamental classes in chemical engineering. And then I also teach researchers, graduate students, postdoctoral researchers. I should say undergraduates are also in my laboratory.

And then I also have a professional short course every year that I teach on bioformulation to professionals in the industry, which, as a matter of fact, I just taught last week.

Q. And can you describe who attends that course and what they learn.

A. Yes. There's a variety of professionals. I would say roughly half, perhaps a bit more than half, are junior formulation scientists. And then the other half are scientists in other aspects of pharmaceuticals discovery, manufacturing, and also managers who want to learn about bioformulation.

Q. Where do people who take this course from you work?

A. Well, they work at -- typically at a variety of companies, from large companies, big pharma, to medium to small, even startup. We also have sometimes people from government, from national labs, and other organizations.

Q. Do you consult with industry?

A. Yes, I do.

Q. Can you describe generally what that involves.

A. Yes. It generally involves two types of engagements. So one is more strategic. For example, I'll be invited to be on a scientific advisory board, and then I'll go to the company and provide general advice on their strategies, like their formulation strategies.

And the other is more targeted. A company might have a problem, a problem with protein stability, for example. And then they'll ask me to try to help them to solve that problem.

Q. Do you work with governments?

A. Yes, I do. I've worked with the FDA for some time, since approximately 2007, but I also work with other regulatory agencies around the world. And we actually just convened a conference in April. For the first time since COVID, reengaging the community on regulations and also development of pharmaceutical manufacturing technologies.

Q. Have you published?

A. Yes, I have.

Q. And approximately how many papers have you published in the field of protein formulation?

A. Well, I've published over 200 papers total, and I would say over 50, maybe close to 60, are in protein formulation.

Q. Have you won any awards of note?

A. Well, I've won some awards.

Q. Any in particular that stand out?

A. Well, the one, I guess, that most stands out is a recent award from my peers at the American Institute of Chemical Engineers. It was an award on drug product quality or advancing drug product quality.

Q. We've talked about protein formulation and stabilization in this case. Is that your only area of expertise?

A. No. I also work in the area of pharmaceutical manufacturing and the interface between the two, between protein formulation/development and manufacturing.

Q. Have you been qualified as an expert in federal court before?

A. Yes, I have.

Q. Have you testified for both patent owners and patent challengers?

A. Yes.

Q. If you could turn to PTX 66C in your binder, and we can maybe put the first page up on the screen.

Doctor, what is this?

A. This is my CV.

Q. And does this summarize your professional experience?

A. Yes.

MR. BERL: We offer Dr. Trout as an expert in formulation and stabilization of protein therapeutics and

small-molecule therapeutics.

THE COURT: Any voir dire or objection to the motion?

MR. RAKOCZY: No objection, Your Honor.

THE COURT: Without objection, then, the doctor is so qualified.

You may proceed, Mr. Berl.

MR. BERL: Thank you, Your Honor.

BY MR. BERL:

Q. Now, before we get into the details, then, of the infringement testimony you're going to give today, Dr. Trout, I'd like to discuss a little background with you.

You said you do research on formulations. What is formulation research?

A. Well, formulation research is kind of a key part here. I'm sure the Court and others remember the pictures from Dr. Csaky yesterday in terms of actually how the eye is injected.

THE COURT: I do.

THE WITNESS: I figured you would, Your Honor. We all do.

So doctor -- I guess my job is -- so professionals, doctors like Dr. Csaky, doesn't have to be concerned about various aspects of injecting the pharmaceutical. And, for that matter, the patient doesn't either. For example, the product is stable, doesn't form particulates which might go in the eye.

The other is of course we talked -- we don't want the needle clogged while doctors or any doctor is giving an injection.

And then another aspect is what we call viscosity or the thickness of the formulation. It goes through a very thin needle. And, again, I don't think it's hard to convince everyone that we don't want the needle in there for a long period of time; so it has to be a thin enough fluid so it can go in pretty quickly.

BY MR. BERL:

Q. Is formulation research as simple as taking a formulation and substituting it into a new molecule?

A. No, sir. That's not what we do. That's not how formulation works.

Q. Now, I'd like to discuss the concept of solubility with you. What does solubility mean in the context of protein formulations?

A. Well, with -- many protein formulations are formulated as liquid in aqueous or water solutions. And solubility is the concept of keeping it in solution under whatever condition it might be subjected to.

Q. And is there one solubility for a given protein in a formulation?

A. No. Even for a given formulation, that solubility will depend on conditions, for example, temperature and pressure, including shear.

Q. Is there such a thing as a protein simply being fully in solution without regard to the temperature or pressure conditions?

A. No. Those are essential conditions in determining and defining solubility.

Q. Dr. Trout, have you prepared demonstratives to help explain the scientific principles relevant to your testimony today?

A. Yes, I have.

Q. Let's take a look, starting with Demonstrative Slide 3.

MR. BERL: And, Your Honor, this has demonstratives as well as portions of documents that we'll be using with Dr. Trout today --

THE COURT: Understood.

MR. BERL: -- so it's useful to follow along compared to the binder, I hope.

BY MR. BERL:

Q. We've shown PDX 5-3.0003, Dr. Trout. Can you explain what's shown here?

A. Yes. Here I just show a comparison between a typical small-molecule pharmaceutical aspirin and a biologic or large-molecule pharmaceutical like aflibercept. This is more or less to scale. Hopefully, the Court can see there's a little speck there which is represented as aspirin. And you

can see here is the molecular weight. And that's 0.18 kilodaltons. That was brought up yesterday in court. And it's just a measure of the weight but in molecular units like pounds or kilograms. And then the aflibercept is about 115 kilodaltons. So it's about 1,000 times bigger in terms of size, which is reflected in the relative scale here.

THE COURT: Just so I'm clear, when we say aspirin, we're talking about aspirin?

THE WITNESS: Yes, sir. Well, in a certain sense we're talking just about the molecule aspirin, not the formulation aspirin.

THE COURT: A singular molecule of aspirin?

THE WITNESS: Yes, sir. Correct.

THE COURT: Understood. Thank you.

BY MR. BERL:

Q. So these proteins like aflibercept, do they come in solution, in a liquid state, or are they in a powder state like something like aspirin?

A. Not like aspirin. They're in a liquid state from manufacturing. And, again, the idea is to maintain them in a liquid state. Aspirin I think we're familiar with is typically formulated into a tablet, and it comes from manufacturing as a powder and is made into a tablet.

Q. So what do solvents do for proteins if it's already a liquid to start with?

A. Well, solvent does what solvents do to molecules that keep it in solution. For example, water will interact with the protein around the surface of the protein and will orient itself to keep it in solution.

Q. Are solvents added to dissolve or remove aggregates in protein formulations?

A. No. Typically, aggregates are irreversible. So once they form, they don't go backwards.

Q. So is making a protein formulation, is it like what I talked about a moment ago, like taking sugar and dissolving it in your coffee?

A. No, on the contrary. Again, aspirin, we could make an analogy with sugar. That can be dissolved and then formed a solid again, a powder. But proteins, typically, we want to keep them in solution. Again, they come in the liquid state from manufacturing. And if they start precipitating or becoming insoluble, it's typically irreversible.

Q. I'd like to discuss now with you how that happens and how those aggregates can form.

If we could go to Exhibit PTX 1556.

Is this an article by Wang in 2005 that you reviewed in connection with your work in this case?

A. Yes, it is.

Q. If we look at the abstract on the first page, it says, "Protein aggregation is arguably the most common and

troubling manifestation of protein instability encountered in almost all stages of protein drug development."

Can you explain what Wang is conveying here?

A. Yes. This is the first sentence of the abstract, so really the first sentence in the paper. And it talks about, right here, protein aggregation. That's the protein molecules coming together, which we don't want. That's a manifestation of the instability. And it's omnipresent is what Wang is saying here.

Q. Let's go to page 3 of the article. And we have blown up a paragraph that begins with "protein aggregation has been observed frequently."

Can you explain what Wang is saying here?

A. Yes. Well, again, Wang is talking about protein aggregation, as I just mentioned from the abstract.

And specifically I've highlighted, Your Honor, two places, shearing/shaking. So that's an example of a pressure or pressure disturbance which is going to be omnipresent in --

THE COURT: And shearing would refer to the propulsion, if you will, of the solution through the needle.

THE WITNESS: Yes, sir, that can be it. But also during shipping, for example, during usage when the doctor or the medical professional takes it out, it can slosh around, to use a better term. So certainly that's the case. And then also just during storage, to name two examples.

BY MR. BERL:

Q. Are there particular conditions that scientists would think about in assessing intravitreal formulations?

A. Yes. So, again, for intravitreal we want the needle to be as thin as possible, typically, a 30-gauge needle, which has a very thin bore, which means that the solution has to get through that bore. And it can -- it is -- the bore exerts significant shear, a great amount of shear, because of the very small diameter.

Q. Doctor, what is the connection between this protein aggregation that Wang is discussing on the one hand and the concept of solubility that you discussed a moment ago?

A. Well, protein aggregation is, first of all, the first stage of solubility, and then it also -- or first stage towards insolubility I should say, and it also describes the insoluble particles which can be called insoluble aggregates.

Q. Can a protein come out of solution without aggregation?

A. No.

Q. What does it mean for a protein to stay in solution?

A. Well, it means that it is in solution. It is surrounded by the solvent molecules, primarily water molecules, and it doesn't aggregate and eventually come out of solution and precipitate.

Q. What's the problem with a protein not staying in

solution?

A. Well, there are several problems. One problem is that, if it comes out of solution, it's typically inactivated so it's not going to be useful to the pharmaceutical or at least the material that comes out of solution.

But above and beyond that, it can cause serious reactions. We talked about inflammation even earlier today, but then even the most serious one is immune response, which means that the body's immune system can actually attack the molecule which is meant to be a therapeutic.

Q. Let's take a look further down on page 3 of Wang, under the Subsection 2 in the paper "Protein aggregation and its influencing factors."

What is Wang writing here?

A. Well, Wang is just talking about two categories of aggregation, which I've highlighted in yellow. The first category is physical aggregation. So that's molecules coming together, for example, through hydrophobic, hydrophobic effects. I'll have some pictures of that shortly. But that does not involve the breaking of formation of chemical bonds.

And the second is the chemical aggregation, which can involve the breaking or formation of chemical bonds, for example, sulfur-sulfur bond forming.

Q. Doctor, in terms of assessing or determining the solubility of a protein, does it make any difference which of

these mechanisms that Wang is describing caused the protein to come out of the formulation?

A. No. It just matters the degree to which it's soluble or not soluble; it comes out of solution.

Q. How does a scientist know how much of a protein stays in solution under a particular set of conditions?

A. Well, in the extreme case, a scientist can, for example, experiment or do experiments under certain conditions; and if the solution gets cloudy, which one can see visually, then it's come out of solution, it's insoluble, that part that's cloudy.

But that's really an extreme case. Long before one can visually see the cloudiness, we can use analytical techniques, such as probing it with lasers and whatnot to determine the degree of insolubility.

Q. What kinds of conditions are used in these tests of solubility?

A. Well, the kind of conditions at which the protein might be subjected to during its lifetime as a pharmaceutical product, conditions such as shear, shaking, going through the needle as we just talked about, and potential temperature excursions.

MR. BERL: Your Honor, at this point I'm going to start getting into the claims and Mylan's product. I think Mylan has requested that the balance of the examination have a

sealed courtroom.

THE COURT: Understood.

MR. COPLAND: Yes, Your Honor. I discussed with Mr. Berl, and he'll need to go back and forth repeatedly to confidential information. The cross-examination will as well. So we ask the courtroom be closed for the remainder.

THE COURT: Understood. Consistent with -- is there any objection to that, Mr. Berl? I'm sorry.

MR. BERL: No objection.

THE COURT: Consistent with this Court's prior protective order and our prior practice during this trial, I would ask anyone who is not covered under that protective order to step out of the courtroom at this point in time.

(The following proceedings (581/16 to 711/16) were sealed and are filed under separate cover.)

THE COURT: I believe we're ready to hear from our next witness. If we are, go right ahead and hit play.

MR. GREGORY: Your Honor, I think we're all set to play this next deposition.

THE COURT: Thank you so much. Whenever you're ready, sir, you can go ahead and hit play. Thank you.

(Deposition of Vanessa Smith played.)

MR. GREGORY: And I believe that is the end of the video deposition testimony that we're prepared to present today. I'm happy to work with Mylan's counsel and the court

staff after the end of the day to figure out the exhibits that need to be moved in.

THE COURT: Sure. That sounds acceptable to me.

Where are we at overall, then, today, Mr. Berl?

MR. BERL: Your Honor, plaintiffs rest their case in chief.

THE COURT: That answered my question.

Counsel.

MS. MAZZOCHI: Good afternoon, Your Honor. This is Deanne Mazzochi speaking on behalf of the Mylan and Biocon defendants. At this time defendants move for entry of judgment on partial findings of noninfringement on all asserted claims pursuant to Federal Rule of Civil Procedure 52(c). Granting this relief now would also streamline significantly the invalidity portion of this case.

The defendants -- I also note that in the -- I'm sorry. The defendants also move for entry of judgment on partial findings for noninfringement as to all of the asserted claims of the '572 patent, Claims 6 and 25; '601 patent, Claims 11 and 19; and '865 patent, Claims 4, 7, 9, 11, and 14 to 17.

With regard to the asserted dosing patent claims, first, the defendants respectfully move for judgment on partial findings of no direct infringement on all asserted dosing patent claims.

Regeneron has introduced no evidence at trial that defendants will directly practice any of the claimed methods. Regeneron's expert admitted that he was not contending that defendants directly infringed. Regeneron thus has failed to prove by a preponderance of the evidence that defendants will directly infringe any asserted dosing patent claim.

Second, the defendants respectfully move for judgment of partial findings of no induced infringement for all asserted dosing patent claims. An active induced infringement requires first a predicate act of direct infringement, and Regeneron's expert has not satisfied Regeneron's burden of proof in that regard.

All of the dosing patents' asserted claims require a fixed-dosing schedule, including a specific number of monthly doses followed by a very precise eight-week dosing schedule.

Regeneron has failed to prove by a preponderance of the evidence that doctors in the real world actually do adhere to this schedule, let alone by any appreciable degree, and certainly not to the extent that this Court should be justified in inferring a specific intent by the defendants to induce doctors to follow this specific label -- I'm sorry -- this specific method of treatment.

While Regeneron has -- and Regeneron also has not thereby met its burden of proof to show that the defendants do, in fact, have the requisite specific intent to induce

infringement of the claimed precise fixed-dosing regimen.

Regeneron has relied primarily on defendants' Yesafili labeling, but their expert did admit that noninfringing regimens such in the Yesafili labeling include, for example, monthly dosing or every-eight-week dosing. Dr. Csaky was unequivocal that doctors have their own discretion to administer the drug at a dosing schedule of their choice and their control.

In addition, the supposed real-world evidence that Regeneron has presented with their expert having admitted that he did not attempt to quantify any -- the number of infringements that would be potentially in existing if the product were approved -- what he presented that was tied to actual medical records -- likewise cannot cause Regeneron to meet their burden of proof because, again, even in the dosing regimen that was designated as IAI 2q8, the dosing regimen does not fall within the scope of the claims given the wide variation that was permitted both on the, quote/unquote, monthly schedule, which was allowed to be anywhere from three weeks to five weeks, as well as a seven-week or nine-week dosing interval.

Thus Regeneron has not met its burden of proof to show evidence of direct infringement of each and every element of the asserted dosing patent claims, which is required to prove infringement, induced infringement under *Limelight*

Networks, Inc., v. Akamai Technologies, Inc., 134 S.Ct. 2111, 2117 (2014), noting that inducement liability may arise if, but only if, there is direct patent infringement.

And while the internal quotations are omitted, it also was citing *Aro Manufacturing Company v. Convertible Top Replacement Company*, 365 U.S. 336, 341 (1961), for that premise.

Accordingly, the Regeneron has failed to prove, one, that there will be actual direct infringers; two, that defendants will actively encourage direct infringement; and, three, that defendants have the requisite specific intent to infringe, especially where, as here, that intent cannot be inferred, given the overwhelming noninfringing uses of both Eylea and the defendants' Yesafili product, the existence of all of the noninfringing regimens in the label, which Dr. Csaky admitted, which also can be accompanied by the physician's own discretion and clinical judgment to make the choice of which label indication to use.

Thus, Your Honor, the defendants respectfully move under Rule 52(c) for a judgment of partial findings that all asserted claims of the '572 and '601 patents are not directly infringed by defendants and that defendants further do not induce infringement under 35 U.S.C. Section 271.

With regard to the '845 formulation patent, defendants also respectfully move for a judgment on partial

findings of no direct infringement with respect to the '865 formulation patent's asserted Claims 4, 7, 9, 11, and 14 to 17.

All of the '865 patent's asserted claims depend directly or indirectly on independent Claim 1, which requires a, quote, organic cosolvent element, as that term has been construed by this Court.

Regeneron has failed to prove by a preponderance of the evidence that defendants' Yesafili product includes the required cosolvent.

More specifically, under Your Honor's claim construction an organic cosolvent must increase the solubility of the drug substance solute, which here is the VEGF antagonist protein aflibercept.

We simply do not have that here. Plaintiffs have only alleged that the polysorbate 20 may be, could, under particular molecular model involving other products, could meet this element.

The evidence you have heard thus far was no disputes that the polysorbate 20 in Yesafili is a surfactant, a surface-active agent. By name and by definition, polysorbate 20 is acting as a stabilizing agent to protect the protein.

Polysorbate 20 indisputably does not dissolve the protein under this Court's claim construction, and Dr. Trout's effort today to try to reconstrue your definition under what he

claimed was an understanding of the person of ordinary skill in the art is improper.

Polysorbate 20 does not work in conjunction with water to help dissolve aflibercept in the Yesafili formulation. Because there is no evidence that the polysorbate 20 is actually increasing solubility of the aflibercept protein in Yesafili through the use of polysorbate 20, plaintiffs have presented the Court with a theory that fundamentally is unsupported and, in fact, contradicted by the very evidence it presented in its case in chief on infringement.

First, you heard Dr. Trout explain that polysorbate prevents aggregation and protein formulations. Assume that that's true and accurate. It doesn't change the ultimate analysis. Surfactants are well known in the art to be stabilizing agents. Surface active agents that protect the protein from denaturing or degrading and aggregation may be one of those phenomena that can happen in a protein formulation.

Second, you heard Dr. Trout rely on data that Regeneron's counsel characterized as the most important document he was going to show you, but again, there are two problems for Regeneron.

One, this most important document of plaintiff's infringement theory presents data for a different formulation that Mylan and Biocon do not use for Yesafili. No true head-to-head comparison was done at the correct concentration

with the correct ingredients; and, ultimately, the data are specifically for a formulation that uses the components of Eylea, not the formulation components of Lucentis, which we know Yesafili follows, which was that prior art model, not the Eylea model.

Two, Dr. Trout's theory that inhibiting aggregation somehow equals -- or perhaps he says effectively equals -- increasing solubility simply cannot bear any fruit on their infringement analysis.

Why?

Because the actual data of the histidine-buffered trehalose-stabilized formulation used in Yesafili indisputably confirm that no aggregation occurred in that formulation, both with and without the presence of polysorbate. That same data also showed that the components in Eylea, however, do aggregate.

Thus Dr. Trout's model was built on a fundamental flaw. But even assuming Dr. Trout's theory, all he has attempted to do is redefine the meaning of a cosolvent in violation of your Court's *Markman* order. Thus a judgment of noninfringement on partial findings is appropriate because plaintiff has not proven and indeed cannot prove, given the testimony of Dr. Hana Chang you heard and the Integrity Bio report, that the Yesafili formulation is prone to aggregation and thus needs the polysorbate to inhibit aggregation.

Furthermore, Your Honor, at the outset of this litigation, Regeneron did assert a variety of claims that are no longer asserted. So defendants also further respectfully move for judgment on partial findings of no infringement for all of those patents and claims that were asserted against the defendants in the complaint that were supposed to be designated for this part of the case and which are no longer asserted.

Thank you very much, Your Honor.

THE COURT: Thank you, Counsel.

Counsel.

MR. BERL: Good afternoon, Your Honor. I'm happy to respond to as much of that as you'd like.

Obviously, Mylan has made its record of filing a motion for partial findings. Actually, this was a nonwritten motion that they've made here. Obviously, it's a bench trial. We disagree with everything that Ms. Mazzochi just said.

THE COURT: Noted.

MR. BERL: I'm happy to explain why. Your Honor listened to the evidence. We obviously went through the claims in painstaking detail, explaining with expert testimony why Mylan induces infringement of all of the asserted claims of the method patent.

The notion that somehow not enough people will actually practice the claim is legally irrelevant. This is a claim of infringement under 35 U.S.C. 271(e). The issue here

is Mylan's label and whether Mylan's label induces infringement. That's the issue, always has been the issue from the Warner-Lambert case, which is the seminal case on induced infringement under 271(e) in the filing of an FDA application, continuing down through the *AstraZeneca v. Apotex* case, and all of the inquiries that Ms. Mazzochi rested on are essentially not relevant to the proper legal question before the Court.

Those questions before the Court were repeatedly answered by Dr. Csaky over and over and over again. You saw those two questions that were on the screen where he said yes and yes to each one. Claim by claim, limitation by limitation, this infringement case was set forth and made convincingly. And crediting that evidence, there can be no doubt but that a case of infringement was made.

With respect to the '865 patent, Dr. Trout just got off the stand, and you've now heard from multiple witnesses who have experience in protein formulation that the whole notion that Mylan is trying to advance to avoid infringement in this case, that something has to dissolve a protein as if it's some kind of sugar that you put in water and that that's what a solvent means in this context, is just wrong. That's not what anyone thinks. That's not the reality of the world.

And so Mylan is trying to reinterpret this claim to be a claim that never could be infringed because nothing solubilizes a protein under their definition, nothing is a

solvent under their definition, not even water.

And so Mylan basically advances two noninfringement arguments, it appears. One, that Your Honor somehow held that you have to dissolve a protein as if it's some sugar that you're dissolving in water. That's just not true. The evidence shows that that's not true.

And the second proposition that they appear to be advancing is that we have to show that there's aggregation and that, if you have something in solution just sitting on a shelf, that you can't increase its solubility.

That's not right either. We heard repeatedly that solubility is a function of temperature and pressure so that, if a formulation comes out of solution, for example, when you agitate it and then you add polysorbate and it doesn't happen, you've obviously increased the solubility. You're keeping things in solution.

The notion that the documents didn't show that, respectfully, is not true. What Mylan's doing is they're asking for judgment because they have no evidence on the other side. Their expert failed to address the most important evidence in the case, their own testing of their BLA.

You don't have to take it from me; you don't have to take it from Dr. Trout. Their own documents said in black and white what it was attributed to, what was going on with the formulation when they didn't have the polysorbate in it. And

it said it -- I'm happy to repeat it even though the courtroom's open -- but it said that it's protecting --

MR. RAKOCZY: Can we --

THE COURT: I've seen that evidence.

MR. BERL: So it cannot possibly be the case that, when you keep things in solution, you are not increasing the solubility. Their case requires someone to hold otherwise, which, honestly, makes little sense on this current record or given the facts of science that are at issue here.

So again, I'm happy to answer any questions, but given the posture of the case, we think that any judgment at this point or any other judgment with respect to noninfringement is completely unwarranted.

THE COURT: Understood. Thank you, Counsel.

It's your motion, Counsel. You get last word if you'd like one.

MS. MAZZOCHI: Just very briefly, Your Honor. We do believe that the case law has been clear out of the federal circuit, and it was actually in some of the cases we cited in our summary judgment brief in connection with the dosing patents that, if the doctors are allowed to exercise their clinical judgment under the label, your label can describe an infringing use; but if it's not a required, mandatory use and the doctors have the option to exercise their clinical judgment to use another method, then that is not enough for them to be

able to meet their burden to prove induced infringement.

With regard to the '865 patent cosolvent, Your Honor, what -- if I had to basically colloquialize what it seems like Regeneron's argument is is that, well, once you've decided to get married, if you go out and you renew your vows, that somehow means it's adding something to the scope of your legal obligations as a husband and wife. You're really not.

They're talking about -- the whole point of a cosolvent is that it is doing something more to the formulation. Under the Court's claim construction, it has to be increasing, helping to increase the -- I apologize. I don't have the construction in front of me; so I don't want to misquote it. Mr. Salmen will kill me if I do. Fine. He won't kill me. He'll chide he if I do, mercilessly.

THE COURT: I can't do anything about that.

MS. MAZZOCHI: But the ultimate point, Your Honor, is that what they're basically trying to do is suggest that the cosolvent doesn't -- their idea of a cosolvent is that it can be there and not do anything, and if it's not actually causing the formulation to do anything new, if it's not actually increasing the solubility of the aflibercept, then it's not acting as a cosolvent because the whole point is it's supposed to be helping the water to dissolve.

And, furthermore, this notion too that they've been saying is that, oh, it's not like sugar that you put in your

coffee, well, you can have proteins that are -- you heard it from Dr. Furfine earlier. He said, yeah, you can have lyophilized proteins, where they're proteins, they're solids. Then you can use water to help dissolve them, and sometimes you might want to use a cosolvent to help them dissolve.

That is not what we have here because it is undisputed that Mylan's product starts in water, stays in water, and it doesn't need any type of dissolution aid in the form of a cosolvent to either get it there or keep it there. So that's why again --

THE COURT: This is that chiding in writing?

MS. MAZZOCHI: No, but I --

THE COURT: Sorry, Counsel. I couldn't resist.

MS. MAZZOCHI: No, but again, Your Honor, I think that the ultimate point is is that they have only asserted literal infringement in this case, and it sounds like what they're trying to do is say, well, a surfactant is really equivalent to how a cosolvent works. And that's not the way in which they have presented this case. That would be a completely different theory that they have not raised in their contentions, did not do in their expert reports, which requires a different legal standard.

So they're basically to have their cake and eat it too, saying this is something that's equivalent without actually meeting the standards of the doctrine of equivalents,

and that's not appropriate either.

So with that, Your Honor, that's why we believe judgment is appropriate.

THE COURT: No, understood. Thank you. Thank you, Counsel.

Under 52(c) the Court is going to decline to render judgment at this point until the close of the evidence, considering the evidence the Court has heard, the context of a bench trial, of course, and the counterclaims and the rest, I think that's the appropriate step at this juncture.

I'm going to make an assumption, and make it a strong assumption, that Mylan would like to call its first witness tomorrow.

MR. RAKOCZY: That would be correct, Your Honor.

MS. MAZZOCHI: And, actually, Your Honor, two quick housekeeping matters that you did mention this morning.

There is an issue with regard to Regeneron has made the assertion that Dr. Rabinow's obviousness combinations were not set forth in his report. Because Dr. Rabinow is one of the witnesses we would like to try to get done in the next day or two, we're happy to actually provide the Court with the evidence that, yes, it is, in fact, in his expert reports -- it was even disclosed in our original contentions -- so that we can get that issue resolved because, if there is going to actually be a change to the scope of his opinions, we'd

certainly rather know that sooner rather than later. But we don't think that it is.

And I'm happy to turn the floor over to Mr. Hunt to confirm that for you if you would like.

THE COURT: I'd like, sir, if you wouldn't mind filing that sometime this evening or sometime tomorrow morning in response to Regeneron's motion. And it would be my strongest suggestion that a copy of the particular disclosure of that combination again of the Fraser, Dix, Lucentis, which is the Shams and Gaudreault prior art along with Liu where that was previously disclosed.

And I'd also touch upon, assuming it has been previously disclosed -- well, I'll leave it at that at this point, but we'll receive that in writing.

MS. MAZZOCHI: In addition, Your Honor, the defendants were planning on also playing the deposition testimony. I was hoping we were going to have time today; I think we'll do a different one so we can get done roughly before 5:00. But it's the deposition -- the 30(b)(6) deposition testimony of Karen Chu. So here, again, that was part of the letter that went to you this morning. I don't know if you want to take that up tomorrow or --

THE COURT: We're going to take that up tomorrow. I've not had a chance to digest that. And in all candor, I'm making an assumption -- and I don't know who all participated

in Ms. Chu's deposition. I'm making an assumption that there was no clean break between the 30(b)(6) deposition and her testimony as a fact witness. Is that correct?

MR. GREGORY: I don't think that is correct, Your Honor.

Your Honor, part of our problem here is that we think that, while certainly the lines can be blurry in many 30(b)(6) depositions, as you well know, between what is individual capacity testimony and 30(b)(6) testimony, this is actually one of the rare ones where it's pretty clear. I'm not sure if Mr. Schliesske can put it on the screen for me.

THE COURT: So there were two separate depositions of Ms. Chu, one where she served as a designee? No? I'm going to stop assuming. Tell me what happened.

MR. GREGORY: So there's one deposition, Your Honor. I believe it was December 16, 2022. We're looking here at, I believe, page 83 of her deposition transcript, and Mr. Schliesske can put it on the screen.

So you see there's a question from -- right before this there's a question from Mylan's counsel.

Regeneron's counsel, Mr. Oberwetter, says, "Is this a 30(b)(6) question?"

Mylan's counsel replies, "This is just her," i.e., individual capacity.

Ms. Oberwetter replies, "Do you want to tell me when

you go back," that is to 30(b)(6).

THE COURT: The changing of the hats.

MR. GREGORY: Exactly.

And then lest there be any confusion, Ms. Oberwetter asks again -- this is Regeneron's counsel -- "I'm sorry. Are you going to tell me went you go back to asking 30(b)(6) questions?" And Mylan's counsel says, "Sure."

She does not go back to asking 30(b)(6) questions until approximately page 113 of the transcript. And if Mr. Schliesske can put that up. And you see there she flags that we're moving back into 30(b)(6) testimony.

The next break appears at -- there's just two more -- page 123 of the deposition transcript. And, again, there's a question preceding this. And Ms. Oberwetter says, "Is that a 30(b)(6) question?" And again Mylan's counsel says, "That's her"; i.e., this is individual capacity.

And Ms. Oberwetter says, "Can you tell me when you go back to asking 30(b)(6) questions?" And again Mylan's counsel says unequivocally, "Sure."

And she does not go back to asking 30(b)(6) questions until page 273 of the transcript, where there's a question and Ms. Oberwetter says, "Object to form, foundation." And if we're back into 30(b)(6) questions; she poses a 30(b)(6) objection on scope.

So this is one of these situations where we actually

have a pretty clear delineation in the transcript of what's personal capacity, individual capacity, and what is 30(b)(6).

Now, the problem we have here is that they have represented they are only trying to choose 30(b)(6) testimony. That's the only exception to both the rules and the argument, arguably, the joint pretrial memoranda, which was heavily negotiated by the parties and says that "The parties agree that they shall not be permitted to play deposition testimony from witnesses who are testifying live."

Now, frankly, I think that should control above all else. That was negotiated in the context of the federal rules --

THE COURT: Even more so than Federal Rules of Civil Procedure.

MR. GREGORY: We negotiated with that in the background, Your Honor. But setting that aside, if their point is that this is not Ms. Chu's testimony but rather Regeneron's and they should be allowed to play it, they should only, at the very most, be allowed to play Regeneron's corporate testimony. And here we have clear representations from counsel that we relied on, and more importantly that the witness relied upon, when she was giving these answers, she was answering she, I'm sure, believed on behalf of herself, not Regeneron.

Now --

THE COURT: What position does Ms. Chu hold with

Regeneron?

MR. GREGORY: I should have addressed that at the front, Your Honor. I apologize.

Ms. Chu -- her exact title is escaping me. She is within the clinical development team. And we are bringing her next week. You will hear from her live. They'll have the opportunity to take her personal capacity, individual capacity testimony at that point, and we've told them that.

But they're seeking to play over an hour of her testimony today, as you saw in the letter, large swaths of which fall within the breaks that I just showed you where it's just personal.

Now, and my final point, Your Honor, and I hate to have to break this up, but I think I'm compelled to do so.

The joint letter that went in this morning was not a joint letter. That letter was served to the Court or submitted to the Court without Regeneron having the chance to first review it and approve it and sign off on it.

And now setting aside whether or not it's improper or from a procedural standpoint -- I can set that aside. The problem here is that it's substantively misleading in a couple of respects that we could have corrected had we had a chance to actually look at it. It's misleading in the fact that they kind of marched through various pieces of her testimony and made arguments about, well, this relates to Topic 17 and this

relates to Topic 4.

But, again, we would have -- if we knew they were going to do that and we had seen the final letter, we would have showed you in the letter what we just showed you before, the clean breaks in her testimony where they are just explicit that they're doing personal individual capacity, not 30(b)(6).

The other respect with which this is misleading is that one of the documents attached to the letter that went in this morning that we did not have a chance to review and that we did not know would go in with it was a list of the purported topics on which they designated Ms. Chu.

So even if the Court is inclined to go designation by designation -- and, again, we don't think you have to because we have these clean breaks in her testimony. But if the Court were inclined to do that, they put in this list of purported topics, but what they don't tell the Court is that that list was subject to a 25-piece -- 25-page piece of correspondence from Regeneron to Mylan within the days before Ms. Chu's testimony explaining all the problems that we had about the scope and the overbreadth of the 30(b)(6) topics, the ways that we felt they should be limited, and then designating Ms. Chu subject to those objections. And you don't have any of that record.

So, respectfully, Your Honor, I think there are a number of problems with their attempts to play Ms. Chu's

testimony. At the very least I think this Court should not allow them to play individual capacity testimony from Ms. Chu who will be coming live next week.

THE COURT: Counsel.

MS. MAZZOCHI: Yes. First, Your Honor, this is -- it was precisely my concern that Regeneron just wanted a standing objection as to whether something was 30(b)(6) testimony or not. I declined that.

At page 52 of the deposition testimony, Ms. Oberwetter specifically said, "I would like a running objection."

I said, No. I want to know when you're going to object that this is something that is not her -- you know, she's not speaking on behalf of Regeneron precisely so I then have the opportunity to know and follow up on that.

Now --

THE COURT: Why not two separate depositions, though? It makes this incredibly clean.

MS. MAZZOCHI: Well, I can't answer that, Your Honor. I mean, I would have loved to have had two days with Ms. Chu, but they were only offering one. So to try to --

THE COURT: Subpoenas and the rest. She's a high-ranking official within the plaintiff's hierarchy.

I'm sorry. Go ahead.

MS. MAZZOCHI: Sure. But, Your Honor, I do want to

say this, that at the point where she said, oh, will you tell me when you're seeing to go back to 30(b)(6) testimony, yes, in the very next question, I said, "What is your understanding?" relating to the exclusion criteria in the VIEW 1-VIEW 2 studies, asked her one more follow-up question, then asked the question of Regeneron. "Did Regeneron ever consider putting the black box warning in this?"

So two questions later I asked her a question of what is Regeneron's position on one of these issues?

THE COURT: How many questions after that are we going back to individual fact witness capacity?

MS. MAZZOCHI: What I was trying to do was, if I was asking her a question that was in your individual capacity, I would say "do you have any personal knowledge" or "in your individual capacity," and then there were many instances where I would -- like are you aware of this change versus what is your understanding -- so page 131: "Was it your understanding that Regeneron was attempting to file patent applications on all of these methods?"

So I was clearly, I believed, attempting to elicit what was Regeneron's position. And I understand, Your Honor -- so that is replete throughout all of these pages that they're complaining about is not -- somehow not Regeneron testimony.

And, furthermore, Your Honor, if we're going to start doing this, she was designated for a whole lot of topics. She

was designated on conception and reduction to practice, which -- of the '601 and '572 patents. So she's not a named inventor; it was Dr. Yancopoulos. They designated her on that.

A lot of the documents that we are putting into evidence do, in fact, relate to some of those conception issues because they're going to influence the priority date analysis that may have to come up with regard to some of the claims in the patent and whether they can swear back to one of their earlier references.

She was designated to talk about the clinical studies and investigations. So a lot of -- again, that is a large amount of what she was designated to testify to.

So I believed I was asking questions in her corporate capacity, and because I had told Ms. Oberwetter I was not going to agree to a standing objection, I expected her to object if she wanted to say "that's not Regeneron's corporate position" because Ms. Oberwetter is in the best position to know if what she's saying is a position Regeneron wants to take or not. I'm not in that position.

THE COURT: You drafted the designations, and it was noticed as a 30(b)(6).

MS. MAZZOCHI: Yes.

THE COURT: She was produced as a designee. There is no question in my mind that under Rule 32 Mylan may use any 30(b)(6) testimony for any purpose during this trial. As an

adverse party designee, that that is not even up for dispute.

The question becomes, particularly because Regeneron has represented to this Court repeatedly now Ms. Chu will appear to testify during this trial -- I don't think she's considered unavailable under the rules as to whether testimony in her own individual fact witness capacity can be used from this -- I think even the transcript said hybrid deposition.

And so you-all need to get together this evening and figure out, line by line, which goes in which bucket because the 30(b)(6) bucket, Mylan may use for any purpose during trial, without question. I'll note the objection. But I think Rule 32 is clear on that.

I would anticipate, frankly, under 52(c) not rendering any judgment on behalf of anybody until the close of evidence in this case given the significant factual disputes that I believe were apparent in the cross-motions for summary judgment and remain apparent even though we've only heard the plaintiff's case in chief at this point.

So I guess my ultimate question is what is the practical difference if Mylan waits until Ms. Chu is called to question her then?

MS. MAZZOCHI: The practical difference -- there's two, Your Honor. Number one is we did ask Regeneron -- so let me take a step back.

Originally, Ms. Chu was not even on our radar screen.

She was on a may-call list. All of the indications that we had had from Regeneron is that they were not going to be calling her live. It was only about a week ago-ish -- I don't want to be held to a specific date -- that they decided they were going to call her live.

We don't know why. We asked what would be the scope of what she was going to be testifying to? Because, again, what we're worried about is that we have the adverse admissions against them. They're going to have her come in and try to change something, and now we're going to have to have a cross-examination that's going to be twice as long because we're going to have to be -- is she -- was this answer given in her personal capacity and can I impeach her with her testimony or can I -- am I doing this in a 30(b)(6) capacity where I can actually just play the testimony?

I, frankly, believe it's going to be a lot more efficient and time-saving if we do our deposition designations and, if there's a particular issue where they want to say, No, this is something that we are 100 percent clear; this was her alone and she couldn't possibly fit into one of the topics within their letter, okay, I'm happy to have that discussion. But they won't even tell us what she's going to be here to testify about.

THE COURT: You should have asked her that during her deposition. That's the point of fact discovery.

MS. MAZZOCHI: I did. I asked her --

THE COURT: Then you can cross her on it. You can impeach her and the rest.

You all have to get together this evening and work through this list and see what's left in dispute. We'll handle it one at a time in the morning of whatever's left.

30(b)(6) testimony, Mylan may use under Rule 32 for any purpose during the course of this trial. Non-30(b)(6) testimony is a different story. Counsel needs to get the buckets straight which is which, and then we'll deal with the personal testimony issue tomorrow morning.

MS. MAZZOCHI: That's fine, Your Honor. Thank you.

THE COURT: Thank you.

MR. GREGORY: Thank you, Your Honor.

MS. MAZZOCHI: Then with that, Your Honor, our first witness, who we would also like to call by deposition testimony, is Abby Cahn, who is a marketing individual within Regeneron.

THE COURT: How long is that?

MS. MAZZOCHI: I think it's about 35 minutes.

THE COURT: I'm going to exercise Article III privilege, and we're going to play that tomorrow morning.

MS. MAZZOCHI: I do have a shorter one.

THE COURT: Actually, no. I have a summer league high school basketball game up the road that I have, with all

due respect to everyone in this room, more interest in at this point. You all are welcome to attend.

We will hit play on whichever one you'd like to start with tomorrow morning, Counsel.

MS. MAZZOCHI: Then, Your Honor, what we may try to do then because, as we had informed counsel, Dr. Albini does have some scheduling issues. We may call Dr. Albini because we do want to make sure that he can get on the stand tomorrow, off the stand, and doesn't have to be held over for any meaningful period on Friday.

THE COURT: That's fine. And then if that gives you all more time to work through the issues with Ms. Chu's testimony, that's fine by me. I'm not eager to start that --

MS. MAZZOCHI: I understand.

THE COURT: -- first thing; so if there's a witness you'd like to call first, that's fine, other than Ms. Chu. That will be fine.

MS. MAZZOCHI: We'll work on that, Your Honor. Thank you very much.

THE COURT: The best of luck to you all working through that. I'm going to go watch my Fighting Hawks of University High in their summer league game instead.

Anything else we need to take up this afternoon, then?

You've got the mic, Counsel. Go ahead.

MS. MAZZOCHI: Not that I'm aware of, but Mr. Rakoczy did stand up. So if he's got something in mind, I'll defer to his judgment.

MR. RAKOCZY: Nothing, Your Honor.

THE COURT: Understood.

MR. BERL: Nothing from plaintiff, Your Honor.

THE COURT: I don't mean to rush anybody for tip-off. I've got plenty of time to make tip.

Okay. Nothing?

You guys have plenty to do this evening. We'll reconvene tomorrow morning at 9:30 and go from there.

You all have a pleasant evening. Thank you very much.

(Proceedings concluded at 4:50 p.m.)

CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 14, 2023, as reported by me in stenotypy.

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

Given under my hand this 14th day of June 2023.

/s/Cindy L. Knecht

_____

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

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Regeneron Pharmaceuticals, Inc.

Plaintiff,

VS. CIVIL ACTION NO.

1:22-cv-61

Mylan Pharmaceuticals, Inc., and Volume 4

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 15, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

APPEARANCES:

On behalf of the Plaintiff:

David I. Berl
Ellen E. Oberwetter
Kathryn S. Kayali
Williams & Connolly, LLP
680 Maine Avenue, SW
Washington, D.C. 20024
202.434.5000

Andrew E. Goldsmith
Kellogg, Hansen, Todd, Figel & Frederick, PLLC
1615 M. Street NW, Suite 400
Washington, DC 20036
202.326.7945

APPEARANCES CONTINUED ON NEXT PAGE

On behalf of the Plaintiff, continued:

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

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

On behalf of the Defendant:

Deanne M. Mazzochi
William A. Rakoczy
Heinz J. Salmen
Eric R. Hunt
Lauren M. Lesko
Neil B. McLaughlin
Rakoczy, Molino, Mazzochi & Siwik, LLP
6 W. Hubbard Street, Suite 500
Chicago, IL 60654
312.527.2157

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

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

Thursday Morning Session,
June 15, 2023, 9:30 a.m.

- - -

THE COURT: We convene for day four of trial. Good morning, everyone.

Everyone's curious, the University High Hawks played well yesterday, and rising junior combo guard Noah Kleeh at 12 and 18 points in two games yesterday. So summer league is off to a good start. And while sitting at the Marion County Armory, I was reading the Federal Circuit's thoughts on many things as well.

Okay. Let me ask this initial question so we can most efficiently use our time today. What witnesses does Mylan plan to call first?

MR. McLAUGHLIN: We plan to call Dr. Thomas Albini first.

THE COURT: Outstanding. Are there any issues with Dr. Albini that we need to take up before he testifies that anyone's aware of at this point?

MR. McLAUGHLIN: None that I'm aware of.

THE COURT: Counsel.

MS. OBERWETTER: No, Your Honor.

THE COURT: Outstanding. Let's do that.

Yes, Counsel.

MR. HUNT: Your Honor, just a brief administrative

matter. Thank you for taking care of the updating us on the Hawks. I was going to check in on that.

With regard to Dr. Rabinow, we have an outstanding motion to exclude. Defendants filed an opposition, I suppose early this morning.

THE COURT: Yes.

MR. HUNT: In the event that the Court is prepared to take up that issue, I think it would be beneficial to the parties and most notably the defendants to assist in witness preparation. So if there's a particular time that the Court would be willing to take that up today, it would be much appreciated.

THE COURT: Why don't we do that -- because Dr. Albini has a travel issue. Is that correct? Or travel schedule, I should say, not issues.

Hopefully, Doctor, wherever you are, you don't have issues, but I know you have a travel schedule.

Let's take that up at morning break or so, and we'll go from there.

MR. HUNT: Appreciate it. Thank you, Your Honor.

THE COURT: Yes, ma'am.

MS. MAZZOCHI: And, Your Honor, the additional administrative matter to bring up has to do with the deposition designations for Karen Chu. So one of the things that we do have -- I'm happy to hand it up to Your Honor -- is we actually

went through --

THE COURT: I believe I have that.

MS. MAZZOCHI: What got filed was the -- that was our letter that we had previously sent where we -- under the pretrial order where we had specified this was Regeneron's objection; this is ours.

In response to your instructions yesterday, we did have a meet-and-confer. My understanding is that Regeneron's position is that they believe we had an agreement that, therefore, all of Ms. Chu's testimony was converted from 30(b)(6) even if it fell within the notice topics to 30(b)(1). We obviously disagree with that position.

So what we -- we do have a copy of the transcript where we basically have gone through and marked these are the different --

THE COURT: I have the color-coded -- red, green, yellow. I've not had a chance to review that. So we're going to put a pin in that.

MS. MAZZOCHI: I just wanted to know if there was a -- because, again, we were hoping we could play Ms. Chu's deposition testimony today as a 30(b)(6) witness. So I didn't know if that was already something you'd like to take up --

THE COURT: We will when we get to it.

MR. GREGORY: I'm not -- not seeking to argue this right now, just want to clarify.

THE COURT: Not going to, but go ahead.

MR. GREGORY: The deposition transcript that I believe you have is actually one from Regeneron. I think it's probably very similar to the one that Mylan's counsel has prepared. We received the email request this morning for those transcripts.

We have a machine time limitation on the small printer across the hall. We're running copies. I believe we have provided the Court with two. The next one out of the printer will go to Mylan's counsel. The fourth one will be mine.

THE COURT: Understood.

MS. MAZZOCHI: Your Honor, how about to the extent let's make sure everybody's got copies so nobody's surprised. I'll give this to counsel.

Your Honor, how many copies would you like?

THE COURT: Two, please.

MS. MAZZOCHI: Thank you, Your Honor.

THE COURT: I know we've got some pins on things to deal with. We will take them as they come.

Mylan may call its first witness.

MR. McLAUGHLIN: Your Honor, I believe we have some binders. Permission to approach to pass out those binders, documents Dr. Albini is going to be relying upon.

THE COURT: Granted.

MR. McLAUGHLIN: Good morning, Your Honor. Neil McLaughlin on behalf of Mylan Pharmaceuticals, Inc., and Biocon Biologics, Inc. Biocon/Mylan would like to call Dr. Thomas Albini as its first witness in its invalidity case.

THE COURT: Good morning, Doctor, sir. If you want to make your way to the front of the courtroom.

THOMAS A. ALBINI, MD, DEFENDANTS' WITNESS, SWORN

THE COURT: Thank you, Doctor. Once you're seated and comfortable, sir, if you wouldn't mind adjusting that microphone. Don't worry; you can't break it.

THE WITNESS: Okay.

THE COURT: Does everyone have all their binders, slides, and the rest?

If you're settled, Counsel.

MR. McLAUGHLIN: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. McLAUGHLIN:

Q. Good morning, Dr. Albini. Can you please state your full name for the record.

A. Thomas Arno Albini.

Q. You're here testifying on behalf of Biocon and Mylan, correct?

A. That is correct.

Q. Did you prepare demonstrative slides to assist the Court with your testimony today?

A. That's correct.

Q. And looking at the screen -- this is DDX 6 -- are these the slides that you prepared?

A. Yes.

Q. So, Dr. Albini, I'd like to first talk about your qualifications and experience that are relevant to this case.

What is your area of expertise?

A. I am a vitreoretinal surgeon who, among other things, treats patients with angiogenic eye disorders on a routine basis. And I've been doing that now for over 15 years as faculty at the University of Miami Bascom Palmer Eye Institute.

Q. Could you describe your academic experience that led to your eventual appointment to Bascom Palmer Eye Institute.

A. I finished medical school in 1999 at Johns Hopkins University in Baltimore. I then went to Los Angeles to the University of Southern California Doheny Eye Institute, where I finished a three-year residency in ophthalmology. I also undertook a one-year fellowship in intraocular inflammation and ocular pathology.

Subsequent to that, I went to the Cullen Eye Institute at the Baylor College of Medicine in Houston, Texas, where I undertook two years of training as a fellow in vitreoretinal surgery.

And immediately subsequent to that, I was hired as an assistant professor at Bascom Palmer, University of Miami.

Approximately six, seven years later, I was promoted to associate professor. And back in 2018 I was promoted to a full clinical professor of ophthalmology at Bascom Palmer.

Q. You made a reference to the term "vitreoretinal."

Can you describe for the Court what vitreoretinal disorders are?

A. Vitreoretinal disorders are a number of diseases within the back part of the eye behind the lens involving surgery and medical -- and/or medical treatment of the retina and the nearby tissues in the back of the eye.

So these would be things that people might have heard of, like retinal detachments on the surgical side, epiretinal membranes, and on the medical side, most of the diseases that we'll be talking about, such as macular degeneration and diabetic macular edema.

Q. And looking at the next slide, Slide 3 of DDX 6, can you tell the Court a little bit about your experience working as a medical doctor in the field of vitreoretinal disorders.

A. Sure. So as I mentioned, I started as an assistant professor back in 2006. I've been a staff ophthalmologist at a fully equipped eye hospital, the Anne Bates Leach Eye Hospital, and at Jackson Memorial Hospital, which is the county health system at University of Miami.

Since 2016 I've been codirector of the vitreoretinal surgery fellowship, and then in 2018 I was promoted to full

professor of clinical ophthalmology.

As of this morning I have decided to become the medical director of the retinal division within Bascom Palmer Eye Institute.

Q. Congratulations.

Now, turning to the -- your next slide, Slide 4, can you describe some of the things that you do on a day-to-day basis in your roles at Bascom Palmer?

A. We have a number of educational conferences for fellows and surgical and medical retina. I routinely participate in those. I have fellows and residents who are with me in clinic virtually every time I'm in clinic. And part of my responsibilities are not only to manage patients as best I can but also to help educate younger doctors who are becoming vitreoretinal specialists themselves.

I also have fellows with me in the operating room, either watching me operate or me watching them operate, and that's also on a routine basis. And I've been doing that for years.

Of course, my primary emphasis is on diagnosing and treating vitreoretinal diseases in patients. I have a very busy clinical load. I see somewhere between 4,000 and 5,000 patient visits per year, and I operate every week.

And as part of those responsibilities, I administer a lot of vitreal anti-VEGF agents such as the ones that we'll be

discussing the rest of this testimony.

Q. And turning to the next slide, can you describe some of the other contributions and roles that you have within the vitreoretinal specialist community.

A. I've participated in a lot of national and international societies, professional societies, within retina and ophthalmology. I've been given the Senior Achievement Award by the American Academy of Ophthalmology, the Senior Honor Award by the American Society of Retina Specialists. And these awards reflect scientific contributions that I've made to the meetings over the years.

I'm a member of The Retina Society and serve on the nominations committee for The Retina Society.

I'm a member of The Macula Society, serve on the bylaws committee for the Macula Society. And I'm a founding member of the Vit-Buckle Society, which has now become a large organization focusing on mentorship of young surgeons in their residency and fellowship and in the first part of their careers.

I'm codirector now for the last, I think, five years of the annual Angiogenesis meeting that was started by my colleague Dr. Phil Rosenfeld, and I do that along with Dr. Harry Flynn. The three of us are codirectors of one of the largest scientific meetings dealing with angiogenic eye disorders.

I've been editor on the *Journal of Vitreoretinal Diseases*, although I stepped down recently due to time constraints. And I've been an editor for a professional magazine called *Retina Today*, I think, for about 12 years.

Q. In the context of providing your opinions in this matter, did you provide a definition for a person of ordinary skill in the art?

A. Yes, I did. I believe it's on the next slide.

Q. Is that definition shown here on Slide 6?

A. That's correct.

Q. Now, I'm just going to take some time to read this into the record so we have a clear record of what that definition was.

THE COURT: Slowly, please, Counsel.

MR. McLAUGHLIN: Understood.

BY MR. McLAUGHLIN:

Q. So from paragraph 91 of your expert report it begins:

"After considering the above-mentioned factors, it is my opinion that a person of ordinary skill in the context of both the '601 patent and the '572 patent would have:

"1. Knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and

"2. The ability to understand results and findings presented or published by others in the field, including the

publications discussed herein.

"Typically, such a person would have an advanced degree, such as an MD or PhD, or equivalent or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field with practical academic or medical experience in:

"1. Developing treatments for angiogenic eye disorders, such as AMD, including through the use of VEGF antagonists; or

"2. Treating of same, including through the use of VEGF antagonists."

Did I read that correctly?

A. That's correct.

Q. And in your opinion, do you meet the definition of a POSA with regard to the '601 and '572 patents?

A. I believe I do. I hold an advanced degree; I think I can understand a publication result; and I diagnose and treat those disorders.

Q. Would you have met that definition in the 2010 time frame?

A. Yes, I would have.

Q. At this time could you please turn to DTX 8205 in your -- set of binders you've been provided.

A. I'm not sure where the binders are. Maybe I should have grabbed that.

THE COURT: Of all people, the witness does not have a binder.

One second, Doctor.

THE WITNESS: I apologize.

You're directing me to Volume 1?

BY MR. McLAUGHLIN:

Q. DTX 8205.

A. I recognize that document. Yes, I see it.

Q. Is that a copy of your current CV?

A. That's correct.

MR. McLAUGHLIN: So, Your Honor, at this point we would like to move to admit DTX 8205, Dr. Albini's CV, into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 8205 was admitted.)

MR. McLAUGHLIN: At this time we also proffer Dr. Albini as an expert in the diagnosis and treatment of vitreoretinal disease.

THE COURT: Any voir dire or objection?

MS. OBERWETTER: Yes, Your Honor, as follows. We don't have any objection to him being offered as a treater of angiogenic eye disorders. We have some concern there are going to be opinions elicited today on formulation topics. We do not

believe that Dr. Albini is an expert on formulation issues. And if he intends to speak on his own account about what certain references do or do not disclose about formulations, we do have voir dire from that standpoint, Your Honor.

THE COURT: We'll take that up if and when we tread into those grounds.

But no objection to the present motion as a treater of these certain eye disorders, correct?

MS. OBERWETTER: Correct, Your Honor.

THE COURT: Without objection, that motion is granted, and the doctor is deemed so qualified.

MR. McLAUGHLIN: Thank you, Your Honor.

BY MR. McLAUGHLIN:

Q. Turning to Slide 7. Dr. Albini, before we get to the substance of your opinions, did you conduct your analysis from the perspective of a person of ordinary skill in the art as you described it as of January 2012?

A. I did. And I reviewed the subject matter of the dosing patents and of the asserted claims, the prior art prosecution histories, the technology at issues. And I bring to that my 20 years of experience as described.

Q. In the context of formulating your opinions, did you review Dr. Csaky's responsive expert report in this case?

A. I did.

Q. And did Dr. Csaky provide a definition of a person of