ordinary skill in the art that is different from your definition?

A. He did.

Q. Would your analysis change under Dr. Csaky's definition of a person of ordinary skill in the art?

A. No.

Q. Let's turn to a little bit of a background about this case, just starting with Slide 9.

Have you assessed in this matter the issue of invalidity with respect to U.S. Patent Numbers 10,888,601 and 11,253,572?

A. I have.

Q. Is it okay if I refer to those as the '601 and the '572 patents going forward?

A. Yes.

Q. Would it also be okay if I refer to those as the dosing patents in some instances today?

A. Yes.

Q. You'll understand I'm referring to the '601 and '572 patents?

A. I will.

Q. So let's talk about the asserted claims. Do you understand that the claims shown here on Slide 10 are the claims that are being asserted in this matter by Regeneron?

A. That's correct.

Q. Those include Claims 11 and 19 of the '601 patent and Claims 6 and 25 of the '572 patent?

A. That's right.

Q. Are you rendering opinions on the anticipation and obviousness of each of those patents?

A. Yes.

Q. Do you understand that other experts will be opining on certain elements of one or more of those patent claims?

A. Yes.

Q. And one of those, you understand, will be Dr. Rabinow --

A. That's correct.

Q. -- writing opinions with respect to Claim 6?

A. That's correct.

Q. Did you rely on Dr. Rabinow for opinions regarding Claim 6?

A. Yes, I did. I do not see myself as an expert in formulation, just in vitreoretinal disorders and their treatment. So I did rely on him in that regard.

Q. If we flip ahead to Slide 11 here, can you briefly provide a description to the Court of the opinions that you're going to be presenting today?

A. The basic arguments are going to be that these claims, as you outlined -- the DME, DR claims -- are anticipated by the September 14th, 2009 Regeneron press release

and the 1999 '747 patent; that they are also obvious through those prior art pieces in combination with others; and that the patent Claim 6 of the '572 patent as regards formulation is anticipated and obvious.

Q. Dr. Albini, I would like to start by talking about a little bit of scientific background before we delve into your opinions and the ways of treating various angiogenic eye disorders before 2011.

Let's start with the anatomy of the eye. Can you -- and the Court has heard a lot of this already, but can you briefly describe what you've shown here on Slide 13?

A. Sure. This is a cartoon cross section of the eye, showing the front parts of the eye, the cornea -- the clear part that you see when you look into somebody's eyes -- and the lens.

And the -- shows deeper into the eye. You have the vitreous gel, which occupies most of the volume of the eye, especially that back component. And then that orange-colored tissue that you see there is sort of the wallpaper lining of the inside of the eye called the retina. This is neurologic tissue that connects to the optic nerve and sends visual impulse information back to the brain for you to be able to see.

And if you want to progress the slides, this cartoon starts to move.

When light comes into the eye, it goes -- it's focused by the cornea and the lens onto the fovea. The fovea is a specific part of the macula, the center part of the macula, and the macula is a part of a retina in general.

And that's the part where you have your highest definition vision. That is the part that's affected by the diseases at issue here, both diabetic macular edema and exudative, or wet, macular degeneration.

In those disease states, either because the blood vessels are leaky, as they are in diabetic macular edema, or because they're leaky because of abnormal growth of vessels that develops in macular degeneration, the retina becomes distorted which, in turn, distorts your vision.

And the miraculous discovery over the last two or three decades is that a lot of that disease process is driven by a molecule called vascular endothelial growth factor and that blocking this vascular endothelial growth factor not only causes some of these immature blood vessels to disappear, but it decreases the fluid buildup and consequent distortion of the retina; and, even more miraculously, it improves patient's vision. And this blockage has been responsible for greatly reducing cases of blindness due to macular degeneration and diabetic macular edema over the last few decades.

Q. Thank you, Dr. Albini.

Now, I'd like to shift to a discussion of state of

the art and the background with regard to what was known prior to 2011, including with respect to some of these VEGF inhibitors that you just made reference to.

Do you understand first -- we'll be filling in this timeline as we go along, but do you understand that 2011 to be the year the patents-in-suit were filed?

A. That's my understanding.

Q. Let's start by talking about the VEGF drugs that were being administered in trials -- or the clinic prior to 2011.

Would that have included ranibizumab?

A. Ranibizumab and bevacizumab -- a very similar molecule to ranibizumab but different in many ways -- were the two main agents that were in use prior to the 2011 date.

Q. And was aflibercept also being tested in clinical trials prior to 2011?

A. It was available for clinical trial use only, that's correct.

Q. So if we flip to Slide 21, can you describe what's shown here on this slide, Dr. Albini.

A. This is a review article that was published in 2009 by Dixon and coauthors, and it describes the -- what became known as the aflibercept molecule. It's VEGF Trap-Eye, which was a scientific name, as Dr. Yancopoulos testified the other day, that was used for this molecule prior to the aflibercept name and the Eylea names being given to it. But it is a fusion

protein with key binding receptors of the VEGF receptor 1 and receptor 2 fused with the FC portion of an antibody.

Q. And here on the slide you're referring to DTX 0204, pages 1 and 3 from the Dixon reference?

A. That's correct. Also here there is another reference from Adis in 2008 which makes reference to the same protein.

Q. And Adis, that's DTX 4008 that you're referring to?

A. That's correct.

Q. What's the year of the Dixon reference?

A. 2008.

Q. And was VEGF Trap-Eye also known as aflibercept in the prior art?

A. That's correct.

Q. And is that shown here on Slide 22 in excerpts from DTX 0204 and DTX 4008?

A. Especially in the Adis 2008 article. The title of the article itself is "Aflibercept."

Q. In the abstract of Adis, the reference is aflibercept, and it says that Regeneron and Bayer are developing the agent for eye disorders?

A. That is correct.

Q. And turning to the next slide, Slide 23, you've shown the '747 patent on the left hand. Is that one of the patents and references you've relied on in forming your opinions in this case?

A. That is correct.

Q. And did the '747 patent recite a molecule called VEGFR1R2-Fc delta C1(a)?

A. That is correct. That is the name given to the fusion protein of the VEGF receptor 1 and 2 bound with the Fc receptor that was in clinical use.

Q. Is that molecule also known as aflibercept?

A. That is correct.

Q. Flipping ahead to Slide 24, this is another disclosure from the '747 patent that you provided here.

Does the '747 patent disclose a method of treatment for an angiogenic eye disorder?

A. It does. In the specification there are outlined patient visits that should occur when the patients are being treated with this molecule, and it says that after the first 30 days, the patient should return for periodic examinations on a monthly basis thereafter.

It also describes that the patient needs to be continuously monitored through periodic examinations for fluid in the retina. And at the time fluorescein angiography is mentioned as an imaging modality to do that with. And it also mentions that, in a preferred embodiment of what's taught in this patent, the initial treatment is followed by subsequent treatments that are given at dosing intervals ranging from one- to six-month dosing intervals.

Q. And looking at the face of the '747 patent, do you see the date of the '747 patent's priority application?

A. I'm not so clear on all of the legal terms; so maybe -- but I see the date there, December 4th, 2007, although my recollection is that this patent was first filed in 1999.

Q. Thank you.

And flipping to the next slide, Slide 25, is that '747 patent now reflected on this timeline that you've provided?

A. Yes.

Q. And that '747 patent, that's DTX 2730?

A. That's correct.

Q. Now, moving on to Slide 26, let's talk about some of the other VEGF inhibitors that were known and being used by ophthalmologists before the '601 and '572 patents were filed.

What was the first anti-VEGF antibody approved by the FDA for treating an angiogenic eye disorder?

A. The first antibody molecule that was approved was ranibizumab. There was a prior medicine called Macugen, which was an aptamer. It's a slightly different type of technology. It is a binding molecule much like these others all targeting various subtypes of vascular endothelial growth factor.

Ranibizumab became FDA approved for use in wet macular degeneration in 2006. And what we have here is a picture of the label of the drug with an excerpt describing

dosing frequencies of intravitreal injection once a month and another approved dosing regimen of one injection every three months for the first four injections and quarterly injections thereafter.

The other main drug in use was bevacizumab. Bevacizumab is quite an interesting story. It's another molecule that also targets vascular endothelial growth factor. It was also developed by the Genentech. Both these drugs were developed by Genentech.

Ranibizumab was developed specifically for use in the eye while bevacizumab was developed for intravenous use in cancer patients. Bevacizumab was available prior to the availability of ranibizumab. And in 2005 a number of physicians began to inject bevacizumab off-label intravitreally to treat angiogenic eye disorders. There was already good data coming from Phase II studies and other studies showing that there was great efficacy with ranibizumab.

And there was a desire to have this efficacy available to patients before the molecule was actually approved by the FDA; so bevacizumab was used. And that quickly in 2005 spread throughout the world, where this became the major drug that was used in this sphere. And it remains to this day probably used just as often as the name-brand drugs in the United States.

One of the main driving factors for the use of

bevacizumab, even though it's not specifically FDA-approved for this indication, is a huge differential in cost. The ranibizumab was approximately $2,000 per injection whereas bevacizumab, when you bought a bag of drug for intravenous use and you aliquoted it out to inject it into the eye, the cost of a single ocular injection came out to about $50. So it was a great drug to have especially for patients of limited means.

Q. In your discussion of the ranibizumab label that we just had prior to your discussion of bevacizumab, were you referring to DTX 4056?

A. That is correct.

Q. Thank you.

If we flip ahead, can you briefly tell the Court what you've shown here on Slide 27 with respect to ranibizumab and how it was being used in clinical trials?

A. These are three outcomes from trials with ranibizumab that were available in the 2006 to 2008 time frame. And I think these are really important graphs of top-line data from these drugs.

The first to the left is the top-line visual acuity results from the ANCHOR trial of monthly ranibizumab for the treatment of wet macular degeneration.

The line that you see there going down on the bottom is the control arm. And that was treatment with standard of care at the time, which was a type of laser and photodynamic

intravenous treatment called photodynamic therapy. That was the best treatment that we had when I was a resident. And as seen there, patients continued to lose vision. Although they lost vision less quickly than they might have without this therapy, it just retarded the rate of vision loss, but patients still continued to lose vision.

The really earth-shattering result that was seen in ANCHOR study and other studies, the MARINA study which we'll be talking about later, was this quick rise in visual acuity that was then maintained over time as you see in the other two lines that go up to where patients are gaining about ten letters, what we call ETDRS letters of visual acuity. That translates into being able to read two lines further down on the eye chart, roughly, in that area. So that was really a very welcome and amazing improvement in the treatment of macular degeneration.

In the center box you see the top-line data from a smaller prospective study called the PrONTO study, which just to have institutional pride, was performed at Bascom Palmer Eye Institute. And this study tested the concept whether we could reduce injections, not necessarily inject patients every month as was done in the original ranibizumab study, but make decisions on a monthly basis whether or not a patient needed an injection by considering certain clinical factors and considering the state of the retina, especially as evidenced by

imaging technologies, newer technologies that were available at the time, especially something called optical coherence tomography, or OCT, examinations, which are now pretty ubiquitous in the retinal world as a way of evaluating the health of the macula.

So this study showed, as you can see there, that you could get very profound benefit and visual acuity results, really very nicely mirroring the benefits that you see in ANCHOR with this as-needed treatment strategy. This is the so-called prn treatment strategy which became very poplar very quickly in that 2007 and beyond range.

And, finally, you have the results of a quarterly dosing study with ranibizumab, the EXCITE study, which showed that monthly dosing, which is the triangle line up on top, outperformed quarterly dosing. So these were initial monthly loading doses and then followed by quarterly dosing. And that although that treatment strategy resulted in a success compared to photodynamic therapy, certainly compared to observation alone and no treatment, it was not as good as monthly dosing.

Q. And when you were referring to these charts here, you're referring to excerpts from DTX 4061?

A. That's correct.

Q. With respect to the PrONTO study, did you also rely in the process of formulating your opinions on DTX 3115, the Fung 2007 reference?

A. I did.

Q. Now, turning to the next slide, could you tell the Court a little bit about how bevacizumab was being used in the clinic and how it was being evaluated in clinical trials?

A. This is a clinical trial of bevacizumab for exudative macular degeneration, a one-year prospective study, showing that this drug could be used to obtain similar results with that seven- to eight-letter gain by 12 months. And this was also done with initial loading doses and then reinjection of the drug on an as-needed basis going forward.

Q. So flipping back to the timeline now, so just to summarize, by 2006 there was an anti-VEGF agent, ranibizumab, that had been approved for monthly dosing and for every-12-week dosing?

A. That's correct.

Q. And by 2007 the results of the PrONTO study using as-needed maintenance dosing, had that been reported?

A. That's correct.

Q. And by 2008 had data been reported with respect to the use of bevacizumab in the treatment of AMD and is that reflected here --

A. Yes.

Q. -- on the timeline?

I would like to shift focus a little bit. And can you tell the Court how ranibizumab was being used in the

context of treating DME in that time frame.

A. This is a review article by Dr. Lalwani from 2009 that reviews the results of a early study with ten patients who received injections of ranibizumab at baseline, month one and month two, so essentially three loading doses, and then received q8-week dosing for the month four and six. And it showed that there was good visual acuity gains from this treatment strategy in this small number of patients with diabetic macular edema.

Q. Is that Lalwani reference now referenced on this timeline here at Slide 31?

A. That is correct.

Q. And that's from DTX 2733?

A. That's correct.

Q. Now, turning to the next slide and turning back to that Dixon reference which you've referenced earlier, was aflibercept being used in a Phase II AMD trial prior to 2011?

A. The Dixon article from 2009 describes both -- describes a Phase II study, the CLEAR-IT 2 study, of 2 milligrams for 12 weeks of the -- of aflibercept being used followed by a prn treatment regimen after the loading dose phase of the study.

And it also describes a Phase III study for wet macular degeneration using the 2-milligram dose administered either every four weeks or every eight weeks and compared to

ranibizumab.

Q. And these are selections from DTX 0204?

A. That's correct.

Q. And flipping to the next slide, Slide 33, can you tell the Court how else aflibercept was being used prior to 2011?

A. This is a Regeneron press release dated September 14th, 2009. And it describes a Phase III study in retinal vein occlusion. That's another angiogenic eye disorder treated -- VEGF-driven and treated with these same agents. And this describes a protocol with six monthly doses and then prn dosing thereafter.

And it also describes a Phase II study in diabetic macular edema with a monthly arm, also an arm where there were three monthly loading doses and then every-eight-week injections and another arm where there were three monthly doses and prn injections going forward.

Q. And those selections are from DTX 3198?

A. That's correct.

Q. Can you tell the Court how aflibercept was being used in the treatment of DME prior to 2011?

A. This is a manuscript from Do in 2009. And it describes a small study of a single injection of 4 milligrams of aflibercept in a small number of patients, and it describes a visual acuity benefit from that single injection.

Q. And that visual acuity benefit, again, that was nine letters at one month?

A. That's correct, which is an impressive benefit.

Q. And are those Dixon disclosures and the Do disclosures referenced here on the timeline at Slide 35?

A. Yes.

Q. So now we've reviewed what was being done in clinical trials up to now. Let's shift focus and discuss what physicians were doing in actual clinical practice before 2011.

So on this next slide, Slide 36, can you explain what's shown here?

A. These are excerpts from a roundtable discussion that was published in a professional journal called Retinal Physician in 2007. And I think this is a great way to get a snapshot of what the POSA was thinking at that time.

These are three prominent retina specialists in the United States, and they're describing their treatment protocols. The first one there is Dr. Rosenfeld from Miami. He was the lead investigator and designer of the PrONTO study. And he describes his treatment regimen trying to minimize the number of injections but treat the patients until there's no fluid in the retina. And once they're dry, then having the ability to skip those injections.

Dr. Reichel from Boston also says that he's a big believer in prn dosing. He gives only one injection on a

routine basis, sees the patient four weeks later, and already makes a decision whether or not to re-treat. So this would be a regimen that would be essentially one loading dose, or just a single primary dose, followed by immediate prn protocol injections.

And Dr. Hariprasad from Chicago also gives his opinion that he doesn't necessarily give three full loading doses, but he gives monthly injections until the patient's retina is dry and then presumably stops injecting until there's reaccumulation of fluid.

THE COURT: Counsel, if I could interrupt.

Doctor, when you reference dry, you're referring to the elimination of any leakage or bleeding from the VEGF-spurred blood vessels and the rest; is that correct?

THE WITNESS: Yes. I'm so sorry that I didn't explain that.

So we often use that as a colloquial term for seeing that there's been resolution of fluid. And you're right on point there with what that means. That's right.

THE COURT: When you say fluid, would there be any other fluids that are offshoots of these various diseases of the eye other than blood?

THE WITNESS: So most of the fluid is clear. It doesn't have red blood cells in it. It's a serous fluid that's in there that extrapolates from the vessels. But the red blood

cells are usually contained within the vessels. You can have blood also. So it can be either blood, but the majority of the time it's actually not full blood.

THE COURT: But it's fluid that's coming from the blood vessels?

THE WITNESS: That's exactly right.

THE COURT: Understood. Thank you.

Sorry, Counsel. Go right ahead.

THE WITNESS: Sorry I didn't explain that better.

THE COURT: Oh, no. That's good.

Go ahead, Counsel.

BY MR. McLAUGHLIN:

Q. The excerpts that you've been referring to, those are coming from DTX 2035?

A. That's correct.

Q. Turning to the next slide, Slide 37, can you describe what's shown here?

A. This is a quote from the same roundtable discussion. This is Dr. Brown from Houston, Texas, another prominent retina specialist. And he says that he uses treat and extend from the start. I'd just like to point out to everybody that this is back in 2007 that he's describing this treatment strategy.

The treat-and-extend strategy is another strategy that came into vogue slightly after the prn strategy, but the concept here was to not only reduce the number of injections

but to reduce the number of visits that patients needed to come back. And so that if a patient established themselves as someone who was -- who could maintain the retina free of fluid for a longer period of time, then the physicians became comfortable with having those patients come in at longer periods to minimize the burden of visits over time.

And so this is just a nice historical document showing that already in 2007 this type of treatment strategy was indeed being employed.

Q. Is that something that you employed in your own practice prior to 2011?

A. Yes.

Q. Was Dr. Brown's description of treat and extend consistent with the general understanding of the treat-and-extend regimen in that time frame?

A. Yes.

Q. And turning to the next slide, Slide 38, can you describe what you've shown here?

A. This is a survey result from a survey that's performed by the American Society of Retina Specialists every year. And it basically serves as a way to communicate amongst the profession what the treatment modalities are, treatment trends are within the community of retina specialists.

So this -- for example, this question is asking physicians to identify what their treatment strategy is for

exudative macular degeneration or wet macular degeneration. And in 2010, out of 337 respondents to this survey, 43 percent said they were using a prn strategy and 34 percent were already using a treat-and-extend strategy.

Q. Turning to the next -- sorry. Flipping back just to confirm, you're referring to DTX 2040?

A. Yes.

Q. Flipping to the next slide, Slide 39, can you explain what's shown here?

A. This is an article showing a study result for intravitreal bevacizumab -- that's Avastin -- for myopic choroidal neovascularization, a short-term and one-year result. And the interesting thing to me was that this is already making reference to the treat-and-extend approach, just to document that this was already something that was seen as a treatment strategy that was well known within the field in 2009 by the time this was published.

Q. And this is from DTX 4113?

A. That is correct.

Q. So are all these references that you've been discussing over the last several slides represented here on Slide 40 of your presentation?

A. Yes.

Q. So let's just wrap this up and summarize what we've gone through and what we've now shown on this timeline.

So in terms of drugs that were available, would that have included ranibizumab, bevacizumab, and then aflibercept being in clinical trials prior to 2011?

A. Yes.

Q. And what types of dosing regimens had been reported with respect to those agents?

A. There were fixed regimens such as monthly fixed or a number of loading doses, and then every eight -- then every-eight-week injection on a regular basis; a number of loading doses, and then every-12-week injections given on a fixed basis. There were also individualized regimens such as the PrONTO study that sought to evaluate patients and make decisions about whether or not to reinject on a patient basis.

And those included the treat-and-extend protocol that we've discussed, the loading doses and then prn regimens that we've discussed, and continuous injection until the macula is dry as Dr. Hariprasad evidenced in his quote. And this was across the indications of exudative or wet macular degeneration, diabetic macular edema, diabetic retinopathy, and retinal vein occlusion.

Q. Dr. Albini, do you intend to provide testimony today regarding the invalidity of the '601 and '572 patent claims?

A. Yes, I do.

Q. Would that include Claims 11 and 19 of the '601 patent and Claim 25 of the '572 patent?

A. That's correct.

Q. Is it okay if, going forward, I refer to those as the DME-DR treatment claims?

A. Yes.

Q. So can you briefly describe for the Court the anticipation opinions that you're going to be giving in this portion of your testimony?

A. Every limitation within the claims that we're discussing is either explicitly or inherently available within two single references: the September 14th, 2009, press release from Regeneron and also in the U.S. patent '747 that we've discussed that was filed back in 1999.

Q. Let's start -- we're on Slide 46 now. Let's start with a discussion of these claims.

So you've reviewed the '601 and '572 patents, correct?

A. Yes.

Q. Have you reviewed Claim 11 of the '601 patent?

A. I have.

Q. Is that what's shown here on Slide 46?

A. That's correct.

Q. And do you understand that Claim 11 of the '601 patent depends from independent Claim 10 of the '601 patent?

A. Yes.

Q. Can you describe in your own words for the Court the

dosing regimens set forth in Claims 10 and 11 of the '601 patent?

A. Yeah. In these two claims taken together, they describe a dosing strategy using 2 milligrams of aflibercept for treating diabetic macular edema given as five initial monthly loading doses or five initial monthly injections followed with subsequent eight-week injections.

Q. And looking at the language of Claim 11, when it says every 28 days, for example, would you understand that the disclosure of something occurring exactly every 28 days as the type of regimen that would fall within the scope of this claim?

A. Exactly every 28 days would certainly fall within the scope of approximately every 28 days, that's correct.

Q. Turning to the next slide, Slide 48, did you also review Claim 19 of the '601 patent?

A. Yes, I did.

Q. You also reviewed the claim from which it depends, Claim 18?

A. Yes.

Q. Can you describe in your own words for the Court the dosing regimen set forth in Claims 18 and 19 of the '601 patent?

A. This is the same dosing regimen set forth in the 10 and 11 claims. And in these claims the disease state is different. This is being used for the larger disease entity

called diabetic retinopathy, including other types of diabetic disorders of the retina in addition to macular edema.

And here it describes again the administration of 2 milligrams of aflibercept with five initial loading doses followed by q8-week regular dosing.

Q. Can you briefly describe the relationship between DME and DR?

And by the way, is it okay if I refer to diabetic macular edema as DME and diabetic retinopathy as DR going forward?

A. That's fine with me. I hope it's fine with everybody else.

THE COURT: I think I've got those acronyms down by now, Doctor. So if it works for you, it works for me.

THE WITNESS: Fantastic.

So I think that DME is technically a type of diabetic retinopathy. It is a diabetic eye disease of the retina. It is a specific subtype of diabetic retinopathy. It is the most common cause of mild to moderate loss in diabetic patients, very commonly seen. And it is usually described as a complication of diabetic retinopathy or a subtype of diabetic retinopathy.

BY MR. McLAUGHLIN:

Q. Flipping to Slide 49, have you reviewed Claim 25 of the '572 patent?

A. Yes, I have.

Q. And you've reviewed the claim from which it depends, Claim 15?

A. Yes, I have.

Q. Can you briefly describe the -- how you understand the subject matter of Claims 15 and 25 of the '572 patent?

A. These two claims describe an identical treatment strategy for diabetic macular edema, again administering 2 milligrams of aflibercept with at least five initial monthly injections and subsequent eight-week injections.

Q. In your opinion, are there any substantive differences between Claim 25 of the '572 patent and Claim 11 of the '601 patent?

A. No.

Q. If we could turn to Slide 50. So turning to the references that you referred to earlier, I believe what you've shown on the left here is the 9-14-2009 press release. Is that the reference that you relied upon?

A. That's correct.

Q. And shown on the right is the '747 patent. That's patent number 7,303,747, DTX 2730. Is that one of the other references you relied upon in your anticipation --

A. That's correct.

Q. And turning to the next slide, can you explain what you have highlighted here on Slide 51?

A. This is a text from the Regeneron press release describing a Phase II DME VEGF Trap-Eye, or aflibercept, study using the 2-milligram dose. There were three dosing arms or dosing strategies described in this press release for DME. One was a monthly dosing arm or a three monthly injections followed by prn dosing thereafter. And there was a third strategy described of three monthly injections and then every-eight-week dosing thereafter.

Q. When looking at the 2-milligram dose of VEGF Trap-Eye reported here, would a POSA have understood that to refer to an intravitreal dose of aflibercept?

A. Yes. VEGF Trap-Eye, as far as I know, was only available for intravitreal use in clinical trials at the time.

Q. And just another housekeeping matter. We've used the acronym POSA a couple times. Just so the record is clear --

A. A POSA is a person of ordinary skill in the art, of which I believe I am one and was one.

Q. Thank you.

Turning to the next slide, you mentioned a prn dosing scenario mentioned in this 2009 press release. Can you explain how a POSA would have understood a prn dosing scenario in that time frame?

A. So I think that the dosing regimen that's described stipulates that the patient receive three monthly injections at the beginning of treatment. And then thereafter decisions are

made whether or not to inject based on clinical measures and imaging findings for that patient.

One can immediately envision that a patient might require three initial loading doses and might require that a fourth injection when they come in for that visit and then have a subsequent visit where there's no injection required, resulting in an eight-week interval.

Q. And in typical prn dosing scenarios used in that time frame, monthly visits were the norm?

A. That's correct.

Q. You mentioned immediately envisioning a dosing scenario. So is that something you've illustrated here on Slide 53 of your presentation?

A. Yeah. I think this graphic helps greatly to understand the point here. But what's seen there is the syringes represent injections for the patient, those monthly visits. And the first three are with blue needles, and those represent the monthly loading doses that would be described in that treatment strategy.

At Week 12 and Week 16 you see green needles representing doses that are given during the prn portion of the study. At Week 20, presumably, the patient meets criteria by lack of fluid in the retina, does not require that injection, and then comes back at Week 24 and, again, does require an injection.

So in the end what you have is five regular monthly injections with an eight-week gap and then the sixth injection.

Q. Turning to Slide 54, can you explain how that scenario relates to Claim 11 of the '601 patent?

A. This treatment strategy, this particular iteration of the prn dosing schedule, is identical to the treatment strategy that's laid out in Claims 10 and 11 and 18 and 19. In every real sense the same number of injections are given at the same time periods and are the same treatment.

Q. So the three monthly loading doses given at Weeks 0, 4, and 8 followed by the two prn treatments at Weeks 12 and 16, those would be injections given every four weeks for the first five injections?

A. That's correct.

Q. And then the injection given at Week 24, after having skipped an injection at Week 20, that would be an injection given once every eight weeks?

A. That's correct. I think the POSA would immediately envision this type of a treatment protocol when a treatment strategy of three monthly loading doses and prn dosing subsequently are entertained.

Q. Would that same analysis apply to Claim 19?

A. That's correct.

Q. Turning to Slide 55, would that same analysis also apply to Claim 25 of the '572 patent?

A. That's correct.

Q. Now, the claim language is a little bit different here; so let's just walk through the claim language real quick.

The dose given at time zero, that would be the single initial dose of 2 milligrams of aflibercept?

A. That's correct.

Q. And then the next two loading doses given under that prn scenario followed by the two prn doses at Weeks 12 and 16, those would be the four secondary doses required by Claim 25?

A. That's correct.

Q. And then the injection given at Week 24, that would be the one or more tertiary doses?

A. That's correct.

Q. So turning to Slide 56, can you explain to the Court what you have shown here with respect to the '747 patent.

A. This is the older patent which we were relying upon as a source for anticipation for the DME-DR claims. And it describes improved pharmacokinetics with the use of the aflibercept or VEGF Trap-Eye molecule for age-related macular degeneration and mentions diabetic retinopathy as well.

Q. If we turn to the next slide, Slide 57, you have highlighted here a selection from the '747 patent highlighting that molecule name.

Why do you have that molecule name highlighted from the '747 patent?

A. Yeah, just showing that there's a clear line that can describe to the POSA the exact molecule that's being discussed and that there is no ambiguity in the '601 and '572 specification that this is aflibercept.

Q. Turning to the next slide, Slide 58, what have you highlighted here from the '747 patent?

A. The dosing range of aflibercept that's being taught in the '747 patent is a dosing range of 25 to 4,000 micrograms, and I just wanted to make the point that the 2-milligram dose of aflibercept, which we've been mentioning over and over again, falls within that range. That's 2,000 micrograms. So it's within the range of what's described in the '747 patent.

Q. Does the '747 patent at this selection here at DTX 2730, page 16, also reference an intravitreal injection of the VEGF inhibitor?

A. That's correct.

Q. Turning now to Slide 59, looking again at the DTX 2730, '747 patent, does the '747 patent here describe a dosing regimen for the treatment of angiogenic eye disorders?

A. Yes. As we've mentioned previously, it describes an initial injection given and then relates it in a preferred embodiment and initial treatment is followed by subsequent treatments given within one- to six-month intervals.

Q. Following such a treatment strategy as described in the '747 patent with monthly examinations, would a POSA reading

the '747 patent in 2010 immediately envision a scenario in which a patient received four more monthly injections?

A. I believe that's true. In a very analogous fashion to the discussion we just had, one of the iterations that one immediately would envision is five initial doses given four weeks apart and then a subsequent dose given eight weeks apart.

Q. And then could a POSA reading the '747 patent in 2010 immediately envisage a scenario in which, following a series of monthly loading doses, the patient were assessed at the next monthly visit and a decision was made to not give an injection, for example, at Week 20?

A. The specifications for the '747 patent do describe in some detail the need for continuous monitoring of patients, including for retinal fluid, which is exactly what we do. And so I think that, having read that patent, that would be very easily envisioned, this type of a treatment protocol.

Q. Following the decision to withhold treatment at Week 20, would a POSA, reading the '747 patent in 2010, immediately envisage a scenario where, on the next visit at Week 24, fluid had recurred and the patient required an injection at that visit?

A. Yes.

Q. So turning to Claim 61, is that scenario that you described accurately portrayed here on Slide 61?

A. That's correct.

Q. Can you describe how that relates to Claim 11 of the '601 patent?

A. Yeah. Again, there is a single primary injection that's given at Week 0; and then at Weeks 4, 8, and 12 and 16, a decision is made to reinject. At Week 20 there's no injection required, and at Week 24 there is an injection that's given eight weeks after the prior injection.

Q. So those injections at Weeks 0, 8, 12, and 16 would be injections given every four weeks for the first five injections?

A. That's right.

Q. And then the injection given at Week 24, that would be an injection given once every eight weeks?

A. That's correct.

Q. Would the analysis be the same for Claim 19 of the '601 patent?

A. That's correct.

Q. Turning to Slide 62, can you explain the -- or summarize for the Court the opinions you're going to be giving in this section of your testimony?

A. Yeah. I believe that, largely based on the same sources in combination with some other sources which we'll go through, that these -- all of these same claims that we've been discussing are rendered obvious given what was known at the date -- in the date.

Q. Turning to Claim 63 -- or Slide 63, did you analyze Claim 12 of the '601 patent in the process of formulating your opinions in this case?

A. Yes. Claim 12 is dependent on Claim 10, and it describes that after 20 weeks there's an administration of aflibercept every four weeks, suggesting a change in the dosing frequency at some points of every-four-week dosing at some point after 20 weeks.

Q. Would your interpretation be the same for Claim 21 as it relates to Claims 18 and 19 of the '601 patent?

A. That's true. Under this claim this particular version of the dosing schedule would be similar to monthly dosing and would be very similar to the monthly dosing regimens which we talked about were the first dosing regimens for ranibizumab that were used back in 2006.

Q. In this case did Dr. Csaky provide his interpretation of Claim 12 of the '601 patent?

A. Yes, he did. While I think there a number of interpretations that could be made of those two claim combinations, he describes a scenario where the initial five loading doses are given, as you see here, at Weeks 0, 4, 8, 12, and 16. And then there's an eight-week loading dose -- there is an eight-week injection given at Week 24, and at that point the injection frequency is reverted back to a four-week dosing schedule, as described here in this graph.

Q. Did you understand Claim 12 to depend from Claim 10?
A. That's correct.
Q. Is it your understanding that, because Claim 12 depends from Claim 10, that Claim 10 also includes within its scope the dosing scenario of Claim 12?
A. That's correct.
Q. Turning to Slide 67, was the monthly dosing of aflibercept for the treatment of DME disclosed in the prior art?
A. Yes.
Q. Where would that disclosure have come from?
A. This was in the Regeneron press release that we've been describing from September 14, 2009. Describes a Phase II clinical trial that included an arm with monthly dosing, as we've mentioned before. And the claimed subject matter of the combination of claims that we just discussed, including Claim 12, are virtually identical to monthly loading doses, certainly easily envisioned having a protocol with monthly loading doses that one might miss a month at one point.
Q. This is an excerpt from DTX 3198?
A. That is correct.
Q. Would your analysis be the same with respect to the '747 patent and the dosing regimen described therein?
A. That's correct. The dosing regimen described in the '747 patent is somewhat broader, encompassing more treatment

regimen possibilities. But it also describes an initial dose with subsequent treatments given between one and six months apart and so that these treatment strategies would fall within the scope of these teachings as well.

Q. And these disclosures are from DTX 2730?

A. That is correct.

Q. So can you provide to the Court your overall opinions on obviousness of Claims 11 and 19 of the '601 patent?

A. I would say that, due to the great similarity between the virtually monthly treatment that's described once Claim 12 is incorporated in that Claim 10 and 11 and Claim 20 is incorporated in the Claim 8 and 19 of the '601 patent, that this dosing strategy is virtually indistinguishable from monthly administration of aflibercept, which is well described prior to 2011.

Q. Just to clarify the record, I think you said Claim 20 of the '601 patent. Would you be referring to -- I'll flip back. Were you referring to Claim 21?

A. I was. I'm so sorry. Claim 21.

Q. No problem.

A. Thanks for catching that.

Q. Then can you -- now we're on Slide 70, and can you describe what you've shown here on Slide 70 of your presentation?

A. I picked a reference to speak to the reasonable

expectation of success that was available, knowing the clinical data from aflibercept in that period prior to 2011.

This is a report of a Phase I study from 2009 by Diana Do that shows the outcomes from a single injection of 4 milligrams of aflibercept with, as I think we mentioned already, a very remarkable result of eight- or nine-letter gains from just a single injection.

So I think that, given this, the POSA would see a reasonable expectation of success moving forward with dosing regimens that involve more injections.

Q. And this is coming from DTX 3102?

A. That's correct.

Q. Now that the Do reference -- Do 2009, that disclosed just a single vitreal injection of aflibercept?

A. That's correct.

Q. After obtaining that data, would a POSA have been motivated to seek extended long-term dosing regimens for aflibercept in the treatment of DME?

A. Absolutely.

Q. And it's your opinion that, based on these results, after a single intravitreal injection of aflibercept, multiple repeated injections of aflibercept would have -- a person of ordinary skill in the art would have had a reasonable expectation of success using such a regimen?

A. Absolutely. I think Regeneron had a reasonable

expectation of success and went forward with this clinical project.

Q. Turning to the next slide, Slide 71, can you explain the data that's shown here.

A. This is from the review article on Lalwani, which we've looked at already, from 2009. And this describes a ten-patient study, the READ 1 study, for diabetic macular edema with injections given at -- three loading injections given at zero, one, and two months and then two-month injection intervals with injections given at month four and month six. And this article also described good visual acuity outcomes amongst these patients.

So, again, given this data in ranibizumab, which is a molecule with an identical mechanism or very similar mechanism of action as aflibercept, one would have a reasonable expectation of success for the injection strategies that are being described in the patents at issue.

Q. Turning to the next slide, Slide 72, are these the visual acuity gains you had referenced regarding Do 2009? I'm sorry. Lalwani 2009.

A. Yes. Patients gained an average of eight letters in the READ 2 study.

Q. This is from DTX 2733?

A. That's correct.

Q. So, overall, what would the disclosures of Do 2009

and Lalwani 2009 tell a POSA about the reasonable expectation of success of using the regimens described in both the press release and the '747 patent?

A. I think that, overall, the POSA would have thought that there would be a reasonable expectation of success in using aflibercept in the described dosing strategies, given its efficacy as described in these studies, the safety that was seen in the preliminary study by Do, and again in the efficacy and safety that was seen in the similar compound, the ranibizumab, in the READ 2 study.

Q. If we turn to the next couple slides here, so prior to this, you've told the Court about your anticipation --

A. That's correct.

Q. -- regarding the press release and the '747 patent?

A. Yes.

Q. Do you rely on these same references to show obviousness of the DME treatment claims of the '601 patent?

A. Yes.

Q. So turning to the next slide, Slide 75, is this an accurate summary of some of those immediately envisaged scenarios that we described with respect to the press release and the '747 patent that you discussed in your anticipation section?

A. That's correct. I think that given the prior teachings, one would immediately envision this type of dosing

strategy as described in the patents.

Q. Turning to the next slide, can you tell what was known about VEGF level or what was hypothesized about VEGF levels in DME patients in the 2009 time frame as shown here on Slide 76?

A. Sure. The Lalwani review article references a concept that there are higher VEGF concentrations in patients with DME relative to wet macular degeneration, and she talks about strategies that were being clinically investigated at the time to use higher doses of drug in DME relative to macular degeneration. And I think that the POSA would have immediately thought that, if higher doses were not available, it may be more practical to administer more doses of the drug to try to obtain optimal efficacy.

Q. Turning to Slide 7, can you explain to the Court what you've shown here?

A. I wanted to put together side-by-side DME data, as was described in Lalwani, with injections of aflibercept given over a year.

And one sees in this top line data that there is an improvement in visual acuity up to about ten letters at the 12-month mark, but it is a slow and steady rise over that time period, whereas the data that I brought back to remind us of is the MARINA data from Rosenfeld in 2006 in wet macular degeneration treated with monthly ranibizumab, showing that

there is an initial rise with ranibizumab and then it plateaus and is maintained, so again evidencing that the diabetic macular edema visual acuity gains are more difficult to obtain and require more injections until you get there than what's seen in wet macular degeneration.

Q. What did you conclude with respect to loading doses after reviewing this data?

A. I think the POSA would have concluded that more loading doses for DME relative to treatment strategies that are employed in AMD make a lot of sense given that it takes more injections to get a better visual acuity in these patients.

Q. Can you summarize briefly your reasonable expectation of success opinions that you're going to be talking about over the next few slides?

THE COURT: Doctor, if I could interrupt.

We're going to change topics, Counsel?

MR. McLAUGHLIN: We will in a few minutes. Or now. It's up to you, either way.

THE COURT: Why don't we go ahead and take a break at this point. We'll take ten minutes. We'll take our morning break.

Sorry to interrupt, Doctor. Apologies.

As you may have heard over the last few days, no one can talk to you during our breaks, and no one's being rude or discourteous when they flee. But you're a man without a

country since you're midstream in your testimony at this point. But you can go ahead and step down if you'd like.

THE WITNESS: Great. Thank you.

THE COURT: We'll take ten minutes, and then we'll resume, and then we're going to take up the question of Dr. Rabinow's opinions. Then we can resume with the good doctor's testimony. See everyone in ten minutes.

(A recess was taken from 11:03 a.m. to 11:18 a.m.)

THE COURT: Now, Counsel, before we -- what are you doing there?

MR. BERL: I thought you wanted to address the Rabinow issue. If you don't want to do that --

THE COURT: I'm going to address. I've read all the parties' briefs. I'm going to grant Regeneron's motion. Mylan will be precluded from offering testimony or opinion related to obviousness with respect to the combination of Fraser, Dix, Lucentis, which includes Shams and Gaudreault and Liu, as prior art. The Court is specifically finding, after reviewing the reports and all briefing, that opinion was not disclosed as required under this Court's scheduling order.

The separate and independent basis for granting that motion is that, as required under Federal Circuit precedent, that not only the combination but also the explanation as to why the combination of that prior art would support an opinion

or finding of obvious was likewise not disclosed.

Let me be clear, though. That is the only relief the Court grants with respect to Regeneron's motion, which is Docket Entry 529. The other opinions previously disclosed remain undisturbed, but that opinion, the Court finds, was not timely disclosed and will not be received here at trial.

We will take up the Chu deposition issue at our next break.

Anything else we need to take up at this point before we resume the doctor's testimony?

MR. BERL: Not from Regeneron, Your Honor.

THE COURT: From Mylan?

MR. HUNT: No, Your Honor. Thank you.

THE COURT: I would note the Court will -- recognizing it is a significant issue although a discretionary decision of this Court, there will be a separate order more eloquently stating the Court's reasons for granting Regeneron's motion, again Docket Entry 529.

With that said, Counsel, you can resume your direct examination.

MR. McLAUGHLIN: Thank you, Your Honor.

BY MR. McLAUGHLIN:

Q. Welcome back, Dr. Albini. We were at Slide 78 of your presentation here, and we're about to launch into discussing reasonable expectations of success with respect to

this obviousness ground.

Can you just give a brief summary of the data and the documents that we're about to walk through over the next few slides?

A. Yeah. These are documents dating from 2006 to 2009 that I think demonstrate the known efficacy at the time of both ranibizumab and aflibercept in treating DME and AMD, which would have given a POSA reasonable expectation of success.

Q. Let's go ahead and take a look at some of these articles. We've seen this one before, Do 2009. It's slide 79, DTX 3102.

Can you explain what you've presented here on Slide 79.

A. Yeah. Again, this is the Phase I study report authored by Dr. Do that describes a small study with a single injection of 4 milligrams of aflibercept, resulting in a significant visual acuity gains of eight letters.

Q. Turning to the next slide, Slide 80, can you describe what kind of data was presented in Dixon that would have given a POSA a reasonable expectation of success?

A. In Dixon there is disclosed published results from aflibercept AMD Phase II data showing visual acuity gains from -- in macular degeneration. And I think that, although these are two different diseases, they are both mediated by vascular endothelial growth factor, which is the target of both

of these therapies, and I do think that the success that was seen in macular degeneration was relevant to the reasonable expectation of success in DME regimens as well.

Q. Turning to Slide 81, you've had the opportunity to review internal Regeneron documents --

A. I have.

Q. -- in the process of formulating your opinions?

A. I have.

Q. And is DTX 8190, shown here on Slide 81, one of those documents?

A. That's correct.

Q. And on this document did Regeneron state that "We believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III and DME can be selected based on results of the Phase II study in patients with AMD"?

A. Yes. And I think that evidence is that the POSA as well would have used results from one disease state to infer reasonable expectations in the other disease state.

Q. And this document also states that "We consider this Phase II data as providing an adequate basis for dose selection for the Phase III DME program"?

A. That's exactly right.

Q. Turning to the next slide, Slide 82, can you describe what's set forth here on this slide in terms of the data from ranibizumab?

A. These are the results for the MARINA prospective randomized trial that was published in the *New England Journal of Medicine* with Rosenfeld as the lead author in 2006, and this was really game-changing data within our field, showing great visual acuity improvements with monthly doses of ranibizumab for wet macular degeneration. Again, a different disease but I think relevant across disease states, as evidenced by the Regeneron communication as well.

Q. And just to confirm, when you're referring to Regeneron, you're not suggesting that Regeneron -- that your reasonable expectation of success is coming from Regeneron's statements. Those are just confirmatory in nature for a POSA?

A. Yeah. My point is simply that it's reasonable to include the ranibizumab data when you're trying to make an opinion about the expectation of success of aflibercept. That's all.

Q. If we turn to Slide 83, can you also explain what's shown here and how that's relevant to reasonable expectation?

A. Again, this was a Phase I study, the READ 1 study, describing three monthly loading doses of ranibizumab followed by eight-week injection intervals, showing good visual acuity outcomes in diabetic macular edema.

Q. If we turn to Slide 84, going back now, is this an accurate summary of the data that you just walked through?

A. That's correct. So that there's -- what really,

historically, were impressive visual acuity benefits compared to what was available for patients prior to the advent of these anti-VEGF therapies, that there was good success with either ranibizumab or aflibercept in either AMD or DME already available to the POSA.

Q. And did you have the opportunity to review Dr. Csaky's rebuttal opinions in this case?

A. Yes.

Q. Is that one -- is this, shown here on Slide 85, one of those rebuttal opinions?

A. That's correct.

Q. And here, do you agree with Dr. Csaky that concerns about overtreatment would have dissuaded a POSA from using five monthly loading doses in the treatment of DME?

A. I don't agree. I think that there were studies already available with ranibizumab with another anti-VEGF agent that showed that larger number of doses in diabetics were well tolerated. There was safety data already available from Phase I study with aflibercept showing adequate safety, and I certainly think that it was a concern, but I think that the addition of one or two more loading doses compared to other treatment regimens would not have dissuaded somebody from trying the regimens that are detailed in these patents.

Q. And do you agree with Dr. Csaky that use of intravitreal injections and potential side effects, like

elevated intraocular pressure, would have dissuaded a person of ordinary skill in the art from using five monthly loading doses in the treatment of DME?

A. I think that Dr. Csaky's comments in this regard were focused on the use of intravitreal steroids, which have a class effect of raising intraocular pressure. And I think they have limited relevance to anticipated complications for anti-VEGF agents, especially by the time that you get to 2010 and '11 when there's been such great experience in multiple trials conducted in thousands of patients with these agents without seeing this type of pressure elevation that's seen with intravitreal steroid use.

Q. And do you agree with Dr. Csaky's opinions that concerns about systemic side effects would have dissuaded a person of ordinary skill in the art from using five monthly loading doses to treat DME?

A. I think that, although there was always concern for systemic side effects, the addition of one or two loading doses would not significantly dissuade the POSA from increasing the number of injections by one or two, especially with the perceptions that we've talked about, the increased efficacy of doing that and the anticipated necessity for more injections that are seen in DME. So overall no, I don't think that this would have dissuaded the POSA from using more injections. And historically that's what happened.

Q. Was it also the case that at that time there were trials, including trials run with aflibercept by Regeneron, that were including monthly dosing regimens that involved monthly dosing out to one year and more?

A. That's true.

Q. Now, let's talk about some of that data that you talked about regarding the safety and -- the safety of aflibercept and what was known in the prior art.

Can you explain what you've shown here on Slide 88.

A. This is the article by Do from 2009 showing an early phase study with 4 milligrams of aflibercept. We've seen this before. And it evidences that there were no serious adverse effects in this small study. And they had a reasonable expectation of safety that allowed them to move on to a Phase II study following this.

Q. Based on that, would a POSA have a reasonable expectation of success?

A. I believe they would go through the same thought process and would reasonably have a good -- a reasonable expectation of success, yes.

Q. Turning to the next slide, can you -- this is Slide 89. Can you tell the Court what Dixon disclosed about the safety of aflibercept?

A. Again, in this Phase II study of VEGF Trap-Eye and CLEAR-IT, it remarks that the therapy seems to be well

tolerated, with no serious drug-related adverse events.

Q. And do you agree with Dr. Csaky that a person of ordinary skill in the art would have felt constrained to just three to four monthly loading doses when designing a DME treatment regimen?

A. I don't see anything in the science or in the prior art that would limit the comfort with only three or four but not five loading doses.

Q. So is it true, Dr. Albini, that there would have been a range of monthly loading doses that a POSA would have envisioned for use in treating a patient with diabetic macular edema?

A. I think that this slide nicely encompasses that range. It demonstrates it. There were available, as we've seen, the CLEAR-IT 2 data in AMD with four monthly loading doses, the DA VINCI study in DME with three monthly loading doses with prn dosing following three monthly loading doses.

And in a retinal vein occlusion study that is described in the prior art, even six monthly loading doses followed by prn treatment were all already in the literature and tried. And so I think that anywhere in this range would have been obvious to the POSA in that time period.

Q. And, again, you've had the opportunity to review Regeneron internal documents in this case?

A. Yes, I have.

Q. Is this one of those documents, DTX 4129?

A. Yes, it is. And it shows that Regeneron internally claimed that a target scenario for their novel therapy would be no more than three to six doses, including monthly loading doses for the first three months and described an induction period in the first six months; so saying that they were working -- or demonstrating that they were working within the same dosing range.

Q. Thank you.

And now we're going to move on to another obviousness ground. This is on Slide 93 going to Slide 94.

Before we dive into this ground, I just wanted to make clear. You understand -- or you were led to understand and asked to assume for purposes of this ground only that a priority date of July 12th, 2013, applies to the asserted claims?

A. That's my understanding, yes.

Q. So turning to Slide 95 and looking at the Do 2012 reference here, DTX 3105, can you explain what's shown here on this slide?

A. Sure.

Do describes a study in treating diabetic macular edema with VEGF Trap-Eye or aflibercept, meaning that highlighted part of the Claim 10.

Q. What else did Do 2012 disclose?

A. It disclosed an intravitreal injection of the 2-milligram dose.

Q. And turning to the next slide, can you explain what's shown in this graphic here, Slide 97 from DTX 3105?

A. These are the treatment arms for the study disclosing that in the 2-milligram arms there is an arm with regular -- four weekly injections, an arm with three loading doses and then injections given every eight weeks. And there is an arm with prn dosing described where there are three loading doses given by necessity. And then subsequent to that, there are visits at which there may or may not be doses on any particular visit.

In that arm that would include the possibility of five loading doses with a q8-week interval subsequent to that, as we've described a couple times already in this testimony.

Q. If we were to turn to the next slide, does this slide show the results from that Phase II study?

A. Yes. This shows the mean number of injections was 7.4, greatly less than the number of injections that were seen in the Q four months. So this describes a protocol where fewer injections were required.

Q. And the 7.4 injection number you're referring to, that was from the prn --

A. That's correct.

Q. -- group?

A. That's correct.

Q. This also discloses that in the 2q8 group they required a mean of 7.2 injections over the first year?

A. That's correct.

Q. Did you have a sense for how that compares to the number of injections that patients received in a prn regimen in the AMD clinical trials?

A. Yeah. Dixon teaches that in the AMD VEGF Trap-Eye there was a mean number of 5.6 injections in prn dosing of VEGF Trap-Eye. And for DME it was 7.4, which was in line with the anticipation, as we discussed before, that in DME more intravitreal injections were going to be needed to achieve optimal treatment of patients than there are in AMD.

Q. What conclusion would a POSA draw from that data?

A. One of the conclusions would be that a greater number of loading doses would certainly be likely to be beneficial in developing a treatment strategy for DME.

Q. If we take a look at the data from that Phase II trial displayed here, the visual acuity data, can you explain or walk the Court through what's shown here?

A. So one can see the outcomes of the four arms with aflibercept showing an improvement in visual acuity that is maintained then through the life of this 52-week study. And in the laser control arm there is ultimately a decrease of vision starting at about 28 weeks going on.

Q. This is on Slide 101, and this data is from DTX 3105?

A. That is correct.

Q. If we flip forward to Slide 102, can you tell the Court what you've shown here on Slide 102.

A. Highlighted in green is the visual acuity outcomes line from the 2q8 arm. This is 2 milligrams given with three monthly loading doses and then given q8 weeks thereafter. And one can see that, in between the injections given at Week 12 and Week 20, at Week 16 there is a drop in visual acuity, suggesting that the addition of a subsequent dose given at that week would improve the visual acuity.

I think this data could have been interpreted and would have been interpreted by the POSA, especially in combination with the other points that we've made, that an additional loading dose would be a very effective thing to try in treatment strategies for diabetic macular edema.

Q. And is that additional loading dose shown here in green?

A. That's correct.

And that would essentially be consistent with the therapy of five loading doses followed by q8-week loading, essentially indistinguishable from that treatment strategy.

Q. So can you summarize or provide your overall conclusion with respect to the DME -- Claim 11 of the '601 patent with respect to Do 2012?

A. I think that the Do article gives a reasonable expectation of success and that it would be obvious to the POSA, having read that article, that a more robust dosing strategy would be needed with more loading doses than have been used with AMD, given the data that showed that it is more difficult to achieve optimal visual acuity benefits with fewer injections in DME relative to AMD. So I think the POSA would have seen that and designed a strategy with more loading doses and could have designed a strategy with a q8-week loading arm thereafter as well.

Q. Would that same analysis apply to Claim 19 of the '601 patent as well?

A. That's correct.

Q. Would that same analysis apply to Claim 25 of the '572 patent?

A. That's correct.

Q. We're going to switch gears now and leave the DME-DR treatment claims and move over to Claim 6 of the '572 patent.

Can you briefly explain to the Court the opinions you're going to be offering in this section of your testimony.

A. These opinions are largely based -- as I think we mentioned already early on, on the opinions of Dr. Rabinow, who's a formulation expert, regarding the anticipation and obviousness of the claim regarding isotonic preparation of aflibercept.

Q. Do you understand Slide 108 to summarize Claim 6 and the claims from which it depends?

A. That's correct.

Q. Do you understand that, with its pretrial order submissions, Regeneron provided a compiled version of Claim 6 that incorporated the limitations of the claims from which it depends?

A. Yes.

Q. Is that what you have shown here on Slide 109?

A. That's correct.

Q. Is it okay if we use this version of Claim 6 to conduct your analysis in this section of your presentation?

A. Yes.

Q. Do you also understand that Regeneron has stipulated to the invalidity of certain claims, including Claims 1 through 5 of the '572 patent?

A. Yes.

Q. So is it okay if we mark with highlighting the material -- or the subject matter of Claim 1 and the compiled Claim 6 in yellow highlight as shown here on Slide 111?

A. Yes.

Q. Are you aware also that the Court issued a claim construction, also called a Markman opinion, that held that the visual acuity elements of the claims do not carry any patentable weight?

A. Yes, I am aware.

Q. And you understand that Regeneron also represented to the Court that the visual acuity limitations also did not carry any patentable weight?

A. That's correct.

Q. So in light of that, is it okay if we highlight in blue that visual acuity element of compiled Claim 6?

A. Yes.

Q. So, with that, can you tell the Court what remains of Claim 6?

A. The text highlighted in green here stipulating that aflibercept is formulated as an isotonic solution.

Q. Turning to the next slide, Slide 116. So even though this material has been stipulated, we're still going to walk through very quickly where these dosing regimen elements are found in Dixon.

Can you explain to the Court what you have shown here on Slide 116.

A. This is the Dixon reference that we looked at numerous times in this presentation. And it does describe a Phase III study for treating an angiogenic eye disorder here. And so we can check off the first check mark there.

Q. And that's -- you're looking at the title of DTX 0204?

A. The "VEGF Trap-Eye for the treatment of neovascular

age-related macular degeneration" is an angiogenic eye disorder, yes.

Q. The Phase III regimen called out there on the bottom of the slide from DTX 0204, that also describes method of treating an angiogenic eye disorder?

A. Absolutely.

Q. Can you describe what's shown here on Slide 117 from DTX 0204?

A. A Phase III study using 2 milligrams of aflibercept, or intravitreal VEGF Trap-Eye, for the treatment of wet macular degeneration.

Q. And then does Dixon also disclose a treatment method that involves sequentially administering an initial dose followed by one or more secondary doses of 2 milligrams of aflibercept wherein each of those secondary doses is administered approximately four weeks following the immediately preceding dose?

A. That's right. It does that in the highlighted text there.

Q. And the highlighted text is the text following three monthly doses?

A. That's correct.

Q. If we go to the next slide, does Dixon also disclose treatment in which those secondary doses are followed by one or more tertiary doses of 2 milligrams of aflibercept wherein each

of those tertiary doses are administered approximately eight weeks following the immediately preceding dose?

A. That's correct.

Q. And then, again, you understand the visual acuity limitation to not carry any patentable weight in this claim?

A. That's correct.

Q. So if we turn to the last element, can you read for the Court what the last element of compiled Claim 6 is.

A. Aflibercept is formulated as an isotonic solution.

Q. And with respect to that portion of the claim, did you rely on the opinions of Dr. Barrett Rabinow?

A. Yes, I did.

Q. And are those opinions shown here on Slide 121?

A. That's correct.

Q. And does he cite to a Dixon article?

MS. OBERWETTER: Objection. Your Honor, at this point, because I don't know precisely what Dr. Albini is going to say in response to any particular question, we have an objection to this witness testifying about the reference that is listed here, Dixon, insofar as his testimony would be as to whether it discloses an isotonic solution for two reasons.

First of all, his report itself does not contain an opinion that the POSA would have understood Dixon to make such a disclosure.

And, second, we believe, from a formulation

standpoint, he is not qualified to render such an opinion.

THE COURT: Understood.

Counsel, aren't we going to hear this from Dr. Rabinow?

MR. McLAUGHLIN: You are going for hear all about isotonicity from Dr. Rabinow. Dr. Albini will be talking about his understanding from the viewpoint of an ophthalmologist of how he would read that aspect of Claim 6 in conjunction with --

THE COURT: Has he offered any opinions in his reports on that?

MR. McLAUGHLIN: He has. He's talked about Dixon. He's talked about the language from Dixon. And we can call that up.

THE COURT: I think I'd like to see what he said in his report, his opinions, because references are one thing, but --

MR. McLAUGHLIN: Sure, sure. Permission to approach?

THE COURT: Granted.

Yes, Ms. Oberwetter?

MS. OBERWETTER: I don't know if I'm on or not.

I believe we're going to be looking at that paragraph, or the same version, elsewhere. But there is a longer paragraph. And I believe that is the entirety of the opinions on it. And there is nothing in which he says he is opining on whether Dixon disclosed an isotonic solution from

the standpoint of a POSA. And it is a confusingly worded paragraph, but that particular statement is conspicuously not present. As you read it, I will flag that for you, Your Honor.

THE COURT: Okay.

Counsel?

MR. McLAUGHLIN: Well, it's a confusingly worded claim, but what I will direct you to is Dr. Albini's opinions at paragraph 556 of his opening report. That should be on the first tab of the binder that we've handed Your Honor. That's on page 196 of the document. It's Exhibit page 197, DTX 7069.

You can see that Dr. Albini, he does cite Dixon about two-thirds of the way down that paragraph. Dixon is an article that's directed to retinal physicians and people in the ophthalmological community, directed to people just like Dr. Albini. This is language that he would have reviewed in reviewing such an article, and it's language that he would understand as a person who administers these types of drugs on a regular basis.

MS. OBERWETTER: Your Honor, it's not that the word Dixon isn't in this paragraph; it's that there's no opinion that the POSA would have understood the disclosures in Dixon. That is a conspicuous and notable absence compared to other portions of his report, and it's obvious the reason why, because at the time he wrote the report he was relying on Dr. Rabinow whose testimony you will hear forthcoming. There's

a reason they want Dr. Albini now to be offering that opinion, and it's not in his report.

THE COURT: And what is that reason?

MS. OBERWETTER: That Dr. Rabinow's testimony on that point did not hold up, Your Honor.

THE COURT: I guess ultimately I will be the judge of that, but -- I understand there will be a challenge to that, Ms. Oberwetter. I'll flag that as a preview.

MS. OBERWETTER: Mutual previews, Your Honor.

THE COURT: Great. Great. Thank you.

Yes, counsel?

MR. McLAUGHLIN: I just want to reiterate Dr. Albini, he's somebody that's administered these formulations on a regular basis for the last 15, 20 years.

THE COURT: He concedes in the report -- and, again, I just read paragraph 556 of Dr. Albini's report -- that formulations are not his bailiwick, for lack of a better term.

MR. McLAUGHLIN: They're not his bailiwick, but he's certainly somebody that's qualified to at least talk about the administration of these formulations, how you expect patients to respond to these formulations that are being injected into their eyes. And he's got publications where he talks about -- where he compares isotonicity to osmolarity of different formulations.

THE COURT: Well, I guess my question then, Counsel,

is what is the relevancy to the questions before this Court? Because paragraph 556, again, of Dr. Albini's report concludes that it's his opinion with respect to the VIEW clinical trial, et cetera -- and Ms. Oberwetter is right. There's no reference to what a POSA would think or expect at that juncture.

With all due respect, Doctor, I'm curious as to what his individual opinion is, what its relevance is.

MR. McLAUGHLIN: That's -- and a lot of this is just the nature of this bizarrely worded claim to begin with. But leaving that aside, he does rely on Dr. Barrett Rabinow to then talk about does this language communicate to a POSA that this is an isotonic solution.

So he's not going to say that those words tell somebody it's isotonic. He relies on Barrett Rabinow for that. But then taking that knowledge from a formulation expert as one would -- as a doctor would who is looking to gain more information from a formulation that he's administering, using that knowledge from Barrett Rabinow, which is what he does in his report as shown here in paragraph 556. He clearly refers to Dr. Rabinow's opinion and his opinions about the isotonicity of this formulation. He then relies on an expert's expert opinion --

THE COURT: Which he's entitled to do.

MR. McLAUGHLIN: -- and incorporates it into his own opinions about Claim 6 overall.

THE COURT: Anything further, Ms. Oberwetter?

MS. OBERWETTER: Only, Your Honor, that he doesn't rely on Dr. Rabinow; he defers to Dr. Rabinow on that question and does not then frame any opinion that he is offering in his report from the standpoint of a POSA on the method of treatment patents. So that opinion is absent, and this is an effort to backfill that.

THE COURT: Understood.

I'm going to overrule the objection at this point with the coming preview with respect to Dr. Rabinow. And the Court will afford this evidence the weight it believes appropriate. But objection noted.

MS. OBERWETTER: My only remaining question is may I voir dire the witness on his formulation expertise?

THE COURT: Yes, you may.

Counsel, if you wouldn't mind abdicating the podium. Thank you.

I would note, Ms. Oberwetter, that the Court has not qualified Dr. Albini as an expert in any fields related to formulation. But with that, a limited voir dire, I think, would be appropriate.

MS. OBERWETTER: Yes, Your Honor.

VOIR DIRE EXAMINATION

BY MS. OBERWETTER:

Q. Good morning, Dr. Albini.

A. Good morning.

Q. You agree, and I think we've heard you say earlier today, that you are not a formulation expert, correct?

A. That is correct.

Q. And, in fact, in your report you specifically rely on and defer to Dr. Rabinow in connection with the things that you say about an isotonic solution, correct?

A. That is correct.

Q. Okay. You are not an expert in the design of therapeutics, correct?

A. I'm not an expert in the design, although I read material about such designs on a regular basis when treating patients with pharmacologic agents.

Q. Okay. And whatever you may read, you're not an expert in that field, correct?

A. That is correct.

Q. Okay. And, in fact, you've testified several times in other proceedings on behalf of Mylan, correct?

A. That is correct.

Q. Okay. Including in IPR proceedings related to the method of treatment patents, some of which are at issue here; some of which are not, correct?

A. I have. That is correct.

Q. And when you had your deposition -- if I can turn you back in time to a January 20th, 2022, deposition, you were

asked some questions in that proceeding about how the osmolality of a drug could affect its half-life.

Do you remember that from 2022?

A. Not specifically. I'm sorry. No.

Q. Okay.

If we could pull up the page from that deposition page.

Let me just start with the front, Dr. Albini. This was a deposition you testified in on January 20th, 2022, correct?

A. I have no reason to doubt that. Yes. Correct.

Q. You do recall testifying in a case at approximately that time?

A. Yes.

THE COURT: Let me interject just because I saw the word "confidential" on there. Do we need to seal the courtroom for any of this discussion?

MS. OBERWETTER: Thank you for asking, Your Honor. No, this is fine for us to have up on the screen.

THE COURT: I'm not doubting your statement. But in a trust-but-verify mode, I'll ask Mylan if they have any thoughts to the contrary on that.

MR. McLAUGHLIN: With respect to the confidentiality, Your Honor?

THE COURT: Yeah. Do we need to seal the courtroom

for a discussion of this testimony? It was an IPR proceeding, I believe.

MR. McLAUGHLIN: No.

THE COURT: Okay. All right.

So, Ms. Oberwetter, my apologies for trusting but verifying. Go right ahead.

MS. OBERWETTER: Always appreciated, Your Honor.

BY MS. OBERWETTER:

Q. If we take a look at page 125 of this transcript. And you recall you were being questioned in that deposition by another attorney for Regeneron, correct?

A. That is correct. I do recall that.

Q. And you were asked in that proceeding a question about whether the composition of an intravitreally administered drug, including its osmolality and excipients, can affect the half-life of the drug in the vitreous, correct?

Do you see that question?

A. Let me just take a second to digest that. Hold on one second.

Okay. I've read the question.

Q. And your answer was you're getting into some very technical issues, correct?

A. That is correct.

Q. And then if we scroll down to the next several lines, you said, "It happens that, as I sit here before you today, I

think off the top of my head that osmolality would not affect half-life, although it would have many effects. But I could be wrong on that. And, again, I am not an expert in the design of therapeutics."

Do you see that?

A. That is correct.

Q. And then you said, "But as a clinician that uses angiogenic drugs and that has written these declarations, I don't think that sounds reasonable. But I don't really have a strong opinion or a lot of experience in that area."

Correct?

A. That is what I said.

Q. And those are answers that you gave with respect to the osmolality of the drug you were being asked about, correct?

A. I don't recall if this was in reference to a specific drug.

Q. Okay.

MS. OBERWETTER: Thank you, Your Honor. That is the extent of my questions on this topic.

THE COURT: Understood. Thank you.

The Court's ruling with respect to the objection remains.

Counsel, you may resume your direct.

MR. McLAUGHLIN: Thank you, Your Honor.

DIRECT EXAMINATION (Resumed)

BY MR. McLAUGHLIN:

Q. So I will resume my direct, but in the meantime I just want to ask you, Dr. Albini, a few questions about your background. I understand that you don't consider yourself an expert in the design of therapeutics, but would you consider yourself to be knowledgeable about the impact of the injection of an isotonic or nonisotonic solution into the eyes of one of your patients?

A. I would consider myself being an expert in the use of these drugs. The question of the importance of the isotonicity and various options for choosing different osmolarity of agents, I'm not an expert in those issues, but I certainly feel myself confident to describe the use of drugs with formulations that have been approved.

Q. In the course of your work and your research, have you published -- did you publish an article in 2014 called "Ziv Aflibercept as a Possible Alternative to Aflibercept"?

A. Yes, I did.

Q. Do you recall publishing that article?

A. I do.

Q. Do you recall who you published that article with, who your coauthors were?

A. I think my coauthors, as I recollect, were Andrew Moshfeghi, and Jonathan Chang.

Q. If you can recall -- but we can also put the article

up for you, if you'd like, but can you recall what the subject matter of that article was?

A. The subject matter was that there was some early interest, particularly in Brazil as I recall, for using Regeneron's product ziv-aflibercept, which is designed for intravenous use as a cancer therapeutic, to aliquot it in a very analogous fashion as bevacizumab is aliquoted for intravitreal use, to use ziv-aflibercept off-label, again with the goal being of obtaining the -- being able to use the VEGF Trap molecule at a reduced price for patients that could not meet the price point for aflibercept.

Q. And is this a copy of your article shown here?

A. That's correct.

Q. And if we could turn to the second page, I don't know if there's a way to -- is there a way to zoom that in?

So in this top paragraph in the upper left of page 68 of that article, do you discuss the osmolality of ziv-aflibercept versus aflibercept?

A. That is correct.

Q. What did you conclude about the osmolality of the two different formulations?

A. I haven't actually read this whole thing in a while, but as I recollect, I remember having a concern that the higher osmolarity of ziv-aflibercept relative to aflibercept that's injected in the eye, I think the numbers are there,

815 milliosmoles relative to 260 -- or compared to 260 milliosmoles, that this higher osmolarity may cause a clinical problem in that I had been familiar with work that was done by Dr. Marmor in the 1970s -- and, honestly, right now sitting here, I can't remember what the point of this paper was.

But I remember that the higher osmolarity of intravitreal injections given by Dr. Marmor in -- I think it was a monkey study, I want to say; it's been many, many years since I've read this paper -- that in that -- with that higher osmolarity, there was a risk, a very high risk, for retinal detachment.

And I remember that some of us who were pondering this issue, including me and my coauthors here, were wondering whether ziv-aflibercept was produced with higher osmolarity just to avoid the possibility of intravitreal injection.

So that's my recollections on this issue, but I think I was concerned in this particular case about higher osmolarity given my prior familiarity with work done by Dr. Marmor, as was cited in this article.

Q. Okay. Now, a few minutes ago you said you couldn't remember what this article was about.

You were referring to Dr. Marmor's 1979 article, not the one in front of you here?

A. Thank you for the clarification. Absolutely, yes.

The Marmor article that -- I have not read that in -- probably since this article was published.

MR. McLAUGHLIN: Okay. With that, with Your Honor's permission, I'm going to resume my direct. See if I can recall where we left off.

BY MR. McLAUGHLIN:

Q. So Slide 121, we were talking about Dr. Rabinow's opinion. This is his opinion that you relied upon in formulating your opinions with respect to Claim 6?

A. That's exactly right.

Q. Okay. And this passage that he cites from Dixon, that comes from DTX 0204?

A. That's correct.

Q. If we could pull that up so we can show the Court this language.

This comes -- this is language from Dixon. That's that 2009 article regarding VEGF Trap-Eye; is that correct?

A. That's correct.

Q. What does Dixon say about VEGF Trap-Eye and its formulation?

A. He teaches that it is formulated with different buffers at different concentrations suitable for the comfortable, nonirritating direct injection into the eye.

Q. Going back to the slide deck here, turning to the next slide, Slide 122, did you also rely on the Eylea label

when formulating your opinions in this case?

A. That's correct.

Q. And is this a snapshot of that Eylea label, DTX 3316?

A. Yes, it is.

Q. And what's this say about Eylea in DTX 3316?

A. It says that it is formulated as an iso-osmotic solution.

Q. And in your opinion as an ophthalmologist, is the FDA-approved formulation typically the one that was used in the pivotal Phase III trials that were responsible for that FDA approval?

MS. OBERWETTER: Objection, Your Honor. That's a fact question, not an opinion question if he's asking about this trial.

THE COURT: Repeat that question, Counsel, please.

BY MR. McLAUGHLIN:

Q. In your opinion as a treating physician, is the FDA-approved formulation typically the one that's used in a drug's pivotal Phase III clinical trials?

A. That's my --

THE COURT: One second, Doctor. Sorry.

Objection overruled.

Now you can answer. Thank you.

THE WITNESS: That's my opinion and would be the opinion of the POSA.

BY MR. McLAUGHLIN:

Q. Did you review Dr. Csaky's rebuttal expert report?

A. Yes, I did.

Q. And did you review the portion in which he was rebutting -- he was providing his rebuttal opinions with respect to Claim 6 of the '572 patent?

A. Yes, I did.

Q. Did Dr. Csaky provide any rebuttal opinion indicating that the FDA-approved formulation of aflibercept was not the one used in the Phase III clinical trial?

A. No, he did not.

Q. Now proceeding forward and now relying upon what you learned from Dr. Barrett Rabinow, the formulation expert that's going to be offered by Mylan, can you provide a summary of your final opinion with respect to Claim 6 of the '572 patent?

A. Yeah. I believe that Claim 6 is anticipated by Dixon, given that a suitable, comfortable, nonirritating direct injection of the eye would inherently be isotonic, as taught to me by Dr. Rabinow.

Q. And now we're going to shift focus a little bit and talk about obviousness of Claim 6 of the '572 patent.

So turning to the Slide 126, can you briefly summarize the opinions you're going to provide in this section of your testimony?

A. Given the text that we've discussed and the Dixon

reference, combined with a source used by Dr. Rabinow, Hecht, it is -- it becomes obvious that the comfortable, nonirritating, safe for intravitreal injection solution described by Dixon for aflibercept would be isotonic.

Q. We're going to be using the same compiled Claim 6 for your analysis in this portion of your presentation?

A. Yes.

Q. And that's shown on Slide 127?

A. Yes.

Q. So in your anticipation opinions you walked through each disclosure from Dixon with respect to these dosing regimen elements of Claim -- compiled Claim 6; so we won't do that again. But you understand -- or you're going to be applying that same reasoning in your obviousness section?

A. That's correct.

Q. You have the same understanding that the visual acuity limitation of this claim does not have -- does not carry patentable weight?

A. That's correct.

Q. Now, with respect to the isotonic solution aspect of Claim 6, in your opinion, would a POSA -- again, you relied on the opinion of Dr. Rabinow in this part of your -- formulating your opinions as well?

A. That is correct.

Q. And you incorporated his opinion regarding the Hecht

reference?

A. That is correct.

Q. In your opinion, would a POSA have been motivated to administer a formulation of aflibercept that was comfortable and nonirritating?

A. That's correct.

Q. And do you intend to rely upon Dr. Rabinow's opinion and trial testimony regarding the disclosures of the formulation prior art and reasonable expectation of success at formulating isotonic ophthalmic formulations?

A. Yes, I do.

Q. And assuming that Dr. Rabinow's later testimony shows the obviousness of formulating an ophthalmic formulation to be isotonic to be obvious, what is your final opinion regarding Claim 6 of the '572 patent?

A. That Claim 6 is both anticipated and obvious given the Dixon prior art and the Hecht prior art.

Q. Now we're going to shift gears now and talk about the secondary considerations opinions that you provided. So we're now Slide 134.

Do you understand that, in rebuttal to your opinions, Dr. Csaky provided five different opinions on secondary considerations?

A. That is correct.

Q. And are those five different secondary considerations

listed here on Slide 135?

A. Yes, they are.

Q. That includes long-felt need, failure of others, unexpected results, industry praise, commercial success?

A. That's correct.

Q. Do you understand, when formulating your final obviousness opinions, that you are to consider -- to take into consideration any evidence of secondary considerations?

A. That's my understanding.

Q. But you understand that those secondary considerations must have a demonstrated nexus to the claim elements at issue?

A. That is correct.

Q. Now I'd like to start by reviewing again what was known and disclosed in the prior art before the 2011 -- 2010-2011 time frame.

Could you briefly describe what's shown here in terms of what was known about extended dosing regimens in the art before 2010?

A. This is a roundtable from Retinal Physician from 2007 that demonstrated that, as early as 2007, there was a variety of extended dosing intervals, including treat and extend, the prn dosing, that were already in use by the leading vitreoretinal surgeons at that time.

Q. Can you explain to the Court what's shown here on

Slide 137?

A. This -- I believe we've seen this study before as well -- is a study documenting the treat-and-extend approach use with bevacizumab but again showing that the treat-and-extend dosing strategy was -- already had a term and was understood to be a certain type of dosing strategy by the POSA in 2009, as evidenced by its mention here in this article.

Q. And is that the same type of treat-and-extend regimen that was disclosed or discussed by Dr. Brown that we saw in a couple slides previous?

A. That's correct.

Q. Turning to Slide 138, can you describe what's shown on this slide?

A. This slide shows a preferences and trends survey from the American Society of Retinal Specialists in 2009, documenting that, in this survey with 433 respondents, 91 percent of practicing vitreoretinal surgeons in the United States surveyed at that time were using prn dosing or an extended dosing interval well before 2010.

Q. And how many doctors were using a fixed dosing regimen at that point?

A. Injection given every four to six weeks regardless of lesion activity was down to 5 percent by 2010.

Q. And just to clarify, what we talked about on this previous slide is from DTX 4192; is that correct?

A. That's correct.

Q. Now, jumping to Slide 139, can you describe what's shown on this slide?

A. This is a 2010 preferences and trends survey asking similar question, describing treatment strategies for exudative macular degeneration, or wet AMD. And you see that 43 percent of respondents in 2010 are using prn dosing and 34 percent are using treat and extend already.

Q. This is from DTX 2040, page 24?

A. That's correct.

Q. And turning to Slide 140, can you describe what's shown here?

A. This is the 2011 survey, probably data gathered in the first part of 2011. They're usually reported towards the end of the year at the meeting -- well, middle to end, summer to fall. I don't remember exactly when 2011 meeting took place. But most doctors use prn, 32 percent; and treat-and-extend regimen is being used by 60 percent; and, again, less than 5 percent of physicians are using a follow-and-treat-monthly, active or not.

Q. This is from DTX 4194?

A. That's correct.

Q. And turning to Slide 141, can you tell us a little bit more about the PrONTO study that you discussed in your expert reports?

A. This is a trial result from the two-year data from the PrONTO study, which again was a prospective study using ranibizumab in a prn fashion after loading doses, showing very good visual acuity gains with prn dosing at 24 months, 11.1 letters of visual acuity benefit were obtained; 43 percent of patients improved by 15 letters or more -- which were, I think, very impressive results at the time -- showing that this could be achieved with an extended dosing regimen.

Q. Is that also summarized here on Slide 142, DTX 3131?

A. That's right. But the highlighted text here makes the point that, with fewer than half the number of injections in the PrONTO study as compared to the MARINA and ANCHOR studies, very similar visual acuity gains were obtained.

Q. If we turn to the next slide, this is also a selection from DTX 3131; is that correct?

A. That's correct.

Q. Can you tell us what's shown on Slide 143.

A. This shows a text from the paper detailing that the PrONTO study was designed to minimize the number of treatments but not the number of visits and discussing already other treatment strategies that may yield similar or even better visual acuity outcomes that require fewer visits, and it discusses the treat-and-extend treatment strategy that we've discussed a number of times and that this was in -- published in 2009 already.

Q. And can you just briefly summarize then for the Court why the PrONTO results were important?

A. I think in regards to this testimony, they were important because they detailed that in 2009 the need for an extended dosing regimen was already met. And in terms of the weight of those secondary considerations, the variable dosing regimen had already been achieved and in use and certainly would have been readily envisioned by the POSA.

Q. And is this study leading the physicians away from using fixed regimens like monthly dosing?

A. I think very quickly after these data were available, there was a shift. Whether that's causation or just coincidence, I guess is debatable. But certainly it seemed that at around the same time period, physicians started to use prn dosing regimens as evidenced by the *Retinal Physician* roundtable that we've discussed a few times already.

Q. If we turn to the next slide, this is Slide 145, the Engelbert reference, DTX 3215, can you explain what you've shown here?

A. Yea. This paper published in 2010 just evidences that PrONTO-style dosing has become popular within the retinal community. That's the extended prn dosing that we've been talking about. And it also details treat-and-extend dosing with fewer patient visits in addition to fewer monthly injections. So that concept was already there and practiced in

2010.

Q. And to clarify, DTX 3215 also specifies that, as a result of the PrONTO study, PrONTO-style dosing has become popular in the retina community?

A. That is correct.

Q. Is that consistent with your recollection as well?

A. Yes.

Q. Then, again, you've had the opportunity to review internal Regeneron documents in the process of formulating your opinions; is that correct?

A. That's correct.

Q. Are one of those documents shown here, Slide 146?

A. That's correct.

Q. Is this a 2007 email from George Yancopoulos?

A. Yes.

Q. Is one of the statements that he makes in this email "published prn approaches, which are being widely adopted as current standard of care"?

A. That's correct.

Q. Now, did you review Dr. Csaky's secondary considerations opinions in the process of formulating your reply opinions in this case?

A. Yes, I have.

Q. Is one of those opinions shown here regarding long-felt need from Dr. Csaky?

A. That's correct.

Q. So in your opinion, as of the 2010 time frame, was there a long-felt need for an extended dosing regimen for the treatment of an angiogenic eye disorder?

A. I don't think so. I think, given everything that we've looked at right now, you can see that, as early as 2007/2008, that extended dosing regimens were very commonly employed and this need had already been met.

Q. Turning to Slide 148, do you understand that Dr. Csaky also offered opinions regarding purported failure of others?

A. Yes, I do.

Q. Do you agree that there was a failure of others to achieve extended dosing regimens before 2011?

A. I do not. I think that we've detailed a number of studies that have showed success with very good visual acuity outcomes with extended dosing regimens. And certainly given the data that we've gone through in a number of studies with ranibizumab and aflibercept in DME and in AMD, I think there was a reasonable expectation of success that a POSA would have had for an extended dosing interval.

Q. And is this an accurate summary here on Slide 149 of some of the disclosures of extended dosing regimens that were known and being practiced prior to 2011?

A. That's correct.

Q. That includes those -- some of the different scenarios that were offered in the 2007 *Retinal Physician* article?

A. That is correct.

Q. And that includes the treatment of DME using ranibizumab and Lalwani 2009?

A. Yes.

Q. Does it also include the treatment of AMD using various regimens in Dixon 2009?

A. Yes.

Q. Does that include the treatment, including the disclosure of treat and extend, in Spielberg 2009?

A. Yes, it does.

Q. Treat and extend was one of the same regimens that was disclosed in the 2007 *Retinal Physician* article?

A. Yes. That was disclosed by Dr. Brown in particular, yes.

Q. And was this also confirmed by PAT Surveys in the 2010-2011 time frame?

A. It was confirmed that these were very popular treatment strategies in those years, yes.

Q. Now I'd like to shift gears and talk a little bit about unexpected results.

THE COURT: Counsel, before we do that, if we're gear-shifting again, is this a good spot for a lunch break?

MR. McLAUGHLIN: It is.

THE COURT: Perfect.

Doctor, we're going to take a break. As I advised, I think, Dr. Trout yesterday or some others, they are permitted to feed you, but they're not permitted to talk to you. And they are hereby ordered to feed you but, otherwise, not talk to you.

But we'll take a lunch break.

No one can talk to you because you're midstream on your testimony, but you're free to step down, sir.

THE WITNESS: Fair enough. Thank you.

THE COURT: Thank you.

Counsel, let's take a break until 1:00 from our perspective, and then we'll resume with Dr. Albini's testimony. Thank you all very much.

(A recess was taken from 12:24 p.m. to 1:08 p.m.)

THE COURT: Counsel, are you ready to resume?

MR. McLAUGHLIN: We are, Your Honor.

THE COURT: You may proceed.

BY MR. McLAUGHLIN:

Q. Welcome back, Dr. Albini.

A. Thank you.

Q. So can I go to Slide 147, please.

Just want to make sure that we wrap things up here.

Now, going back to Dr. Csaky's rebuttal opinion with respect to secondary considerations, do you agree that there was a long-felt need for an extended dosing regimen for the treatment of angiogenic eye disorders by the 2011 time frame given all the material that we reviewed in the slides prior to this?

A. I think it's been fairly well documented that that need had been answered by 2011.

Q. Thank you.

And going forward to the next slide, Slide 148.

And do you agree with Dr. Karl Csaky, Regeneron's expert, that there was a failure of others to achieve extended dosing regimens with ranibizumab by 2010-2011?

A. I think that there were a number of successes, as we've discussed throughout this testimony.

Q. And then I think we were turning to unexpected results when we broke for lunch. So let's go back to Slide 150 here in front of you.

This is showing DTX 0204, the Dixon reference. Can you describe what's shown here in this section of Dixon.

A. In this section of Dixon he's describing the CLEAR-IT 2 Phase II study, which utilized a four monthly loading doses followed by prn dosing and achieved good visual acuity outcomes.

Q. If we turn to the next slide, are these some of these outcomes that you're referring to?

A. That's correct. In that arm with q4 loading doses and prn treatment thereafter, patients achieved mean improvement of nine ETDRS letters, which is a very good visual acuity result, with 30 percent gaining three lines or more of vision by 52 weeks. So I think these were excellent results.

Q. And is this -- can you describe what's set forth here on Slide 152 of your presentation.

A. Yeah. This details the clinical trial results that would have been available to the POSA prior to the filing patents at issue showing very good visual acuity results with a number of different regimens across diseases and across agents, again, I think really making it difficult to make an argument that good results were unexpected.

Q. What else did Dixon show about the frequency of the injections that were required for reaching those visual acuity outcomes that they saw?

A. That patients were receiving 2-milligram injections with, on average, 1.6 injections over the loading phase time. So over the 40-week prn loading protocol, patients only needed 1.6 injections on average, again showing that, even with extended treatment, good visual outcomes were obtainable.

And the median time to first reinjection in all groups was 110 days, again, further speaking to the extended dosing interval that could be used to achieve good visual acuity results.

Q. And, again, this is coming from DTX 0204?
A. That's correct.
Q. Turning to the next slide, Slide 154. So have you reviewed the unexpected results opinions of Dr. Csaky?
A. Yes, I have.
Q. Do you agree with Dr. Csaky?
A. No, I do not. I think that the trials that we have discussed already paint a picture of a lot of industry successes, and I don't see the argument for overwhelming industry failure.
Q. And then actually I want to back up and ask you about one additional document. So if we look at Dixon. I believe you have it at DTX 0204 in your binder. If you could turn to that, please.
A. I found it.
Q. And if you turn to page 4 of that reference and look at that section on Phase II that you've been discussing.
A. I don't know if you can help me. My pages -- oh, I see it. Never mind.
Q. It's at .00 -- yeah, there you go.
A. I got it. Yep.
Go where? I'm sorry.
Q. The discussion in Section 2.6.2 about the Phase II clinical trial.
A. Yes.

Q. Do you see there's a reference to Reference 45 there?
A. Reference 45, I see that.
Q. So if you turn to the back and take a look at what Reference 45 is. Can you do that?
A. Yes. I see that.
Q. And that Reference 45, is that a presentation entitled "VEGF Trap-Eye in Wet AMD, CLEAR-IT 2: Summary of One-Year Key Results. Paper presented at Retinal Society Annual Scientific, September 28, 2008, Scottsdale, Arizona"?
A. I see that reference.
Q. Is that another one of the references that you reviewed in connection with formulating your opinions in this case?
A. I have seen the slides from that presentation, yes.
Q. Okay.
Can we put those slides up, please. That's DTX 3173.
Is this the presentation that you've reviewed and relied upon?
A. Yes.
Q. Okay.
And if we go ahead to Slide 6, please, of the slide presentation of DTX 3173.
Is this a depiction of the study arms from that study?
A. Yes, it is.

Q. And if we jump to Slide 9, what were some of the conclusions that were reported with respect to some of the results from the Phase II CLEAR-IT study?

A. You see them here, that there was a significant improvement in visual acuity, a significant reduction in central retinal thickness. That means decreased swelling. The groups dosed at baseline and at Week 12 showed improved visual acuity and retinal thickness, although this effect was not as robust as that seen in monthly dosing in the early phase. All the maintenance phase here was prn.

Maintained effect on visual acuity with a single dose to eight weeks and was generally well tolerated with no drug-related serious adverse events -- with no serious adverse events.

Q. If we jump to Slide 16 of this presentation, DTX 3173, can you explain what we're looking at here?

A. These are the visual acuity results from the arm that is a .5 milligrams of the low dose with monthly loading doses followed by prn dosing after Week 12 shown in the blue. And the 2-milligram dose, a higher dose, shown in the green squares, with visual acuity. This arm was also four loading doses initially and then maintained with prn injections after Week 12.

Q. Thank you. And if we could go back to the main slide deck, DDX 6.

And if we could turn now to the issue of industry praise, that secondary consideration. We're at Slide 155, now 156. Did you review the opinions of Dr. Karl Csaky with respect to reported industry praise?

A. I did.

Q. Did you agree with Dr. Csaky's opinions?

A. I agree that there was great praise from the industry, but I don't see the connection of that praise to the dosing regimens which we are discussing in the claims today or to the isotonicity issue.

I think that there was great praise for this molecule and there was great efficacy of the molecule; but, to me as a POSA, because these dosing strategies were actually not widely adopted and retina specialists continued to use prn and treat-and-extend dosing instead of fixed eight-week dosing as described in the claims, I really don't see the connection to claim that the industry praise was due to the practices outlined in the claims in question.

MS. OBERWETTER: Your Honor, I have an objection and motion to strike in part the prior response.

Dr. Albini's report does not contain a disclosure with respect to the isotonic solution limitation as it relates to secondary indicia or industry praise in particular.

THE COURT: Understood.

Counsel?

MR. McLAUGHLIN: I think what Dr. Albini was doing was just responding to Dr. Csaky's opinions, which he noted did not address isotonicity or the aspects of Claim 6 in any way.

THE COURT: I'll overrule the objection at this point considering it's a motion to strike.

Counsel, obviously, you'll be free to address that in the posttrial briefing. And if it was not properly disclosed, the Court would disregard it, but we'll address that posttrial at this juncture. Noted, however.

You may proceed, Counsel.

BY MR. McLAUGHLIN:

Q. Let me ask it this way: In reviewing Dr. Csaky's opinions, did you see any industry praise in those opinions regarding anything having to do with an isotonic solution?

A. I did not.

Q. Did you see in Dr. Csaky's opinions any evidence for any industry praise for the use of five monthly loading doses followed by every-eight-week dosing in the treatment of DME?

A. I did not.

Q. If we could turn now to the issue of commercial success. Dr. Albini, were you asked to provide opinions regarding commercial success in this case?

A. I was.

Q. Do you understand that Dr. Csaky also provided opinions regarding commercial success?

A. Yes.
Q. Did you review those opinions?
A. Yes.
Q. Is one of those opinions set forth here on Slide 158?
A. Yes.
Q. In reviewing his opinions, did you see where Dr. Csaky attributed any of the commercial success of Eylea to the DME-DR treatment regimens of five monthly loading doses followed by fixed every-eight-week dosing?
A. I do not see that specifically mentioned.
Q. And did you read the day two trial testimony transcript from Dr. Csaky?
A. Yes.
Q. Okay.

If we could pull that up.

This is from -- we're going to PDF page 109. There we go.

Did you see Dr. Csaky testify as follows when he was asked, "When you say you've used Eylea to treat patients with DME and DR according to the method of Claim 25, have you also done that for secondary doses step?"

And his response was, "Yes. In certain cases where there's severe DME, you need five injections, multiple injections. And, again, having, as I said before, that confidence of five injections gets us to a good place both

anatomically and visually is a nice approach to take in some patients."

In your opinion, is a regimen that's used in some circumstances of severe DME in some patients something that sounds like being responsible for the commercial success of Eylea?

A. No.

Q. If we could go back to the slide deck, please, DDX 6. Thank you, Dr. Albini.

You also have provided opinions regarding the pharmacologic attributes of the aflibercept protein; is that correct?

A. I have.

Q. Can you explain for the Court what you've provided here on Slide 159 in this callout from DTX 2745.

A. This is an early paper from 2002 describing VEGF Trap-Eye, at that point in preclinical testing, describing that it has a higher affinity and improved pharmacokinetics relative to antibody therapeutics that were being developed at the time. Again, showing that there was reason to believe that this molecule would be a better agent based on its pharmacokinetics early on prior to any consideration of dosing regimen.

Q. And when was this disclosure published?

A. 2002.

Q. If we turn to the next slide, what else was published

regarding the pharmacologic attributes of aflibercept?

A. This is from the Dixon reference that we've referenced many times in 2009, where it also remarks on the high affinity of the molecule and the benefits of the Trap complex increasing its durability and its long duration of effect in the eye, again pointing the potential success of the molecule to its pharmacologic properties rather than to any specific dosing regimen.

Q. What you're looking at here is DTX 0204?

A. That's correct.

Q. Let's go on to the next slide, Slide 161. Can you explain to the Court what you've shown here with respect to this April 28, 2008, press release, DTX 2731.

A. Yeah. This article describes again that, due to its high affinity for all isoforms of VEGF-A as well as its long residence time in the eye, Dr. Quan Nguyen, one of the investigators in the early Regeneron trials, is claiming that that scientific -- or those pharmacologic properties of the molecule are predictive of clinical success.

Q. If we turn to the next slide, Slide 162, is this a summary of those pharmacologic attributes of aflibercept that you've just reviewed?

A. That is correct.

Q. And, in summary, starting with the assumption that Eylea has been a commercial success, in your opinion, is that

success attributable to the properties of the molecule itself or to the features of the isotonicity or the five monthly loading dose DME aspects of the asserted claims?

A. I see not much praise or remark about isotonicity of the molecule. I think that, with regards to the dosing frequency, one of the most telling pieces of information to me was the email from Dr. Yancopoulos that we had a few slides back where he overtly declared that the success of the molecule will be based not on its dosing strategy but that it will be better than the antibody molecules available regardless of dosing strategy. And I think that's the way the success of the molecule was perceived in the community as well.

Q. So in your opinion, the commercial success of Eylea is not attributable to the five monthly loading dose dosing regimen followed by every-eight-week dosing in the treatment of DME patients?

A. Yes.

Q. So do you agree, then, with Dr. Karl Csaky's final opinion with respect to commercial success?

A. No.

Q. The next -- you were asked to provide opinions as to how certain patents assigned to Regeneron might influence whether someone could practice the subject matter claimed by the '601 and '572 patents?

A. That's correct.

Q. Are some of those blocking patents shown here?

A. Yes. Due to the patented molecule, it would have been difficult for people other than Regeneron to have performed studies to demonstrate various dosing strategies and their success.

Q. So the '746 patent claims a method of treating retinal neovascularization; is that correct?

A. That's correct.

Q. And in your opinion, would that have prevented somebody from being able to practice the claimed methods of the '601 and '572 patents?

A. Yes.

Q. If we take a look at the '747 patent, that's -- the claim there is drawn to a therapeutic method for treating or ameliorating an eye disorder?

A. Yes. That would also preclude it.

Q. And so, in your opinion, that would preclude the ability to conduct the dosing regimens of the '601 and '572 patents?

A. Exactly right.

Q. And for the purposes of this analysis, have you been asked to assume that the sequence IDs set forth in these claims are the sequences of aflibercept?

A. Yes.

Q. If we turn to the next slide, one of these is the

'799 patent, 7,306,799, DTX 4116. Is Claim 1 there drawn to a therapeutic method for treating an eye disorder?

A. Yes.

Q. And in your opinion, would that have blocked somebody from conducting or operating the claimed dosing regimens claimed in the '601 and '572 patents?

A. Yes.

Q. And for the '758 patent, it's drawn to a method of inhibiting vascular endothelial growth factor activity in a mammal. Do you see that?

A. Yes.

Q. Would that claim have prevented somebody from operating the claimed regimens of the '601 and '572 patents?

A. Yes.

Q. I want to revisit one more aspect of your testimony earlier today.

So if we could pull up DTX 07 -- sorry -- DTX 7069, paragraph 556.

I just wanted to ask one final question on this. Did you -- you stated earlier that you did review Dr. Csaky's opinions in this regard?

A. Yes.

Q. Did Dr. Csaky offer any rebuttal regarding whether or not the language from Dixon suitable for the comfortable and nonirritating direct injection into the eye inherently

disclosed isotonicity?

A. I do not recall any rebuttal on that specific remark.

Q. Thank you.

MR. McLAUGHLIN: Nothing further from Mylan, Your Honor, with --

THE COURT: Thank you, Counsel.

MR. McLAUGHLIN: -- obviously, reservation for redirect.

THE COURT: Certainly.

Cross?

MS. OBERWETTER: Yes, Your Honor. Can I have just a minute or two to get set up at the podium?

THE COURT: You may.

Whenever you're ready, Counsel, you may proceed.

MS. OBERWETTER: Thank you, Your Honor.

CROSS-EXAMINATION

BY MS. OBERWETTER:

Q. Good afternoon, Dr. Albini.

A. Good afternoon.

Q. Dr. Albini, you've been working with Mylan's litigation counsel since 2017, correct?

A. That sounds correct, yes.

Q. Okay. So for the past five or six years?

A. Yes.

Q. That was years before this case even got filed,

correct?

A. I'm not aware of when exactly this case was filed.

Q. All right. One of Mylan's attorneys, Mr. McLaughlin, and some of these colleagues would fly down starting back in 2017 to meet with you down in Miami, correct?

A. That's correct.

Q. And you would meet in a conference room at the hospital where you worked in Miami, right?

A. That's correct.

Q. And you would sit in a room and look at Regeneron's patents, correct?

A. Among other things, yes. That's correct.

Q. And you were retained at that time to help Mylan generate ideas on how to invalidate the patents, correct?

A. I was hired for my opinions about -- mostly at that time we were discussing what the POSA or what the standard retina specialist at the time would have envisioned as reasonable dosing regimens to use. So I was not really engaged in a way to -- I think you said the words "to create strategy" or "to develop strategies."

I was more engaged in a way to guide them through the prior art and the scientific literature that was available as well as other types of literature that we've seen in my testimony such as the PAT Surveys and some of the articles from trade journals and other types of literature that may have been

more obscure to attorneys new to this area.

Q. Dr. Albini, you've had your deposition taken in this case, correct?

A. Yes.

Q. That was a few months ago, earlier in the spring?

A. That's correct.

Q. And we did that deposition down in Miami, right?

A. That's correct.

Q. You were under oath?

A. I was.

Q. Okay.

And if we could please cue up the video clip.

Did I ask you these questions we're about to play and did you give these answers?

(Video playing.)

"Q And those are conversations that -- I guess starting in roughly the 2017 time period, what was your level of activity in working on this matter over the years through the present?

"A I think that early on every couple of months, Neil and a colleague or two would fly out to Miami, and we would sit in a conference room much like this one but usually on-site at the hospital, and go through these patents. And they -- they would ask me my opinions about the

treatment strategies and what was currently known about various treatment strategies at the time and what the prevailing practice patterns were among retina specialists at the time with regard to the treatment of angiogenic eye disorders with anti-VEGF medications.

"Q Were you retained at that time to help generate ideas on how to invalidate the patents?

"A Yes.

"MR. McLAUGHLIN: I just want to counsel you going forward, you know, to the extent that this goes to any privileged discussions or conversations, that I'll instruct you not to answer."

(Video ends.)

BY MS. OBERWETTER:

Q. Dr. Albini, you know that that role is not the same as being an independent expert, correct?

A. I think that my input into guidance of what -- as I described in that clip, guidance through what the literature was available and what the prevailing practice patterns at the time, I think that is my role as an independent expert.

I can see your concern about my answering yes to the question about developing strategies. I certainly can't tell you exactly what was going through my head as I said yes, but I

think that my answer was that I was involved in developing strategies insofar as my independent opinions of the state of the art and what retina specialists were doing at the time is a very important component of any strategy that one would use.

But I'm not an attorney. I did not develop any of these arguments. I have no experience in patent law. I would be a very poor source to obtain information about how to invalidate a patent. I have no idea. My role --

Q. Sir, I think you've answered the question.

THE COURT: Counsel, he wasn't finished.

Go ahead.

THE WITNESS: No, I just wanted to reiterate again that my role was just to provide my experience and my opinion of what the state of the art was at the time in question.

BY MS. OBERWETTER:

Q. I'd like to pull up a slide from your opening deck, which is Demonstrative 6.152, or Slide 152. This is a slide summarizing, I think you said, the clinical trials from the relevant time period?

A. That's correct.

Q. And there are some AMD trials that are up at the top of this slide. There's three of those there, right?

A. That's correct.

Q. And only one of those, the CLEAR-IT 2 trial, relates to Eylea, correct?

A. That's correct.
Q. Okay. And then below that you've got a couple of DME clinical trials that are listed there, right?
A. That's correct.
Q. And the visual acuity scores that you can get vary by trial; is that right?
A. That's correct.
Q. And the selection of trials on this page, you decided which trials to include on this page, correct?
A. That's correct.
Q. Everything -- and CLEAR-IT 2, I think we determined, was the Eylea Phase II trial in AMD?
A. That's true.
Q. You would agree that Lucentis, referred to on this page as ranibizumab, was further along in development than Eylea was at this point, right?
A. That's correct.
Q. You would also agree that there was much more data for Lucentis in AMD than in DME at this point, correct?
A. That's correct.
Q. And if we take a look at the two DME trials that are listed on this page, the first one is called READ 1. Do you see that one?
A. I see it.
Q. How many patients were in that trial, sir?

A. I think it was a low number of patients. I hope I'm not misspeaking. But to the best of my recollection, it was a very small study.

Q. It was ten, correct?

A. That sounds right, yes.

Q. Ten patients in the READ 1 study?

A. Yes.

Q. The DME Phase I study on that page, how many patients were in that study?

A. I believe it was a similar number, about ten patients.

Q. Was it five?

A. It could have been.

Q. You don't know?

A. I don't remember the exact number right now, but it was a very small Phase I study.

Q. These were both Phase I studies?

A. That is correct.

Q. You would agree that knowledge of how a particular drug performs expands as the number of patients increases in trials over time, correct?

A. That's correct.

Q. You would agree that, once you start treating more people, you are obtaining more information, and that can either confirm or contradict what you've seen in the preceding phase

of your testing, right?

A. That is correct.

Q. You'd also agree that even a low rate of serious side effects can mean you would be considered not to have a safe trial, right?

A. In certain circumstances, yes.

Q. Okay. There are situations where there's even a low rate of really bad side effects, and that can make a trial deemed unsafe, correct?

A. That's correct.

Q. There are drugs that enter into Phase III that fail their Phase III clinical trial end points. Isn't that true?

A. That is true.

Q. And so a drug can get all the way to Phase III and still not make it to the market, correct?

A. Yes. And even further, a drug can pass Phase III and make it into the market and still fail in the real world.

Q. Okay. We'll come back to that.

There was recently an anti-VEGF drug with the maybe not catchy name of KSI-301 that failed its Phase III trial, correct?

A. That's correct.

Q. And you worked on a clinical trial for a different anti-VEGF drug called abicipar or abicipar?

A. That's correct.

Q. And even during the Phase III trials for abicipar significant intraocular inflammation issues emerged, correct?
A. That's correct.
Q. That drug did not make it to the market?
A. That's correct.
Q. I think you touched on one that passes its Phase III trials and then still runs into problems. Beovu is an example of an anti-VEGF agent in that category, correct?
A. That's correct.
Q. Beovu came onto the market in early 2020. Do I have that right?
A. That sounds right.
Q. You only used it twice?
A. That's my recollection, yes.
Q. All right. And that's because, after launch, everyone learned that there is a 1-in-200 risk of severe vision loss for patients that have Beovu, right?
A. That is correct.
Q. And those safety issues for Beovu only became known to doctors after Beovu was approved?
A. That is correct.
Q. And after it passed its Phase III trials?
A. That is correct.
Q. All right. And, in fact, the experience with Beovu made doctors appreciate how lucky -- and I think you've used

the word "lucky" -- doctors have been on the safety side with the first main anti-VEGF drugs like Eylea and Lucentis and bevacizumab, correct?

A. That is correct.

Q. And it's certainly possible that more went into that than luck, right?

A. Yes.

Q. This area of medicine is so difficult that you might not even know if an approved biosimilar will perform the same as the label drug, correct?

A. I would say that's not particular to this area of medicine. There are many areas of medicine that are just as difficult or challenging, but I think that, yes, it's -- it is true that the anticipated success doesn't always materialize.

Q. When deciding on how to design the arms of a clinical trial using an agent like an anti-VEGF, you would agree there's a lot of moving pieces to that, correct?

A. Yes.

Q. All right. You need to consider the route of administration?

A. Yes.

Q. You need to consider how often a drug needs to be administered?

A. Yes.

Q. You need to consider at which visits to the doctor

the drug might be administered?

A. Correct.

Q. You need to consider the concentrations of the drug being administered?

A. Correct.

Q. You need to think about whether and how many loading doses to use?

A. That is correct.

Q. You need to consider whether to have a fixed loading dose component to the regimen?

A. That is correct.

Q. And you need to consider whether there's a fixed extended dosing component to the regimen?

A. That is correct.

Q. You'd have to consider whether to have intervening visits between periods set for fixed dosing intervals, right?

A. That is a decision that -- yes, that is a decision that needs to be made when designing protocol for sure.

Q. You would agree that in the 2010 time period there was uncertainty as to what the best dosing approaches were for anti-VEGF agents, wouldn't you?

A. I think that, as was documented in this -- in my testimony so far, there were a number of protocols that had succeeded with a number of dosing strategies that involved three to six loading doses followed by prn or fixed interval

dosing regimens, either at 4 weeks or with other 8- or even 12-week dosing regimens.

So I think there were a number of protocols to choose from, but it also wasn't an infinite field of reasonable things to try.

Q. You would agree there was uncertainty as to what the best dosing approaches were for anti-VEGF agents?

A. Yes.

Q. You know that throughout the development period for Eylea, both before 2011 and afterward, Regeneron had access to data about the performance of Eylea that the public didn't, correct?

A. I'm aware that such data existed, but I don't know much about it.

Q. Okay. They, of course, had access to such data because it was their development program, right?

A. That makes sense.

Q. I'd like to talk a little bit about some of the terminology that we've been using in this case. Let's talk first about the phrase pro re nata, or prn. Prn means as needed, correct?

A. That's correct.

Q. All right. And prn means you only treat as needed determined by the findings of an OCT scan and other components like clinical examination and visual acuity measurements,

correct?

A. I think that's the way the POSA would have defined it.

Q. And so when you use prn dosing, the decision to redose the patient depends on the outcome of an assessment at the time you see the patient, right?

A. That is correct.

Q. And you don't know until you check the patient according to those things that I just mentioned?

A. That is correct.

Q. All right. And if instead you want to have an ex-ante decision, an ex-ante regimen where you don't have to go to the doctor between injections to get assessed, that would be an extended interval fixed dosing regimen, not a prn regimen, correct?

A. I think there's some ambiguity in the way that the term "extended interval" would be used. It was not, as I recall, a commonly used phrase among retina specialists at the time, extended interval.

So I think -- I can't think of cases in my head right now to give me guidance about how the POSA would have used the term "extended interval," whether that would necessarily mean extended injections or extended visits.

I certainly think it's reasonable to use it in either way. I just don't want to leave the impression that there was

a preferred way to use that term in the years that I'm aware of.

Q. Okay. You had your deposition taken in this case, I think we established, correct?

A. Yeah, that's correct.

Q. Okay. And if we take a look at page 241 from your deposition, I asked the following question: "If you want to have a regimen that doesn't have a required monthly visit to the doctor every month, that would be an extended-interval fixed dosing regimen, not a prn, correct"?

And your answer was, "Correct."

Did I read that correctly?

A. I don't think there's -- as I said, I don't think there's any problem in using the term that way, and I stand by what I said here in the deposition. I just don't want to leave the impression that that was a commonly used definition of the term by retina specialists back in 2010.

Q. You understood it when I asked you that question at your deposition?

A. I understood what you meant, yes.

Q. All right. You would also agree that prn and treat and extend are two different treatment strategies, correct?

A. Yes.

Q. All right. I'm going to change topics a little bit.

You talked during your testimony about a document. I

believe it was DTX 2039 was the version used.

If we can pull that up.

That's a -- you recall generally being asked about this document during your direct examination?

A. Yes, I do.

Q. And the cover says "VEGF Trap-Eye in Wet AMD CLEAR-IT 2."

This was about a Phase II AMD trial called CLEAR-IT 2, correct?

A. That is correct.

Q. And before I ask you additional questions about this, do you have personal knowledge as to whether this was the version that was publicly presented?

A. I have no reason to think it wasn't.

Q. Do you have -- my question was a little bit different. Do you have personal knowledge as to whether this was the version that was publicly presented?

A. I don't have any independent knowledge except that it's labeled this way, and I have no reason to believe that these weren't the slides presented.

But -- you know, I was -- don't have independent documentation that these are the exact slides that were presented or that all these slides were remarked on by the investigator, but this is given as a document of that presentation and available online.

Q. I'm sorry. You did not go find this online?

A. Honestly, I don't recall -- it was so many years ago that we brought this out -- who found it. But I've seen it, and I believe I've googled for it with PDF and CLEAR-IT 2, but I don't know. So many years ago.

Q. You were not at a September 2008 Scottsdale, Arizona, presentation, correct?

A. I was not.

Q. You would agree that the CLEAR-IT 2 trial did not have an arm that tested an eight-week fixed dosing interval regimen, correct?

A. That is correct.

Q. And it also did not have an arm that had three loading doses, correct?

A. Can we go to the slide that shows the different arm treatment strategies? I just want to make sure -- I can't remember now if it was three or four.

There was an arm with monthly loading doses, but with so many of these studies I don't want to give you the wrong answer. It was either three or four that they had, one of those two.

Q. It's possible it was four, right?

A. Certainly possible, yes.

Q. Okay. We can take that slide -- we can take that presentation down.

I'd like to talk a little bit about a study that your counsel asked you about, which was a PrONTO trial. You're familiar with the PrONTO trial?

A. I am.

Q. And I know you mentioned you had institutional pride about the PrONTO trial. That trial was before you got there, right?

A. I was there in 2006; so I think the results were -- those papers were published -- what years? I don't have it. You may have it in front of you -- 2008, 2009. So it was still certainly being talked about at the time when I was there.

Q. If we pull up the Lalwani 2009 article that is DTX 3113, this is an article that you were asked about on direct; is that right?

A. That's correct.

Q. And Dr. Lalwani is a well-regarded retina specialist?

A. That is correct.

Q. The PrONTO trial looked at three loading doses followed by prn treatment for wet AMD using ranibizumab.

Do I have that correct?

A. That's my understanding.

Q. And the PrONTO trial was generally viewed as having some positive results, I think you testified?

A. That's correct.

Q. In your opinion, the PrONTO trial initiated a major

change in the way that ophthalmologists were administering anti-VEGF agents.

Would you agree with that?

A. It was roughly at the same time. As I sort of semi-jokingly said during my direct testimony, I don't know whether it's cause and effect, how much credit you can give to this one trial. There is no doubt that prn dosing became very popular at around the same time. Maybe it would have done it without this trial; I don't know.

But I certainly remember a lot of people talking about this trial as evidence for prn dosing back at that time. So I think it very likely this trial was, at least to some small degree, responsible for the wide adoption of prn dosing back in the 2007-2008 time frame.

Q. The adoption of prn dosing itself was a major change in the way that ophthalmologists were providing these drugs, correct?

A. Yes.

Q. All right. In your opinion, the PrONTO regimen opened the door to more ophthalmologists making use of individualized prn treatment regimens for anti-VEGF agents, correct?

A. Yes.

Q. And in this publication by Dr. Lalwani, if we go down to the bottom of page 1, she says in part, "While the Phase III

trials used monthly injections, it is unclear at this time if monthly dosing is the best dosing interval. Observations made after the earlier Phase I-II studies with intravitreal ranibizumab suggested a role for OCT in determining the appropriate dosing interval for each patient."

Do you see that?

A. I do.

Q. And her reference to OCT, that's prn dosing because that's how you determine whether to re-treat, correct?

A. I think OCTs could be obtained with monthly dosing as well. So I have to be honest. Right now, I'm not exactly certain that I can pull up in my head what data she's referring to here. So I don't want to mislead and say that I know that that was prn dosing. That might have been monthly dosing and that these observations that she's talking about were made from diagnostic imaging that was obtained on patients that were dosed monthly. I don't know that.

Q. Okay. Well, Dr. Lalwani, in any event, is pointing to a lack of clarity as to whether monthly dosing is the best, correct?

A. That's correct.

Q. All right. There's another trial that was not discussed I don't think during your direct examination, which was the PIER trial.

You know the name PIER trial?

A. I'm familiar with that trial, yes.

Q. And the PIER trial was an effort to do a 12-week extended dosing interval for Lucentis, correct?

A. That is correct.

Q. And that was after three loading doses?

A. That's my recollection.

Q. And when they tried that in the PIER trial, you agree that the results were not as good as the PrONTO prn results, correct?

A. They were not as good, but they were still good.

Q. They were not as good.

A. I answered your question.

Q. Those results were viewed as somewhat discouraging with respect to attempting a 12-week dosing interval for ranibizumab, correct?

A. It depends by whom. I mean, they made it into the label for the drug. So they weren't discouraging enough not to have made it into the label.

Certainly the FDA thought that that was an appropriate dosing interval for some instances. I think you and I may have talked about this before at my deposition, but as I recall from the time, there were clinical trials that were using the PIER arm as their standard of care arm, and that was approved by the FDA.

So certainly it wasn't clear to everybody that that

was an inappropriate dosing regimen. I think it wouldn't have made it into the label if there weren't some people who thought it was absolutely appropriate.

Q. Dr. Albini, we did talk about that at your deposition. If we can pull up page 176 of your deposition and look at lines 16 to 19.

I asked you:

"Q And the results of the PIER trial were viewed as somewhat discouraging with respect to attempting a 12-week dosing interval, correct?

"A With ranibizumab, yes."

And that's the answer you gave at your deposition, correct?

A. I think that's not in contradiction with what I just said.

Q. We can take that down.

If we take -- so the PIER results were published in an article by Dr. Regillo in 2008; is that right?

A. To the best of my recollection, yes, and I have no reason to doubt that what you're saying is true.

Q. If we pull up DTX 4099, do you recognize this as the Regillo publication about the PIER study and its one-year results?

A. Yes, I do.

Q. If we take a look in particular at DTX 4099.0009 and

go down toward the bottom conclusion paragraph at the bottom right, Dr. Regillo wrote, "In conclusion, ranibizumab administered monthly for three months and then quarterly provided VA benefit to patients with neovascular AMD and was well tolerated. However, observations from the MARINA and ANCHOR trials suggest that the PIER regimen of dosing every three months after three monthly doses provides less benefit in VA on average than continued monthly dosing. Monthly dosing may be necessary in some patients to achieve maximal treatment benefit from ranibizumab."

Do you see that?

A. I do.

Q. Dr. Regillo did not propose in this article continued efforts at extended fixed interval dosing, correct?

A. I would have to read the entire article to see what else he may or may not have proposed. I think the words speak for themselves that there was a benefit and there was demonstrated safety of this treatment regimen.

The outcomes were not as good as monthly dosing, and monthly dosing may be necessary. Again, I would highlight the word "may." He did not conclude that it definitively was. And he really doesn't make much comments on other types of dosing regimens that may be appropriate.

Q. He certainly doesn't suggest any there, correct?

A. In these couple of sentences that I'm seeing here,

no.

Q. You would agree that -- we can take that down.

You would agree that what most people were doing in the 2010 to 2011 time period were individualized assessments to determine dosing, correct?

A. I believe that's true, yes.

Q. All right. I want to talk about another document that came up during your direct examination. You talked some about a quote from a Dr. Dave Brown who practices in Houston, if we take a look at Slide 37 from the opening.

I'm sorry. It was Slide 37 from the direct examination. Thank you.

And this is the quotation I'm referring to just so you have it in mind. Do you see that?

A. I do see that.

Q. Okay. And if we take a look, actually, at the underlying exhibits, DTX 2035, and go to page 0002 where that language is found, Dr. Brown made his comments about this regimen in the context of ranibizumab, right?

A. Ranibizumab and bevacizumab probably.

Q. Not Eylea?

A. That is correct.

Q. All right. And he limits his comment about who he would go to treat-and-extend with to the population of patients with good initial visual acuity or where it's the primary eye,

correct? That's what he says there?

A. That's correct.

Q. And he excludes individuals, if you look down at that last sentence, you have extrafoveal lesions, right?

A. Can you repeat the question? I'm sorry.

Q. He says, "I administer three doses in all cases except extrafoveal lesions," correct?

A. That's what he says, yes.

Q. That's an exclusion on what he is doing?

A. I mean, he doesn't say what he's doing in the cases of extrafoveal lesions, but, yes, he's making a differentiation in terms of his treatment strategy depending on the location of the lesion.

Q. Okay. He's also not talking here about an eight-week fixed extended dosing interval going forward, right?

A. I don't see any evidence. In fact, I think a disinterested reading of this would say that he is recommending a prn or treat-and-extend type of protocol. The assumption is that he -- after three loading doses or potentially in some cases after fewer loading doses, depending on these exclusions that he's putting in there, that he's making an assessment as he goes along about how the patient is doing. And also he comments here that he's extending the interval to ten weeks in certain situations, documenting that he's employing some extension in the technique.

I don't think that he's rigorously following any particular set-down treatment regimen that's written down somewhere, advised someplace. I think he's using his best clinical judgment in incorporating all the data, clinical data, that was available to the POSA at the time to make individualized decisions for individual patients about dosing frequency and the visit intervals.

Q. There's another part of this document I'd like to take a look at if we go forward to page 4.0004. And there's a comment partway down by Dr. Reichel right after "it is reassuring to know."

Do you see that part of the document?

A. I do.

Q. Am I saying --

A. Reichel.

Q. I hope I'm saying Dr. Reichel's name correctly. What Dr. Reichel says in response to a comment about -- in the prior paragraph where it is unlikely that treating more than often -- more often than is absolutely necessary is deleterious, Dr. Reichel says, "It may not be harmful, but we may be increasing the risk of endophthalmitis and the economic burden by treating more often than is absolutely necessary."

Do you see that, Dr. Albini?

A. I do.

Q. And Dr. Reichel is noting that you don't want to

treat more often than necessary, correct?

A. Yes, he is making that point.

Q. Okay. You would agree --

We can take that document down.

You would agree that the -- strike that. Let me start over.

In preparing your report, you did not identify any literature suggesting prior to 2011 that ranibizumab ought to be administered at an every-eight-week fixed interval, correct?

A. I think I found evidence that it was in some cases administered at an every-eight-week interval in that, for example, the dosing strategies that were employed by the prominent vitreoretinal specialists in that 2007 *Retinal Physician* roundtable shows a great deal of variability in both intervals between visits and intervals between injections, and I'm sure that there were, among those patients, certain patients that were being injected at every-eight-week interval.

So I'm sure that that did exist for some particular patients, but I think the overall concept is that the treatment regimen was being individualized to the patient and there are going to be some patients that are q8-week injection patients.

Q. I'm just going to try my question again.

You did not identify, in preparing your report, any literature suggesting that prior to 2011 ranibizumab ought to be administered at an every-week fixed interval?

A. What I did not find is any literature that specifically said that ranibizumab ought, must, should always be injected at a q8-week interval. I did not find that documentation. That is true.

What I did find was that, from the evidence of the way in which physicians were employing injection frequency and injection intervals, there is no doubt, I think, to the POSA that there were patients who were identified as patients who needed q8-week dosing, and those patients were indeed receiving injections q8-week. But it was not given as an ultimatum that all patients need to be q8-week. It was just patient-specific.

Q. Dr. Albini, I want to take a look at another document that was addressed during your direct testimony if we look at Slide 38.

You received some questions about a couple of what are called, colloquially, PAT Survey documents; is that right?

A. That is correct.

Q. And on this page in particular, I just want to direct your attention to the top line. And this corresponds to DTX 2040, correct?

A. That is correct.

Q. All right. And if you look at the top line on the right-hand side, it says "Anti-VEGF therapy q1 month."

Do you see that?

A. I do.

Q. And that's reflecting that 17.5 percent were using monthly dosing of -- monthly dosing of anti-VEGF agents, correct?

A. That's correct.

Q. And that is what was the first regimen recommended on the Lucentis label, right?

A. That is the first regimen recommended on the Lucentis label. Yes, it is.

Q. We can take that document down.

I'd like to look at Slide 26 from your direct examination, which references DTX 4056, I believe. And on the left-hand side you see the -- an excerpt from the ranibizumab prescribing label, correct?

A. That is correct.

Q. I think during your direct testimony you focused on the one injection every three months after the first four injections, is there in the second bullet.

Do you see that second bullet?

A. I mentioned both, I think, but yes. I see the bullet, yes.

Q. And to clarify, this is just the early Lucentis label that had wet AMD, right?

A. I think so. That's my recollection from reading it, but I'm struggling through the block label what's on there, but certainly -- it could be that, yes.

Q. Okay. The first regimen that was recommended on the Lucentis label for wet AMD was monthly, right?

A. I believe so, yes.

Q. And the second, the one that's here in the second bullet, starts "although less effective," right?

A. That's correct.

Q. And that's what Genentech was required to say in its label when recommending less than monthly, correct?

A. I don't know for sure that they were required to say that or that they just chose to say it, but that's what's stated there, yes.

Q. We can take that document down.

I have a couple of questions for you about the isotonic solution opinions that you offered in connection with Claim 6.

In relying on Dr. Rabinow in your testimony today, did you review his deposition transcript?

A. Yes.

Q. And my other question is you have not disclosed an opinion as to what specific range outside of isotonicity you would or wouldn't use to treat the eye?

A. I have no such opinion.

Q. Okay. I'd like to turn to talking briefly about diabetic macular edema, and I'd like to talk about some of the considerations for treating patients with diabetes.

You would agree that diabetics have a different set of comorbidities than wet AMD patients, right?

A. That is true.

Q. Diabetics have a higher rate of peripheral vascular disease than AMD patients?

A. That is true.

Q. Peripheral vascular disease can increase the risk of a stroke in a patient, correct?

A. That is true.

Q. You would also agree that during the -- what I'll call the pre-January 2011 time period there was, I think as we talked about earlier, an interest in avoiding treating patients more than was absolutely necessary, right?

A. That is true.

Q. And we've heard some about it in this case, but shots in the eye are not pleasant for anyone, right?

A. That is true.

Q. Okay. You're also not aware of any publications prior to 2011 that talked about using five loading doses for the treatment of DME, correct?

A. As we've discussed, there were a number of treatment regimens that would have resulted in five early doses, and given how the -- how it took more injections to achieve visual acuity results in DME than it did in AMD, I think that it was very likely that a lot of patients were being treated according

to prn and did wind up getting five monthly injections or more going forward.

So I do think that five monthly doses up front were given to a lot of patients, yes.

Q. That actually was not my question.

My question is you're not aware of any publications prior to 2011 that talked about using five loading doses for the treatment of DME?

A. Not directly in those terms.

Q. Okay. You're not aware of any that talked about six loading doses for DME either?

A. I don't think so.

Q. Okay. And you're not aware of any from before July of 2013 either?

A. Not that I can tell you with confidence sitting here right now, no. I hope I'm not forgetting anything.

Q. You also didn't identify anything during your direct examination publications that talks about five loading doses specifically for diabetic retinopathy, correct?

A. That is correct.

Q. And you didn't identify any publications that talked about six loading doses for diabetic retinopathy?

A. I don't recall anything that specifically stated six loading doses. But again, the caveat is that many dosing strategies resulted in patients getting six injections off the

top. So even though they weren't specifically labeled as six loading doses, there were many patients that were being treated in exactly that way.

Q. You have not quantified that in your report?

A. Quantified it?

Q. Right.

A. I think I've made the case that it's a permutation, I'd say even a common permutation, of some of the prn dosing regimens. I've made that case. I haven't quantified what percentage of patients got five initial doses, no.

Q. I'd like to take a look at the Diana Do 2012 article that has been discussed some in the case, including on your direct. If we can pull up DTX 3105.

This article -- and you agree Diana Do is a well-regarded retina specialist, right?

A. Yes.

Q. This article discussing the Phase II DA VINCI trial for DME, right?

A. That's correct.

Q. That's the Phase II Eylea trial for DME?

A. That's correct.

Q. And this article is what you might call the official write-up of the DA VINCI trial?

A. That's correct.

Q. At page 7 of the document, if we skip ahead into the

document, about midway down the left-hand column, there's a discussion of safety issues regarding anti-VEGF agents in DME patients. About partway down she writes, "Most of the systemic adverse events observed were attributed to the underlying medical conditions and cardiovascular comorbidities of these diabetic patients."

Do you see that?

A. I do see that.

Q. And likewise she says, "Studies have shown that individuals with diabetes seem to have an approximately two- to fourfold greater risk for both heart disease and stroke," right?

A. That is true.

Q. And that is consistent with the understanding at the time that diabetic patients have special comorbidities that can expose them to adverse events, right?

A. That sounds fair.

Q. She also notes, if we go down a little bit further, that the DA VINCI study was not powered sufficiently to assess the relationship between VEGF inhibition and systemic adverse events or mortality, right?

A. That is correct.

Q. That is her communicating to the reader of this article a limitation on what can be concluded from this article, correct?

A. That is correct.

Q. If you take a look a little bit -- let me ask you a different question.

In this write-up Dr. Do -- you've read this article, right?

A. Yes.

Q. Dr. Do didn't propose five loading doses in this article?

A. No.

Q. And, actually, if we go down a little bit further on page 7, in the paragraph starting "because," she writes, "Because there is considerable individual variation in the progression of DME, patients could benefit from an individualized as-needed treatment regimen," correct?

A. I see that.

Q. That's what she wrote in this article?

A. That's correct.

Q. And if you go down a little bit further in that same paragraph, she wrote, "The results of this study support additional Phase III clinical studies with every-two-month dosing of VEGF Trap-Eye after an initial loading dose."

Do you see that?

A. I see that.

Q. That's what Dr. Do, the lead investigator on the study, wrote as a take-away from the study, correct?

A. I believe so, yes.
Q. We can take that document down.
You agree that DME is a slower-progressing disease than wet AMD?
A. I think that's true.
Q. And that is something that has been known for a while, correct?
A. That's correct.
Q. Lucentis was approved for DME in August of 2012. Does that sound about right?
A. That sounds about right.
Q. The dose amount in the FDA-approved label for DME was .3 milligrams, right?
A. That's correct.
Q. And that's lower than the dose amount that was approved for AMD, which is .5 milligrams, correct?
A. That's correct.
Q. You understood that the reason for the lower dose in the Lucentis label was that the FDA was concerned about possible systemic side effects from a higher dose of ranibizumab, right?
A. That in conjunction with the fact that there was no significant benefit to the higher dose, yes.
Q. All right. I'd like to change topics a little bit and start talking about the Lalwani 2009B article -- or the

Lalwani review article from 2009, if we pull up DTX 2733.

And this is an article you addressed on your direct testimony, right?

A. That is correct.

Q. You would agree that in her 2009 review article that we're looking at here, Dr. Lalwani does not propose an ultimate solution for how to treat DME, does she?

A. I'm just thinking about that question. I think physicians very rarely propose ultimate solutions on treatment. She does not -- she's reporting data that's available and discussing some interpretation of that data that may help educate her therapeutic decisions towards her patients. There is no ultimate treatment regimen proposed or advised.

Q. If you take a look -- if we go forward a little bit to .0002 of this document, there is a paragraph partway down where she writes, in connection with the trial she's been discussing, "Both these higher-dose trials demonstrate a clinical and statistical superiority to sham treatments in terms of visual acuity and decrease in CRT. Additional trials will be necessary to determine the most effective dosing and treatment interval strategies," right?

A. I see that the article says that, yes.

Q. That's what she disclosed after going through her review of some of the current DME trials, right?

A. I think she's specifically here talking about two

trials. I'm not exactly aware of which two trials she's talking about.

Q. All right. If we take a look at the conclusion of this article.

A. Okay.

Q. She writes in part, going down toward the bottom there, "Unlike neovascular AMD, which has in most cases responded to direct VEGF blockade, it appears likely that the treatment of DME will be more of an art form with tailoring of treatments for individual patients," correct?

A. That's what she said, yes.

Q. She's proposing an individualized treatment approach?

A. I'm just trying to understand what the context of this sentence -- do you mind repeating the question again?

Q. I'll get it as close to the same as I can.

Here in this article at her conclusion for treating DME, unlike she says AMD, it "will be more of an art form with tailoring of treatments for individual patients," and that is the approach she is proposing.

A. I think what she's trying to draw a distinction between is that in AMD -- and I hope I'm not taking this out of context, but my reading of this here is that what she means by direct VEGF blockade is that an intravitreal anti-VEGF injection is going to be the most beneficial and probably be used consistently among the entire population of exudative AMD

patients, whereas in DME patients the treating physician may have to take into account other factors -- I'm not exactly sure what, but one could envision maybe the overall health of the patient and the risk for systemic side effects -- in choosing among the different treatment strategies across different pharmaceutical products that might be most appropriate for that patient.

I think that's what she's trying to say because I'm not sure direct VEGF blockade, how that's in contradistinction to tailoring treatment for individual patients. I don't think she's just talking about prn dosing because that's also direct VEGF blockade, right? So I think she's talking about choosing among various different types of treatment strategies that are listed in the second half of this review article.

Q. Dr. Albini, this article is what's sometimes referred to as a review article?

A. That's correct.

Q. And she does not -- you've studied this in connection with your testimony today?

A. I've read it a few times, yes.

Q. She does not identify any trials in which the investigators were experimenting with different loading doses, correct?

A. She describes a few trials, including CLEAR-IT that we've talked about and RESOLVE trial and so on, that have

loading doses. So, no, I don't think your statement is correct. She describes quite a few trials that have -- that are experimenting with loading doses.

Q. She does not identify any trials that are experimenting with different numbers of loading doses against each other, correct?

A. I'm just trying to think. The READ and the RESOLVE. I don't think within each -- any trial there are arms pitted against each other with different loading dose strategies the way they were in CLEAR-IT. I think that's true, yes.

Q. I'd like to touch briefly on a different -- I'd like to go to one other article. One of the trials that Dr. Lalwani talks about is the RESOLVE trial. Do you recall that?

A. I do.

Q. And let's pull up DTX 4209. And this is a publication summarizing the 12-month RESOLVE Phase II study; is that right?

A. That's correct.

Q. And RESOLVE trial was experimenting with different dose amounts of ranibizumab and DME, right?

A. It had a dose-doubling component to the methodology where, if patients met certain clinical criteria, the dose, for a particular injection, could be doubled, yes.

Q. The RESOLVE trial did not have five loading doses, right?

A. I believe it had regular loading doses. I don't want to say off the top of my head what the number is. I would guess it's three, maybe four. Maybe you can tell me. But I think that it did have then prn dosing. So, again, there were some patients that would have -- would have indeed received five regular doses at the beginning of the trial. That's, at least, my recollection of the way this study was designed.

Q. It did not involve anything called five loading doses. You know that?

A. I don't believe that the terminology that you're proposing was used, but I do want to offer to the Court that there were some patients who did in this trial, to the best of my knowledge, receive five regular doses at the beginning of the trial, yes.

Q. I'd like to go to the conclusion paragraph. This is by -- the lead author here is Pascale Massin. Is that right?

A. I'm not sure how to pronounce his name. I'm with you on this one. Massin? I don't know.

Q. That's fine.

A. He's French.

Q. That's fine, Dr. Albini. So we'll share that same perhaps botched pronunciation.

A. Okay.

Q. So if we go down to the bottom of -- I'm actually looking to go down to the bottom of .0006, or the paragraph

that starts "given the nature of diabetes." It's actually -- yes, thank you.

And if we pull that out, what Dr. -- we'll call Massin says is "Given the nature of diabetes and variability in patients with DME with regard to disease progression and vision loss, there is a need for an individualized treatment regimen."

Do you see that?

A. I do see that.

Q. And what Dr. Massin concluded in his resolve write-up?

A. I do see that, yes.

Q. We can take that down.

As of late 2010, there were not any approved anti-VEGF treatments for DME at all, were there?

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

MS. OBERWETTER: I'm sorry. Do you want me to repeat?

THE COURT: Yes, please. Sorry.

MS. OBERWETTER: Oh, of course.

BY MS. OBERWETTER:

Q. As of late 2010 there weren't any approved anti-VEGF treatments to diabetic macular edema at all, correct?

A. I don't think that ranibizumab was approved by 2010. I recall that Macugen, I think, did get a label for DME at some

point, but I can't recall right now off the top of my head what year. But anyway, it probably doesn't matter.

But I just want to put that in there because Macugen may have been approved. I'm not 100 percent certain about that. But to the best of my recollection, ranibizumab was not.

Q. Okay. As of late 2010, Regeneron had not reported the results of its Phase II DA VINCI trial, its one-year Phase II DA VINCI trial, correct?

A. I don't think so.

Q. Okay. Do you know of a doctor named Ursula Schmidt-Erfurth?

A. Yes.

Q. She is well known to the retina community?

A. Yes.

Q. If we take a look at DTX 8151-A -- and we have appended the A to it because it was given to us as part of a broader 8151 collection -- this is a review early about the state of DME treatments.

Do you see that?

A. I do.

Q. It's the same type of article as the Lalwani 2009 review article we were just looking at a few minutes ago, right?

A. I don't remember if I've ever read this article in its entirety, but I'm assuming. It certainly looks like it on

the surface of things, yes.

Q. The date of this article, if we look at the bottom of the first page in the right-hand corner or the left-hand -- that's fine -- is -- actually, if we go down to the publication date in the bottom right, it's December 2010.

Do you see that?

A. I do.

Q. If we take a look at page 4 of this article, there's a discussion of the DA VINCI Phase II trial on this page.

Do you see that?

A. I do now, yes.

Q. Okay. And what Dr. Schmidt-Erfurth -- first of all, she identifies the ongoing DA VINCI trial up there at the top, right?

A. I see.

Q. And then she says, "The study will follow these patients for 52 weeks, and it will be interesting to see if the results suggest that the dosing frequency with anti-VEGF compounds can be reduced from monthly injections based on these results," correct?

A. I see that.

Q. All right. She doesn't offer a prediction there based on the work in her review article, correct?

A. She doesn't here. She's saying that she's interested to see what the outcome is, but I think you cannot infer either

a positive or a negative anticipation of success from what she's saying. Sounds like a very neutral statement.

Q. The neutral statement doesn't offer a prediction?

A. Of course not, no.

Q. If we go to the conclusion of her article that spans pages 5 and 6, she notes, first of all, that laser was still the standard of care, correct? If you look at "Thus the current standard of care is still appropriate."

A. I think one has to be careful when interpreting this comment about the standard of care. I think that, first of all, this physician doesn't practice in the United States; so she's practicing in a community that has very different regulatory bounds on it. And they're of some importance when discussing the treatment of DME in that time period prior to 2010 because in that time period bevacizumab used off-label was increasingly used and, I'm sure by 2010, was fairly routinely used in the treatment of DME.

So in European countries -- she practices in Austria -- I think there is -- there was actually a slower acceptance of bevacizumab and there was more heightened regulation of having to use the governmentally approved substance.

So in her treatment environment, she may not have had an anti-VEGF available for her to use for AMD, but that is not the case for sure in the United States after the advent of

bevacizumab in 2005.

Q. What she wrote midway through that paragraph was "This article presents an overview of the current state of knowledge regarding treatment mechanisms and modalities under investigation for DME," correct?

A. I see that she wrote that.

MS. OBERWETTER: Move to admit into evidence DTX 8151-A.

THE COURT: Any objection?

MR. McLAUGHLIN: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 8151-A was admitted.)

BY MS. OBERWETTER:

Q. Dr. Albini, you've cited this Dr. Schmidt-Erfurth article a couple of times in some of your IPR declarations; is that right?

A. I'll be honest. I don't recall the specific areas where I've cited it, but I'm not surprised to hear that.

Q. And just to refresh your recollection, if we pull up DTX 8151-B, which again we have marked individually out of a broader DTX 8151 compilation, this is your declaration from one of the IPR proceedings where you have offered written testimony?

A. Yes.

Q. And if we go down to paragraph 62 on page 34.

And you can see down toward the bottom of that excerpt that you have cited Dr. Schmidt-Erfurth's December 2010 review article previously, correct?

A. Yeah. Let me just -- I'm sorry. There's a lot of parentheses here. I'm just trying to figure out what I was trying to say.

Yeah, I have to admit I'm not 100 percent certain that that text in brackets there, "The ranibizumab PrONTO study suggested that flexible OCT-guided treatment would sustain visual acuity with fewer injections, a concept which has since become a popular model in clinical practice, particularly in Europe."

I'm assuming that's from that article, but I'm not 100 percent certain. But if you're asking me whether I had cited this article, if that's a correct reference, yeah, I did. I see that.

Q. Okay. You did not include Dr. Schmidt-Erfurth's December 2010 review article about DME on your materials considered list for this case, correct?

A. I don't recall. I don't think so, but I'm not certain.

Q. Okay. We can take that document down.

Dr. Albini, I want to go back to Slide 152 from your direct examination. And Slide 152 we looked at a little bit earlier for its listing of some of the clinical trials that

existed in the pre-2011 time period.

Do you see that?

A. That's correct.

Q. You cite a READ 1 trial, correct?

A. That's correct.

Q. There was also a READ 2 trial, wasn't there?

A. That's correct.

Q. You chose not to include READ 2 on this chart?

A. That's correct.

Q. And that was your decision?

A. That's correct.

Q. You actually cited READ 2 in your opening report in this case; is that right?

A. I believe so.

Q. Let's take a look at your -- an excerpt of your opening report. If we go to PTX 487.

And you recognize this as a copy of your opening report from this case?

A. Yes.

Q. And if we go to paragraph 327 of your report.

THE COURT: Before we do that, Counsel, again recognizing there's confidential information in this report, any concerns from defense?

Negative head shakes. Okay.

MR. McLAUGHLIN: No concerns from us, Your Honor.

THE COURT: Understood.

Go right ahead, Counsel.

MS. OBERWETTER: Thank you, Your Honor.

BY MS. OBERWETTER:

Q. If we take a look at paragraph 327 of this report, you've got a reference to Dr. Lalwani's article and then a reference to the READ 1 article, and then at the last sentence says, "The author further notes the READ 2 program that followed READ 1 employed monthly dosing through 12 months."

Do you see that?

A. Yes.

Q. Okay. Now, you didn't put READ 2 on your list of clinical trials, right?

A. It's not on that list that we talked about, that's correct.

Q. All right. READ 2 did not actually employ monthly dosing, did it?

A. You know, I have to apologize. There's so many different trials and so many different but yet very similar dosing regimens in these trials. Obviously, when I wrote this, I thought it did. If I'm in error, I apologize.

But it looks -- as I read my text here today, it looks that I was under impression that it employed a monthly dosing regimen through 12 months.

So the way you're asking the question, I'm guessing

that I was wrong about that. I apologize if that's true. There's a lot of different studies here. So not that I didn't take this seriously, but these reports are very, very long, as you know, and there are many, many citations here.

But please tell me if I did get that wrong.

Q. Let's take this document down.

Let's take a look at a document that we've marked as PTX 3304 that we can pass around.

MS. OBERWETTER: Approach the witness, Your Honor.

THE COURT: You may.

BY MS. OBERWETTER:

Q. Dr. Albini, what I handed you -- I've been asked to correct the record -- is actually PTX 3340, just so the number is correct.

A. I see that.

Q. Does this -- the title of the article is "One-Year Results Showing Ongoing Benefit of Ranibizumab for DME."

Does this article refresh your recollection that there was a different clinical trial regimen in READ 2?

A. As I'm skimming it here, yes. I see that this article describes "Beginning at six months re-treatment was performed on a prn basis." I'm assuming that's in all the arms. I'm not sure.

But, anyway, I see that it's certainly not 12 monthly injections, which is what I inferred from my opening report

that you showed me.

Q. Okay. I gather you're not familiar with the READ 2 trial even though you cited it in your opening report?

A. I believe that I may be confused about the exact dosing regimen. I wouldn't say that I'm not familiar with the trial, but I would say that I can't recollect the exact dosing regimen.

Q. Is this a trial that you chose not to include on your list of trials or one that you didn't think about?

A. I think I thought about it, as evidenced by the fact that it was cited, although possibly incorrectly. So I wouldn't say that I didn't think about it.

I think that it may have not been evidence -- either because of the timing of when the results were announced or because of the data that was there, it may have not been the best trial to choose to make the point that I was trying to make.

So I don't think that the work that's been submitted is an exhaustive compendium of all the clinical trials with anti-VEGFs that were available at that time. I certainly don't think that this was left out with any sort of covert intention or for some reason.

I think there's only -- so, I mean, this took already six hours today. I don't know how many more trials we could have gone through. There's a limit to what all can be covered.

But so my intention wasn't to have been exhaustive about everything that was there.

Q. The date of this article is February 1, 2010, correct?

A. Of this particular publication. I don't know when the formal publications came out. I'm not exactly sure what the context of this -- this is clearly an internet -- oh, looks like this is an article from *Ophthalmology Times*, and I assume that's dated February 1st.

Q. There were -- if you look at the number of patients who are described in READ 2, it's 126, correct?

A. That's correct.

Q. That's more than ten?

A. I would not disagree with that.

Q. More than ten in the READ 1 trial?

A. That's true.

Q. In the READ 2 trial you would agree that there was a six-month phase where various arms were tested, if you look down at that fifth paragraph of this document.

A. Sorry. The fifth paragraph of the document. The paragraph that starts "initially patients"?

Q. Yes.

A. Okay. I see what's described there.

Q. First of all, one of those arms had a group that received an injection of .5 milligrams at baseline in month one

and in month three and in month five.

Do you see that?

A. I see that. So that sounds like three loading doses and then q8-week interval.

Q. Could that be two loading doses if you do two and then go further?

A. I think the supposition usually in clinical trials is that the patients are treated at month zero. So there's a first initial treatment, and then -- unless this is a very unusual trial and they didn't treat on the first visit, but typically they're treated at zero.

Q. So, Dr. Albini, I don't want to get too hung up here, but there's one at baseline and one at month one and then they skip one, correct?

A. You're right. You're right. I apologize. Yes. So two monthly loading doses followed by two q8-week loading doses. Yes, that's true.

Q. All right. And then starting in the next paragraph, it notes that "Beginning at six months, re-treatment was performed on a prn basis."

Do you see that in the next paragraph?

A. I do see that.

Q. And then it says, "Starting at six months, patients in the ranibizumab arm could be re-treated no more than once every two months and laser re-treatment no more than once every

three months."

Do you see that?

A. I see that.

Q. And that was a every-two-month prn schedule, correct?

A. That's what it sounds like from this description, yes.

Q. All right. Now, at the top of this same page that we've been on, there's a quote from Dr. Do that says, "The results from the READ 2 trial Phase II study demonstrate this anti-VEGF agent has biological activity in treating DME," and then it goes on to say that "More frequent injections may be needed to achieve enhanced visual acuity benefits."

Do you see that, sir?

A. I do. I see it.

Q. And that's a point that Dr. Do made in this article about the READ 2 one-year results in ranibizumab.

A. Is that a question or a statement?

Q. That's a question.

A. Yes, I believe so.

Q. And then if you go to page 2 of this document, it notes that by the end of 12 months the ranibizumab group had gained a mean of, I think, 6.69 letters.

Do you see that?

A. Not really.

Q. It's down under "Outcomes Comparison."

A. "Outcomes Comparison." I see that.

Q. And then if you go down a little further where Dr. Do concludes the article, she notes that "Genentech's Phase III trials for DME were testing monthly ranibizumab," correct?

A. She does say that, that's correct.

Q. And you know that those were the RISE and RIDE trials that were ongoing as of this point in time?

A. That's what she says there, yes.

Q. That's not just what she says. You know the RISE and RIDE trials were ongoing at that time?

A. That's correct.

Q. You did not mention the RISE and RIDE trials in your direct examination either, right?

A. That's correct.

Q. We can take that down.

Now, the READ 2 trial actually continued into a third year, correct?

A. I'd have to refresh my memory.

Q. You're not familiar with what happened in year three of the READ 2 trial?

A. I don't know that I can give you all the details of it. I don't -- I would have to refresh my memory. I don't think I've looked at the three-year results of the READ 2 trial in quite some time.

Q. Let's take a look at another exhibit that I will pass

around, which will be PTX 3342.

MS. OBERWETTER: And before I proceed with this one, I'd move to admit PTX 3340.

THE COURT: Any objection to 3340?

MR. McLAUGHLIN: We do object, Your Honor. So we've been scrambling over here a little bit to find out when it was produced to us. Doesn't appear on their original pretrial exchanges of their exhibits. This is the first time we're aware of this being offered to us. So we do object to it being moved into evidence.

THE COURT: Previously disclosed, Counsel?

MS. OBERWETTER: This is impeachment material, Your Honor.

THE COURT: Overruled.

BY MS. OBERWETTER:

Q. Dr. Albini, do you have PTX 3342 in front of you?

A. Yes.

Q. Okay.

THE COURT: Yes, Counsel.

MR. McLAUGHLIN: Your Honor, it's my understanding that the parties agreed that impeachment materials would not be moved into evidence.

THE COURT: We're going to have a discussion about the parties' agreement. The rules of civil procedure permit the use of impeachment material solely for that purpose. It

wasn't previously disclosed. At this point the objection is overruled.

BY MS. OBERWETTER:

Q. Dr. Albini, you have PTX 3342 in front of you, correct?

A. I do.

Q. And this relates to the three-year outcomes for the READ 2 trial; is that right?

A. That's correct.

Q. And the first author on this paper is Diana Do?

A. That's correct.

Q. And the dates listed on this paper, if you go over to the middle right of the first page, are -- there's a publication of 2013 but also published online October 8th, 2012.

Do you see that?

A. I'm sorry. Published online 2012. I'm not -- oh, over here. I see it. Yes, I see it.

Q. And if we take a look at page 142 of this article under the header "Need for Ranibizumab Injections in Year 3."

A. I see that.

Q. Do you see that page? And it says, "During year three, 14 to 28 patients, 50 percent, in the ranibizumab group met the re-treatment criteria at more than six visits and thus needed injections more frequently than every two months."

Do you see that?

A. I see that.

Q. Okay. And that is what Dr. Do is reporting happened in year three of the READ 2 trial?

A. That appears to be what she's reporting, yes.

Q. And if we take a look at the bottom of page 143 and continuing on to the top of page 144.

If we can pull that up.

And if we look down a little bit, please feel free to read that paragraph. But it says, "Despite a good visual outcome, substantial residual macular edema was noted in several patients, suggesting that receiving intraocular injections of ranibizumab only as frequently as every two months was not sufficient for many of them."

Do you see that?

A. I see that.

Q. And that is the conclusion that she reported in writing up year three of the READ 2 study, right?

A. I see that that's what she reported, yes, or concluded, yeah.

Q. And this is not a component of the READ 2 trial that you included either in your report or in your statements on direct examination, correct?

A. That's correct.

MS. OBERWETTER: Move to admit PTX 3342.

THE COURT: Any objection to 3342?

MR. McLAUGHLIN: Your Honor, at this time, yes, we do object for the same reasons as the previous one. And just to get some clarity, we're not objecting to the use of this on impeachment; our sole objection is its movement into evidence with respect to this one and the prior document.

THE COURT: Understood. For same reasons, overruled.

So the record's clear, 3340 and 3342 will be deemed admitted, recognizing it is being used as impeachment and will be afforded the weight it should be moving forward.

MR. McLAUGHLIN: Is it all right to address that in the posttrial briefing?

THE COURT: I'm sure if Madam Court Reporter has it down, of course, Counsel.

(PTX 3342 and 3340 were admitted.)

MR. McLAUGHLIN: Thank you, Your Honor.

MS. OBERWETTER: We can take that document down.

BY MS. OBERWETTER:

Q. There's a different document that was addressed in your direct examination, Dr. Albini, which was DDX 6.92, so Slide 92.

Dr. Albini, you have this slide back up in front of you?

A. I do.

Q. And it's referencing DTX 4129, correct?

A. That's correct.
Q. And I'd like to -- first of all, this is an internal Regeneron document that you cited, right?
A. That is correct.
Q. And you cited it with reference to that "no more than three to six doses" language down in the bottom right hand of the page?
A. Right. That that would be a target product profile for aflibercept in DME.
Q. You've not found a publication that includes the language "no more than three to six doses," right?
A. I have not.
Q. Okay. It also lists -- it says monthly -- it says, "No more than three to six doses including monthly loading for first three months."
Do you see that?
A. Yes.
Q. And you are not -- first of all, that's the only number of loading doses that appears on this page, is three?
A. That's the only number of doses termed as loading doses, but the range of up to six doses given in the first six months is described there.
Q. So. You -- I apologize.
A. That would be a dose every month for six months.
Q. You have not cited or relied on any testimony

explaining the reference to induction, correct?

A. Explaining the reference for induction?

Q. Let me -- go ahead, Doctor.

A. Well, I think what I am citing here is that within Regeneron, they were discussing the need for three to six doses within the first six months in initiating treatment, which is the way that I read that -- the term "induction" there.

Q. My question is a little bit different.

You haven't relied on any fact witness testimony to explain what the reference to induction is there, correct?

A. I have not.

Q. All right. There's also nothing in that section of the document about fixed extended interval dosing, correct?

A. I do not see anything about fixed interval -- extended interval dosing.

Q. When was this document written relative to when the DA VINCI trial commenced?

A. That, I don't know.

MS. OBERWETTER: We can take that document down.

I'm going to change topics a little bit.

THE COURT: Counsel, if we're going to do that, good time to take a break?

MS. OBERWETTER: This works fine for a break, Your Honor.

THE COURT: Okay. We'll break. I don't want to

interrupt the flow, but let's do that.

Doctor, you continue to remain midstream; so no one can converse with you. No one is being rude or discourteous. It's just the rules we abide by. You get to step down, take a personal comfort break, whatever you need, sir.

THE WITNESS: Fair enough. Thank you.

THE COURT: We'll take a break and be back in ten minutes. Thank you all.

(A recess was taken from 2:57 p.m. to 3:11 p.m.)

THE COURT: Counsel, are you ready to proceed?

MS. OBERWETTER: I'm ready to proceed, Your Honor.

THE COURT: Doctor, are you ready?

THE WITNESS: I sure am.

THE COURT: Great. Go right ahead.

BY MS. OBERWETTER:

Q. Dr. Albini, I'm going to return briefly to some of the opinions you've offered on Claim 6 and the isotonic solution limitation we were talking about earlier.

A. Okay.

Q. You would agree there could be formulations, comfortable and nonirritating, that are outside of the range of isotonic, right?

A. Not through what I've learned from Dr. Rabinow. So, no, I'm not sure that what you're saying is true.

Q. You don't know anything about that absent Dr. Rabinow, correct?

A. I am definitely relying on him because I have not offered myself as an expert in formulation. So I am using his teaching in addition to my reading of Dixon to make a conclusion about that issue.

Q. You would agree that, as of 2011, it was not known publicly what formulation Eylea was?

A. I would anticipate that that's true. I don't know for a fact what exactly about the formulation of Eylea was known in 2011. So I can't be 100 percent certain, but I would guess that the exact -- that the exact formulation was not known.

Q. You would agree that it was not public in 2011 what formulation was used in the Phase III trial described in Dixon, correct?

A. When you say what formulation, I believe that it was -- it's -- that the POSA and myself as a POSA would have interpreted that the formulation used in the clinical trials was the same as the formulation that was used in the commercially available product.

Q. The commercially available product was known later, right? Not in 2011?

A. Was known later?

Q. Right. It came onto the market after the Phase III

trials, correct?

A. Yes, but it was known well before it came out to the market.

Q. You would agree that it was not public in 2011 what formulation was used in the Phase III trial described in Dixon prior to Eylea coming onto the market?

A. As I've said, I think that the POSA would have known that the formulation that's used in the clinical trials is the same as the formulation that's brought to market.

Q. You know that once the product is brought to market, not before, correct?

A. No, I think you'd know that the product that will be brought to market is the product that's studied in the trials. I think there's an assumption that it's the same product; otherwise, we wouldn't use the clinical trials to help guide us with the use of new product.

Q. You have not identified a publication that spells out the formulation of Eylea publicly prior to it coming onto the market?

A. I have not.

Q. Okay. I'm going to change topics.

I'd like to -- you offered some opinions on your direct testimony about the '747 patent and anticipation.

Do you recall that generally?

A. I do.

Q. So let's pull up DTX 2730 and go to Example 17, which is at Column 20.

Dr. Albini, you agree that Example 17 does not itself talk about diabetic macular edema, correct?

A. I believe that this patent directs itself at angiogenic eye disorders.

Q. So my question was different. There's a title on Example 17 that says "Treatment of Age-Related Macular Degeneration," correct?

A. Yes.

Q. Example 17 does not talk about DME?

A. That is correct.

Q. Example 17 does not contain a reference to a loading phase of dosing a patient, correct?

A. It does not use that term "loading phase," that is correct.

Q. And, in fact, Example 17 discusses repeated visits back to the doctor during the first month, right?

A. It does.

Q. You have to go outside of the embodiment of Example 17 in this patent to find DME anywhere, right?

A. I believe that's true.

Q. And in forming your opinions in this case, you did not attempt to calculate the total number of regimens that are contained in Example 17, correct?

A. I did not quantify that, no.

Q. Or in the patent as a whole, correct?

A. That's correct.

Q. And I think you testified at your deposition you weren't interested in doing that because you don't like to do infinite things; is that right?

A. I don't recall if that's exactly what I said, but I think I would be very bad at doing something that's infinite.

But there's a very large number of possible regimens that are covered by this if one doesn't have a limit on the time extension that you're looking at.

But within a 6-month period or a 12-month period, there's a more limited number of regimens. But even within that period, I have to admit I have not calculated the exact number of permutations possible.

Q. Looking at Example 17 during your deposition, you referred to it as "infinite"; is that correct?

A. Honestly, I don't remember that text in the deposition, but I can't see why you would be misleading me. I'm sure that I did.

Q. I'd like to talk a little bit about the September 2009 press release that was the subject of your direct testimony, if we can pull up PTX 2617.

And this is the September 2009 Regeneron press release that you testified about.

A. That's correct.

Q. There is a section on page 2, if we scroll forward to that, that talks about the Phase II development program in DME.

Do you see that right above "about wet AMD"?

A. I see that.

Q. Now, that discussion talks about three monthly loading doses on its face, correct?

A. Yes.

Q. And after the loading doses, any additional doses are based on prn assessment, correct?

A. That's correct.

Q. Those are not going to be fixed interval doses, right?

A. The most frequently they can occur is every month. So in that sense, they're fixed interval in that they certainly can't happen at every two weeks or every three weeks or something like that. So they are partially fixed. But they are not fixed in that patients are not going to be necessarily getting an injection every single month, although they might.

Q. In your anticipation analysis that you performed in this case, you're also assuming that these are monthly prn visits, correct?

A. That's correct.

Q. Okay. And let's take a look at Slide 52 from your direct examination. This is a slide that you used to talk

about anticipation in connection with the September 2009 press release; is that right?

A. Yes.

Q. Giving someone three loading doses and then a prn regimen does not necessarily result in that person receiving a dose at Week 12, correct?

A. The Week 12 dose is one possibility from that dosing regimen, but it is not necessarily going to occur.

Q. And if you give someone three loading doses and then you give them a prn dose at Week 12, that also does not necessarily result in that person receiving a dose at Week 16, correct?

A. It would -- correct. It would depend on the assessment of the patient at that visit.

Q. You would agree that the terminology of "loading doses" implies an early adherence to monthly treatment regardless of patient outcome for a certain number of doses, correct?

A. That sounds fair.

Q. Okay. And prn doses after loading doses would be quite different because it would include regular visits but doses only when needed, right?

A. That's correct.

Q. We can take that slide down.

I want to return briefly to we talked about the

RESOLVE trial a little bit in connection with dosing studies for ranibizumab.

Do you recall that?

A. I do.

Q. You have not undertaken an analysis of the RESOLVE trial to understand if anyone in that trial got five initial doses, whether you call them loading doses or not, right? That's not an analysis you performed?

A. You mean historically whether that actually occurred to go back and look at the trial data and find how many patients may have obtained that? I have not had access to the data to be able to do that.

Q. Okay. You haven't found out how many, if any, correct?

A. I haven't found out how many, that's true.

Q. Okay. I want to change topics a little bit. And let's look at Slide 91, which was part of your direct testimony.

There's a reference in the bottom line to the Copernicus trial. Do you see that?

A. I see that.

Q. You mentioned there the Copernicus trial you refer to always having six monthly loading doses on that page. Do you see that?

A. I do see that.

Q. Let's take a look at DTX 3198, which should be another press release.

And we're back at a September 2009 press release, and if we go again to page 2 of the press release, there's a reference in that top paragraph to the COPERNICUS trial.

Do you see that?

A. I do.

Q. There's no terminology there that refers to six loading doses, correct?

A. I don't see the term "loading doses," but again, it seems to describe six monthly intravitreal injections of VEGF Trap-Eye.

Q. Dr. Albini, it refers to six monthly injections when there is a primary end point of six months, correct?

A. That is correct.

Q. We can take that document down.

I'm going to change topics a little bit. I have a few questions for you about VEGF agents generally. You would agree that early on in the development of aflibercept, researchers recognized the promise of targeting angiogenesis as a therapeutic strategy for treating diseases characterized by increased vascularity?

A. Specifically neovascularization, but yes.

Q. You agree that angiogenic eye disorders are generally characterized by increased vascularity?

A. Specifically new vessels and also by decreased patency of less of the vessels where there's fluid that leaked into the retina. By both those characteristics, yes.

Q. Prior to the January 2011 date that we've been talking about, there was literature that, in your view, that VEGF Trap may be useful in the treatment of retinopathies given the contribution of pathological angiogenesis, correct?

A. That is correct.

Q. You also believed that the medical community believed before January 2011 that VEGF Trap-Eye could translate to good clinical efficacy outcomes, correct?

A. I think that was evidenced by a number of the publications that were reviewed towards the end of my direct testimony.

Q. Okay. And that's good clinical efficacy outcomes for angiogenic eye disorders, correct?

A. That is correct.

Q. And you believe that subsequent work by Regeneron reinforced VEGF Trap's potential as a possible angiogenic therapy for vascular eye diseases, correct?

A. That is correct.

Q. You understand that some of the claims in the patents use the word "approximately"; is that right?

A. I've seen that, yes.

Q. And the terms "approximately every four weeks" and

"approximately monthly" can be understood as meaning the same thing in the context of anti-VEGF dosing regimens, correct?

MR. McLAUGHLIN: Objection, scope. It's beyond the scope of his testimony, Your Honor.

MS. OBERWETTER: Your Honor, it's in his report, which is context for the patent claims which he is purporting to talk about in this case.

THE COURT: Is it in his report, Counsel?

MR. McLAUGHLIN: If it is, I would like to see it. I'm not sure exactly what Ms. Oberwetter is referring to.

MS. OBERWETTER: Why don't we pull up paragraphs 144 to 145.

BY MS. OBERWETTER:

Q. Dr. Albini, in your report you wrote that, in your opinion, you viewed --

THE COURT: Hold on, Ms. Oberwetter, before he gets any questions.

Counsel, does that fall within this line of questioning?

THE WITNESS: I see that.

THE COURT: One second, Doctor. Thank you.

MR. McLAUGHLIN: I see the paragraphs that counsel's referring to, but this is not something where he provided an opinion on what the word "approximately" means. What he's talking about here is the difference between every four weeks

and monthly with respects to Claim 11, I believe -- yeah, Claim 11 of the '601 patent.

But he has not offered an opinion, nor did I ask one on his direct, what his views of "approximately" are in this claim.

THE COURT: Okay.

MS. OBERWETTER: Two responses Your Honor. One is we heard three hours of testimony this morning about the claims, which he is interpreting and applying, and I think this is relevant to his understanding of them.

Point two, I would rather do this all as a whole rather than figure out do we have to recall Dr. Albini in our case? I'd rather do this today. It makes sense to do it. This is part of his opinions that were disclosed and that he has said are his views.

THE COURT: Understood. Overruled.

Ask your question again, Counsel.

BY MS. OBERWETTER:

Q. Dr. Albini, you understand the terms "approximately every four weeks" and "approximately monthly" as meaning the same thing in the context of anti-VEGF dosing regimens, correct?

A. I think that what I was trying to say here -- and it is somewhat confusing with this language and the way this claim is written, but I do think that four weeks and monthly have an

equivalence to them. They are nearly the same thing. There may be differences in the way that "approximately" modifies the four-week period versus the monthly period.

So as to say as the time around the four-week period that's approximated, the range of time that would fall within that "approximately every four weeks" may be different than the range of time that falls in the term "approximately monthly" so that, when you say approximately monthly -- and this is just my interpretation of common usage of the English language -- I do agree that this claim is difficult to understand completely.

I would think that "approximately monthly" could mean monthly plus/minus one month, and approximately every four weeks could mean every four weeks plus/minus one week so that that interval might be difference if you really get down to it. Obviously, the terms are very, very similar.

Q. Dr. Albini, in your report you understood the phrases "approximately every four weeks" and "approximately monthly" sufficiently to equate them as meaning the same thing, right?

A. I did write that they mean the same thing. I may have not been focused as you've asked me -- or as least as I've perceived you've asked me to do here to look at the meaning of the word "approximately" within that.

And I do appreciate that "approximately" may be applied in slightly different ways to a four-week time interval versus a monthly interval, but I do think that monthly and four

weeks are very, very similar and the same thing.

Q. We can take that slide down.

Dr. Albini, you would agree that as of 2011, the POSA would have known how to intravitreally administer an anti-VEGF agent, correct?

A. That is correct.

Q. And the POSA would have known how to do that approximately every four weeks?

A. Well, on the face of it, the obvious answer to the question is, if a POSA knows how to do it once, they know how to do it at any time interval.

The part that I'm hesitant about is I don't know that it would have been obvious necessarily what "approximately" means in and of itself. Certainly I think that, for example, if you were conducting a clinical trial and the trial said we're going to inject this drug approximately every four weeks, the trialist or the principal investigator would want to know what exactly does "approximately" mean? How big is that window? Can we be off by two days? by three days?

So I don't know that -- certainly the POSA would know how to do the injection. The question is whether the POSA would need more clarification as to that time interval.

Q. Dr. Albini, I'm going to see again if you remember your deposition in this case.

A. Sure.

Q. If we could please pull up page 230 from your deposition. And if we can put that side by side with 231.

I asked you, if you go down to line 18: "Okay. And maybe I'll get a similar answer here. But would the" --

Actually, I'm sorry. Can we pull that down and go up a little further? Apologies.

I asked at line 8:

"Q Would the POSA know how to do that approximately every four weeks?

"A He would know how to. He may not choose to, but he would know how to do that, yes."

And then I asked again at line 18:

"Q Maybe I'll get a similar answer here, but would the POSA know how to perform intravitreal injections approximately once every eight weeks?

"A I think if he can do it once, he can do it at any time interval."

Do you see that?

THE COURT: One second, Doctor.

Yes, Counsel?

MR. McLAUGHLIN: I'd like to object based on this being improper impeachment testimony. These are not the same questions that he was just asked, and he's not providing any

inconsistent testimony here.

THE COURT: I don't think that's been suggested yet. Understood. Overruled.

BY MS. OBERWETTER:

Q. Dr. Albini, these are the answers to my questions about "approximately" that you gave at your deposition, correct?

A. I think that, if you look at the context there, I was careful to say I'm still talking about the physical steps of doing it as opposed to understanding how the span of the time interval between the injections.

So if you're asking me would the POSA know how to administer the drug? Yes, they would know how to administer the drug. Would they know necessarily what "approximately every week" means? I don't think that they could know that without further clarification.

Q. That is not --

A. And I think that is consistent with the testimony that's on here.

Q. That is not clarification you sought when I asked you these questions at your deposition.

A. It's right there. I mean, I don't know. Do you not see it? I said, "And I'm still talking about the physical steps of doing it."

Q. Dr. Albini, would you agree that as of -- I'm going

to change topics slightly.

Dr. Albini, we haven't spoken much yet about Avastin. That's bevacizumab, correct?

A. That's correct.

Q. And that was originally approved as a cancer treatment, correct?

A. That's correct.

Q. And we talked about how it's now used off-label to treat angiogenic eye disorders?

A. That's correct.

Q. I think you've testified on whatever the exact number is, it's inexpensive, and whether it's $50 or somewhere south of $200, it's in that range?

A. That's correct.

Q. In your view, any difference in efficacy -- this is your view -- any difference in efficacy between Avastin and Eylea is small, correct?

A. That's correct.

Q. You think Avastin is a good drug?

A. That's correct.

Q. And in your practice you've used a lot of Avastin, correct?

A. That's correct.

Q. Including through the present?

A. That's correct.

Q. Dr. Albini, you agree that important advancements in treating retina need to come from industry, right?

A. I know that I've said that on many occasions, and I think that given the complexity now of bringing a drug to market, I stand by that statement; they need to come from industry.

What I think might not be 100 percent true is to say that they can only come from industry. Avastin is a great example of a drug that was developed as a therapeutic agent for angiogenic eye disorders in spite of industry.

So I think there are few such examples in medicine, but I do think that Avastin is a good example where that rule that I -- or that teaching that I've given on the importance of industry and the further development of therapeutics, I think that that's an exception that proves the rule, but there are likely to be other exceptions too of important therapeutic advances that occur either without the support of industry or in spite of industry.

Q. Okay. And you have said there's an important role for industry because large organizations have more resources to bring to bear to get products to market, correct?

A. That is true.

Q. And those are things that cannot necessarily be done by physicians alone, correct?

A. Well, I wouldn't say cannot. So, again, I'll use the

example of bevacizumab. There, Dr. Rosenfeld pretty much single-handedly brought that drug to its use. I'm sure other individuals were involved. But it was largely done by an academic institution and by a particular provider.

And so I don't know that it always has to be industry. I think in the vast majority of major progresses that are going to be made, I think it's safe to say most of them will have industry as a component of a product's success.

Q. Dr. Albini, you agree that a drug's formulation can be important to whether it is a good drug or not, correct?

A. I do agree.

Q. And, in fact, the formulation of a drug can be the key to the clinical success and efficacy of a treatment, correct?

A. I don't think the formulation can be a key to the efficacy of a treatment. I think that formulation can certainly get us into trouble with toxicity, presumably. But I think that formulation alone, aside from things like, you know, intravenous fluids, very simple things, if you're getting into more complicated molecular therapeutics, formulation alone can definitely not bring great efficacy.

Q. I'd like to take a look at page 129 of your June 22, 2022, deposition. And if we can put that side by side with 130.

And you were asked -- this is questions put to you in

another deposition by another attorney, but you see at line 10 on 129 you were asked:

"Q Okay. And what I'm trying to understand is is it fair to say that, while the attributes of the molecule may be necessary, that they're not alone sufficient for the molecule to work on a given dosing regimen?

"A Certainly there are other attributes other than the molecule that are very important in the clinical success and efficacy of a treatment. The formulation, for example, is key."

Is that testimony you provided?

A. Yes, it is.

THE COURT: Yes, Counsel?

MR. McLAUGHLIN: Just want to object to this as being beyond the scope. This is a deposition that was taken in a different matter on a different patent and not this litigation.

THE COURT: Understood.

Counsel.

MS. OBERWETTER: Yes. It's proper impeachment evidence taken from another -- it wouldn't matter what case it was taken from.

THE COURT: What point are we impeaching the doctor on with this?

MS. OBERWETTER: Where he said he would not call formulation key.

THE COURT: Understood. Overruled.

MS. OBERWETTER: We can take that down.

BY MS. OBERWETTER:

Q. Dr. Albini, you would not prescribe a drug if it had an unsafe formulation, correct?

A. It depends on the context. I think that everything is a risk-benefit ratio. So if there was something that was, quote/unquote, unsafe about a drug but it was -- that the patient was certain to either go blind or lose their life without the drug, I think that you would administer that drug regardless of safety concerns.

So I think there's always a risk-benefit ratio. It's not -- I don't mean to make it sound as if it's always so stark between life and death, but there can be gradations within there.

Sometimes drugs with imperfect safety have such a big potential efficacy improvement that it makes sense to use them even with the safety concerns.

Certainly no drug is without safety concerns. We'd use no drugs ever if we never used any drugs with some safety issue.

Q. And you would agree that all attributes of a drug can be important to its commercial success, including things like

its stability, its binding capacity, and its clearance, correct?

A. I believe all of the properties of a drug can be important attributes for that drug's safety and efficacy, yes.

MS. OBERWETTER: Nothing further, Your Honor. Pass the witness.

THE COURT: Understood. Thank you, Counsel.

Redirect?

MR. McLAUGHLIN: Yes, I do. Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. McLAUGHLIN:

Q. So I'd like to revisit with you, Dr. Albini, some of the questions that you heard from counsel today.

So when providing your opinions on reasonable expectation of success, you were considering the visual acuity outcomes, correct?

A. That's correct.

Q. And you understand that a reasonable expectation of success analysis, like what you've conducted in formulating your opinions in this case, requires a different standard than what is required for FDA approval; is that right?

A. That is correct.

Q. Do you also agree that drugs can fail for a number of reasons that are not related to the visual acuity outcomes, like the visual acuity that we've been discussing here today?

A. That's correct.

Q. You were asked at one point about uncertainty as to the best dosing approaches for anti-VEGF agents.

Can I ask you, in your experience, in your practice, how were you treating patients in the clinic prior to 2010?

A. I think that much like what was described in that 2007 *Retinal Physician* report, I was using a prn and then progressing -- I don't remember exactly when I might have shifted -- to a treat-and-extend protocol.

And I don't think that I made that transition -- you know, that I decided one day I'm going to shift from one to the other. It was done on a patient-by-patient basis depending on issues. Certainly patients that had difficulty with transportation and coming in would be patients that I would shift to a treat-and-extend- protocol earlier than patients who had no problem coming in for their visits.

So I think there was a gradual transition where I shifted from prn dosing. I think I also used fewer loading doses as time went on in that time period from 2007 to 2010.

Q. But you don't dispute that there were regimens like treat and extend, as you indicated and showed in your presentation today, in use as early as 2007; is that right?

A. Absolutely. And documented in the literature, as was in my testimony.

Q. And treat and extend, is that the same type of

protocol that's currently used today?

A. I believe that that's the most commonly used treatment protocol today, yes.

Q. And does treat and extend involve individualized assessments?

A. It does. The -- one of the concepts of treat and extend is to try to determine what a dosing interval is that's required for a particular patient and then to stick to that interval. So some patients are seen as patients who require injections every four weeks, some every six weeks, some every eight weeks, and so on. And that's determined through trial and error for each individual patient.

Q. Were you using prn dosing as well in the pre-2010 time period?

A. Yes, I was.

Q. And that involved -- that was a regimen that would allow you to administer fewer injections to patients compared to a monthly dosing regimen, a fixed monthly dosing regimen, correct?

A. Yeah, that's true. And what I recall happening is that, as patients were coming in -- some patients, not all -- but as some patients came in for their, let's say, third month visit and there was no fluid seen and then they came in for their fourth month visit and there was no fluid seen, then it was a natural progression to say, "You know what? You don't

have to come in next month. Come in in six weeks. Let's see you then." And then if there was no fluid -- so treat and extend kind of built out of prn in a very natural way for a lot of us.

Q. And treat and extend was an individualized dosing regimen that would allow not only an extension of time between injections but also an extension of time between office visits; is that right?

A. That's correct.

Q. Now, I'd like to ask you about a -- that 2008 presentation that you were shown earlier.

If I could ask to be put up on the screen, side by side, both DTX 0204 as well as that 2008 presentation. I believe it's DTX 3173.

Actually, while they're doing that, I wanted to ask you -- I'll jump ahead and ask you something else while they're finding those documents.

You were also asked about isotonicity by counsel?

A. That's correct.

Q. And your view of the injections of potentially nonisotonic formulations.

A. That's correct. I was asked about that, yes.

Q. Do you have a sense -- actually let me back up.

You were asked about the confidentiality of the Eylea formulation and what was known about it prior to 2011; is that

right?

A. That's correct.

Q. And you were asked about whether you were aware of any public disclosure of that formulation?

A. I was, yes.

Q. And you were asked about whether that formulation was confidential or not?

A. That's true. As you're asking me this question now, I'm realizing that there were certainly elements of that formulation that may not have been confidential that were known. So I maybe shouldn't have answered that as a blanket that it was not known. Some parts of the formulation I think probably were readily available and certainly could have been tested by anyone who bought the drug.

Q. Let me ask you this: Are you aware that in this litigation Regeneron is also asserting a formulation patent?

A. Yes, I'm aware of that.

Q. And I will represent to you that that formulation patent lists on its face an earliest application date of 2006, and I will also represent to you that Regeneron has represented the '865 patent covers Eylea.

Would that knowledge have been important to you in answering counsel's questions about the confidentiality and public nature of the Eylea formulation?

A. Yeah. Yes. Obviously, yes, it would have been. And

I'm sorry that I may have not answered that in the best possible way.

Q. No need to apologize, Dr. Albini.

A. I did not know that they had patented the formulation. I still don't know, sitting here now, whether the -- all the exact attributes of the formulation are available in this patent; but, again, certainly some components of the formulation would have been available, and some components of the formulation are disclosed in Dixon, as we've described earlier today.

Q. You were asked about the induction versus loading doses.

In your view, is there any real difference between induction doses and loading doses as the terms are used in practice?

A. I don't think that there was much use of the term "induction doses," and I certainly can't think of any loading doses that would not be induction doses. So I think there's a lot of overlap in those terms, and I don't know that there's any meaningful distinction in clinical practice -- or there is no meaningful distinction in clinical practice.

Q. Now that we have these documents up, let me go back to Dixon. That's 0204.

Now, you recall you were asked questions about the availability of this presentation. I believe in your earlier

testimony, you confirmed that this presentation was cited in the references section of Dixon?

A. That's correct.

Q. And if we can go to that and take a look at that.

Let's go to the references portion of this article. Should be the second-to-last page. If we pull up Reference Number 45. If we can put it so that Dr. Albini can still see the image on the right.

It's the same title that we're looking at here?

A. Yes.

Q. Is that the same date?

A. Yes.

Q. If we go back to 0204, page 4, and if we move to page 12 of the document on the right.

So if we can look at Dixon, left-hand column towards the bottom, where it says, "Patients initially dosed on a 2-milligram schedule received an average of 1.6 more injections over the course of the treatment phase," is that consistent with the data shown to the right with respect to that dosing arm in the CLEAR-IT 2 clinical trial shown at Slide 12 where it says 1.55?

A. In here it says -- I'm sorry; I'm just confused. Here it says 1.6, and here it says 1.55. I would say those are consistent.

Q. And the 2 mg q4 regimen, do you understand that to be

the one with the every-four-month loading doses following by prn dosing?

A. That's right.

Q. Then if we flip to page 13 of this -- of the document on the right. What does it tell you about the time to reinjection in all patients in the CLEAR-IT 2 trial?

A. Somewhere it discloses the median time to reinjection. Just a minute here.

"The median time to first reinjection in all groups was 110 days," and that does look to be the exact same data that's reported in the slide on the right.

Q. Okay. Thank you.

We can take that down now.

Actually, one more thing. Can we just go back to 3173 and go to Slide 16.

Can you describe what's shown in this data here on Slide 16 of 3173?

A. This is mean change in visual acuity over time in two arms of the study, the 2-milligram dosing group that started off with the four monthly loading doses and then the .5 milligram dose with the four monthly loading doses and then prn treatment thereafter.

And do you see that there's -- in the 2-milligram group, there is a better visual acuity outcome of nine letters compared to 5.4 letters in the .5-milligram group.

Q. Thank you. We can put that away now.

And if you recall, you were also asked about -- going back to isotonicity and your experience in injecting isotonic solutions, did the questions that were asked by counsel, did that change your opinion that a POSA clinician like yourself would accept that the aflibercept formulated for comfortable, nonirritating injection was inherently isotonic?

A. Especially after considering the teachings of a formulation expert like Dr. Rabinow, I don't think that the POSA would have -- that there's nothing in the cross-examination here today that would change anybody's mind about that.

Q. Okay. Do you recall you were also asked about the '747 patent by counsel?

A. That's correct.

Q. Specifically Example 17?

A. That's correct.

Q. That Example 17 is an example of a method of treating angiogenic eye disorder, like AMD?

A. That's correct.

Q. Is there anything that would have prevented somebody from also trying that with the diabetic retinopathy that's also disclosed in the '747 patent?

A. I think no. And, again, as an argument for the rationality of looking across diseases, we have the internal

communications of Regeneron showing that they based some of their study design in the DME trials based on AMD trial data.

So I think people did use information from one disease space to guide their therapeutic approaches in another disease with these anti-VEGF agents.

Q. If we can pull up DTX 2198.

Just like to ask you a question that you were asked about that document with respect to RVO.

A. Sure.

Q. If we could go to page 2 of this document, top paragraph.

This is the paragraph that you were shown by counsel?

A. Yes.

Q. And this discloses that patients in both studies will receive six monthly intravitreal injections via the VEGF Trap-Eye at a dose of 2 milligrams or sham-controlled injections.

Do you see that?

A. Yes.

Q. But then this section also continues, doesn't it? At the end it says, "At the end of the initial six months, patients will be dosed on a prn, as-needed basis for another six months."

Do you see that?

A. Yeah. You know, I recalled that, but I couldn't find

the text. I don't know what I was shown. But, yes, I see that now, yes.

Q. Does that help clarify whether or not the person of ordinary skill in the art reading this would have thought those six monthly intravitreal injections to be loading injections or not?

A. I think they would be interpreted to be those first loading injections, followed by prn dosing, just like in so many of the other trials that we've seen.

Q. You were asked questions about the formulation of Eylea and whether it can contribute to the commercial success of the product.

Ask you a question. Would you buy Eylea for your practice if it didn't have aflibercept in it?

A. No.

MR. McLAUGHLIN: Nothing further. Thank you.

THE COURT: Counsel, recross?

MS. OBERWETTER: Briefly, Your Honor.

RECROSS-EXAMINATION

BY MS. OBERWETTER:

Q. Dr. Albini, Mr. McLaughlin had questions for you about PTX 0002, the '865 patent that he directed your attention to briefly.

If we could just put that up on the screen.

I just want to be clear for the record. You have not

undertaken any exercise to determine what this patent does or does not disclose as it relates to the Eylea formulation, correct?

A. I was not -- as we've said multiple times, I was not engaged here as an expert on formulation and my efforts were not focused on the formulation patent as a consequence of that.

MS. OBERWETTER: Nothing further.

THE COURT: Thank you.

Reredirect then, Counsel?

MR. McLAUGHLIN: Nothing further, Your Honor.

THE COURT: Doctor, I have wonderful news for you. You can step down, sir.

THE WITNESS: Fantastic.

THE COURT: Outside, you're fair game.

THE WITNESS: That was a lot of fun. Thank you.

THE COURT: I'm sure it was. Thank you very much. I appreciate it, but you're now fair game. Folks can talk to you again.

THE WITNESS: Oh, great.

THE COURT: Thank you, sir.

MR. McLAUGHLIN: Your Honor.

THE COURT: Doctor, hold on one second. Let's go ahead and --

MR. McLAUGHLIN: Read into the record the exhibits.

THE COURT: You may do so, slowly.

MR. McLAUGHLIN: This would include DTX 204, DTX 2034, DTX 2035, DTX 3173, DTX 2040, DTX 2062, DTX 2730, DTX 2731, DTX 2733, DTX 2745, DTX 3102, DTX 3105, DTX 3115, DTX 3131, DTX 3198, DTX 3215, DTX 4008, DTX 4013, DTX 4056, DTX 4061, DTX 4113, DTX 4116, DTX 4120, DTX 4129.

THE COURT: A little bit slower, Counsel.

MR. McLAUGHLIN: Sorry. DTX 4192, DTX 4194, DTX 4900, DTX 4903, DTX 8190. And I believe we've already moved this one in, but just in case, DTX 8205.

And if I could just get clarity from my cocounsel on three remaining ones.

THE COURT: Certainly.

MR. McLAUGHLIN: There will be two more. Thank you. DTX 3144 and DTX 3316.

THE COURT: Any objection to any of those?

MS. OBERWETTER: No, Your Honor.

THE COURT: Without objection, the aforementioned list are all hereby deemed admitted.

(DTX 204, DTX 2034, DTX 2035, DTX 3173, DTX 2040, DTX 2062, DTX 2730, DTX 2731, DTX 2733, DTX 2745, DTX 3102, DTX 3105, DTX 3115, DTX 3131, DTX 3198, DTX 3215, DTX 4008, DTX 4013, DTX 4056, DTX 4061, DTX 4113 ,DTX 4116, DTX 4120, DTX 4129, DTX 4194, DTX 4900, DTX 4903, DTX 8190, DTX 8205, DTX 3144 and DTX 3316 were admitted.)

MR. McLAUGHLIN: Thank you, Your Honor.

THE COURT: Ms. Oberwetter?

MS. OBERWETTER: I have just a few more that I did not do during the course of cross.

I think I heard DTX 3105 on Mr. McLaughlin's list. We move to admit that. DTX 4099, DTX 4209, DTX 8151-A.

THE COURT: Any objection to those?

MR. McLAUGHLIN: No objection, Your Honor.

THE COURT: Without objection, Ms. Oberwetter's list is hereby deemed admitted.

(DTX 4099, DTX 4209, and DTX 8151-A were admitted.)

THE COURT: Everyone satisfied their respective lists have all been checked off? Okay. Great.

Doctor, now you can exhale.

I do need to ask counsel about any exhibits from our video experts.

MS. MAZZOCHI: I think that --

THE COURT: Video witnesses.

MS. MAZZOCHI: Yes. My understanding is that thus far, everything has been moved in. I know our court reporter has copies, I think, of all the PTX/DTX exhibits electronically; so she should have those. And, obviously, at the end of the proceedings, I'm assuming Your Honor will want a flash drive complete with everything on it.

THE COURT: Please.

MS. MAZZOCHI: Maybe you want to keep the paper; but as a general rule, you know, I think people might let that go by the wayside.

But I think we've been keeping track of which ones are which. Teagan had a few things he wanted to reconcile from yesterday, but otherwise, with that, I think we'll be up to date.

THE COURT: Counsel.

MR. GREGORY: Ms. Mazzochi is correct.

We have a little bit of housekeeping from the video testimony from Vanessa Smith and Parag Goyal yesterday. I believe we can read into the record and move into evidence the following, which I believe we have consent on: PTX 0353, PTX 0354, PTX 0364, PTX 0472, and PTX 0478.

MS. MAZZOCHI: And my understanding is, if that's a list that came out of meet-and-confer, then those are the ones that are agreed to.

THE COURT: Those are thereby deemed admitted.

Who does Mylan intend to call next?

MS. MAZZOCHI: So, Your Honor, we had -- again, we would like to call Karen Chu at some point as the Regeneron 30(b)(6) witness. I don't know if you want to do that now or wait till later.

Or we could -- we have roughly another 45-ish

minutes, maybe 50 minutes of two of our last -- basically, the last two ones of ours going in by designation. Then our plan would be we would start with Dr. Rabinow tomorrow, followed by Dr. Stewart. If you'd rather kick the Chu issue till tomorrow, we could do that. The only thing is we might not have clip reports in time. That's the one concern on that.

THE COURT: Let's go ahead, and we can do the other two videos first. We'll discuss the Chu issue so we can have that ready to go going forward.

MS. MAZZOCHI: And then, Your Honor, I also wanted to make clear, our next and, I believe, last live witness as part of our case in chief will be Dr. MacMichael. Plaintiffs have been aware he is not available until Tuesday. So I don't know how long plaintiff's crosses are going to go tomorrow. So they may actually start putting on their rebuttal case. And then our last live witness will be Dr. Hofmann, but he has to come in response to their expert Dr. Manning. So I suspect that will happen next week.

THE COURT: Understood.

Any disagreement with that projected plan?

MR. BERL: Well, that's the first I've heard of it. We're fine with Dr. MacMichael, who apparently has some health issue, not coming till Tuesday. I suspect their case will take most if not all of the day tomorrow. I don't think it makes any sense for us to start our rebuttal case until they finish

their case in chief. So we were planning to do that after Dr. MacMichael testifies on Tuesday. That's one thing.

The second thing is before the end of court today, I think it would be wise to address another issue that has arisen with respect to Dr. Rabinow. We just received their amended slides in view of Your Honor's ruling, and let's say we don't think it complies with Your Honor's ruling, to put it mildly.

THE COURT: We're going to put a pin in that.

Let's go ahead and receive the next two videos we discussed, Counsel. Then we'll take up the issue with Ms. Chu, and then we'll get to that when we get to that.

MS. MAZZOCHI: All right. Thank you, Your Honor.

Defendants next call by video deposition Ms. Abby Cahn, a Regeneron employee.

THE COURT: Thank you so much.

MS. MAZZOCHI: Your Honor, I think we may have the exhibits for Cahn. I don't know if you want a paper copy or if you would like them up on the screen and then we just submit them.

THE COURT: Are they synced on the screen?

MS. MAZZOCHI: Yes.

THE COURT: I can just watch them from there. That's fine. I'm going to work on, hopefully this evening, clearing out some space for any additional binders that might be necessary.

VIDEO DEPOSITION OF ABBY CAHN

Q. Good morning, Ms. Cahn. If you could please state your full name and your home address for the record.

A. My name is Abby Margo Cahn. I live at 209 East 56th Street, New York, New York 10022.

Q. You understand that you're appearing here and providing testimony in your personal capacity?

A. Yes, I understand.

Q. And do you also understand that Regeneron has designated you as a witness to speak on behalf of marketing subject matter with respect to Mylan's 30(b)(6) notice?

A. Yes, I understand and am aware.

Q. This is DX 802. It is plaintiff's Regeneron, their second supplemental Rule 26(a) initial disclosures.

Have you seen this document before, Ms. Cahn?

A. Yes. I was shown this document by my lawyers during preparation.

Q. Are you aware that Regeneron identified you as a person with knowledge about the marketing and commercial success of Eylea?

A. Yes, I am aware.

Q. Okay. What is your current title at Regeneron?

A. My current title at Regeneron is executive director, marketing and customer engagement, as of January 3rd.

Q. So Regeneron, with respect to Eylea, provides both

tabletops and booths at conferences where appropriate?

A. If that is part of the tangible method of a sponsorship, then Regeneron would be able to exhibit at that medical conference.

Q. Okay. And then another thing you mentioned was providing ads at conferences. What did you mean by ads?

A. Depending upon each meeting's prospectus, which is submitted to the sponsorship portal, there are very specific -- there's a specific outline of benefits. That would include, for example, a banner, and that would be placed in either a certain location or potentially, if it's a virtual conference, on the meeting website.

Q. When Regeneron has podium time that you referred to, who speaks on behalf of Regeneron?

A. Depending upon the availability of individuals as well as the meeting, the Regeneron employees would be able to give an approved presentation at the meeting. So that, yeah.

Q. Does Regeneron ever sponsor talks given by physicians or clinicians or health care professionals?

A. So at medical conferences in general, there's a number of ways that physicians are able to appropriately educate their peers at the conference. As a marketer, I am aware of one of those -- one of those opportunities, which is referred to, essentially, as a product theater.

Q. And what is a product theater?

A. As part of the meeting prospectus, the product theater would be part of the request for support. If the sponsorship is approved, the marketing team would have the ability to work with a physician to give the on-label approved educational speaker program presentation at that meeting or convention.

Q. You used the word "thought leader liaison." What is that?

A. So at Regeneron a thought leader liaison is a field-based marketing role, and the main responsibility of that field-based marketing thought leader liaison is to gain insight into the evolving retina landscape through engagement with thought leaders in the retina community.

Q. Does Regeneron provide compensation for thought leaders?

A. Regeneron, and specific to Eylea and my role in the marketing team, we contract with advisers for -- in insight-gathering settings, such as advisory boards. We also have contracts with retina specialists who are part of the Eylea educational speaker bureau.

Q. What is Eylea educational speaker bureau?

A. The Eylea educational speaker bureau is a program that enables physicians to give approved on-label presentation of Eylea to other health care professionals.

Q. In your opinion, is it important for Regeneron to

enable physicians to give presentations concerning Eylea?

A. It is my opinion that it is important for physicians to be educated about the on-label -- the on-label information for Eylea when making treatment decisions for their patients.

Q. What are the ways that you're aware of?

A. So from the -- within the marking organization, there is a team that is responsible for scientific marketing. They are responsible for the Eylea educational speaker program, which is the presentations that physicians give to other health care professionals around the on-label use of Eylea.

The patient marketing or consumer marketing team is responsible for providing educational materials about Eylea as well as education around the diseases that Eylea is indicated for. And the promotional marketing team is responsible for developing the sales materials which our sales team uses to educate physicians and their offices about the on-label use of Eylea.

Oh, it's aligned to the regional directors. Under each regional director are medical specialists or diabetic eye medical specialists.

Q. So Eylea4U program has been active since the launch of Eylea and it continues today; is that correct?

A. So a version of Eylea4U patient assistance programs were available at launch. I would not be able to speak to the difference in the program between launch and today.

Q. But a program Eylea4U has existed within -- the name Eylea4U has existed continuously since Eylea's launch and is ongoing today?

A. A program called Eylea4U has existed since launch and does exist today.

Q. Do you know, what insights have you gained on why physicians express an interest for a prefilled syringe?

A. So based on my conversations with physicians around the availability of treatment options for patients, there is a perception that administering intravitreal injections with a prefilled syringe may have an improved -- is an improvement on the -- sort of the safety of and decreasing the risks associated with the intravitreal injections.

Q. And based on the sales numbers, do you agree that there is a preference for the prefilled syringe over the vial of Eylea?

A. So my understanding of preference comes from insights from physicians in different settings, and based on my personal conversations with some physicians, there is a preference for a prefilled syringe.

Q. Ms. Cahn, before the lunch break I recall you mentioned a promotional marketing team for Eylea. Is my recollection correct that Regeneron has a promotional marketing team for Eylea?

A. So Regeneron has a marketing team, and there are

individuals on that marketing team who are responsible for promotion.

Q. Ms. Cahn, are you familiar with the acronym ATU?

A. I am familiar with the ATU market research surveys. I do not recall what the letters ATU stand for.

Q. DX 514 was marked as a previous deposition. The first page includes the Bates numbers RGN-EYLEA-MYLAN-701395. It's a Q3 2020 ATU combined full report.

Is this the type of document that you review in your marketing role at Regeneron?

A. So I am part of the marketing team and get invited to the market research meetings where these types of reports are shared with the marketing team.

Q. What is your understanding of the phrase "out-of-pocket costs"?

A. My understanding of "out-of-pocket costs" would be the portion of the cost that is not covered by insurance.

Q. With that understanding of out-of-pocket costs, is it your opinion that physicians might not prescribe a drug if the out-of-pocket costs for that drug are unaffordable to the patient?

A. So although I'm not a physician, it is my understanding that physicians have conversations with their patients around all of the treatment options that are available to them and make decisions together based on a number of

factors, including out-of-pocket costs based on their insurance.

Q. This is the current August 2022 label, and it's been labeled DX 520-A because it now has Bates numbers on it. The prior version used at another deposition did not have Bates numbers.

Ms. Cahn, based on your testimony, you're familiar with this package insert -- or I refer to it as a label -- this package insert for Eylea?

A. Yes, I am.

Q. You've seen this document before?

A. Yes, I have.

Q. Does the dosing and administration instructions for wet AMD provide flexibility for a clinician to dose Eylea?

A. Yes, the wet AMD dosing administration section does provide flexibility for physicians who choose to treat with Eylea.

Q. And that flexibility is with respect to the dosing schedule?

A. Yes. It would -- dosing schedule is one way to describe the time between treatments.

Q. Okay. And for wet AMD here, the label states that the physician may dose Eylea as frequently as 2 milligrams every four weeks; is that correct?

A. Yes. Some patients may need every-four-week dosing

after the first 12 weeks, which is the loading dose phase.

Q. And if we go down to the next indication, RVO, are you familiar with RVO?

A. The indication is macular edema following retinal vein occlusion, yes.

Q. MEfRVO; is that correct?

A. Yes.

Q. And the recommended dose of Eylea for MEfRVO is once every four weeks; isn't that correct?

A. Yes, that is correct.

Q. And so for DME and DR, Eylea may be dosed as frequently as 2 milligrams every four weeks; is that correct?

A. Yes. Some patients may need every-four-week monthly dosing after the first 20 weeks, which is the first five months of the loading dose in diabetic macular edema and diabetic retinopathy.

Q. So I think -- do the dosage administration instructions on the Eylea package insert require a physician dose Eylea every eight weeks?

A. No. There is the -- some patients may need every-four-week dosing as indicated in the label in each of the indications we previously reviewed.

Q. Ms. Cahn, right before the break I had you pull up DX 514. If you could turn to what is page 90 of 142. The Bates number ends in 484. And then it's pulled up on the

screen share as well.

Okay. This slide with Bates number ending 484 is titled "Wet AMD Dosing Update." Do you see that?

A. Yes. Yes, I do.

Q. And, Ms. Cahn, do you agree that the mean dosing frequency for Eylea that's reflected on this slide is 7.5 weeks for the dosing interval?

A. So this is a -- as per the source, a Q3 2020 ATU study of 171 retinal specialists and 30 comprehensive ophthalmologists.

This -- under the sentence we just covered, projected percentage of treated eyes receiving dosing schedule with an asterisk, ongoing, following initiation of therapy.

So based on this group of physicians projecting intervals of treatment following a loading dose of Eylea for these physicians, their perception is a loading dose of what you -- mean frequency of 7.5 weeks.

Q. Okay. And if we could go to two pages down.

A. Okay.

Q. It's page ending in number 486.

A. Okay.

Q. And does this slide reflect that the mean frequency for the dosing interval for Eylea with respect to DME is 7.7 weeks?

A. So for -- again, for based on in this quarter, Q3

2020 ATU, this 164 retinal specialists and 36 comprehensive ophthalmologists, their projected percent of treated eyes receiving dosing schedule, what they project to be true, following a loading dose is the mean frequency of injections is 7.7 weeks.

Q. Okay.

Mike, if we can bring up DX 515.

DX 515 was marked at a previous deposition. First, page Bates number is RGN-EYLEA-MYLAN-700292. It is the Q4 2020 ATU combined full report.

All right. Have you seen this document before?

A. So I have reviewed a number of performance updates in my role as -- in marketing. I also reviewed a performance update with my lawyers in preposition for today. I do not recall if it was Q4 2020.

Q. If we could turn to what is page 92 of 137 in this document. The Bates number ends in 383.

A. 383. Okay. 383. Okay. It's loading.

Q. Sure. And does this slide reflect the mean dosing frequency for Eylea of 7.3 weeks?

A. So these specific physicians are recalling treatment intervals for their patients, and they are -- on average, the mean frequency of this set of physicians with this recall of their patients is 7.3 weeks.

Q. Okay. If we could go two pages down, it ends in 385

in this document.

A. Can you repeat your question.

Q. Sure. This slide is titled "DME Dosing Update."

Can you agree that the data shown here is that on average the mean frequency for Eylea dosing for DME is every 7.5 weeks?

A. So for this 2020 ATU study of 172 retina specialists and 30 comprehensive ophthalmologists who were recalling treatment intervals for a specific number of patients, the mean frequency for Eylea is 7.5 weeks.

Q. Mike, can we pull up DX 516, please.

This was previously marked at another deposition as RGN-EYLEA-MYLAN-700931 on the first page. It's on the Q4 2019 ATU report.

Okay. And if we could turn to page 98 of 153 in this document. The Bates number ends in 028.

A. Got it. I'm right there. Hold on. Yep, I do have it up.

Q. Okay. And, Ms. Cahn, do you agree that in this Q4 2019 ATU report, the data shows that the mean dosing frequency for Eylea for wet AMD is 7.0 weeks?

A. So for these 200 retina specialists surveyed for the Q4 2019 ATU study, their recollection or recall of patients on each of these agents, the mean frequency of Eylea injections is 7.0 weeks.

Q. If we can go two pages down, it ends in 030, titled "DME Dosing Update."

Ms. Cahn, do you agree that this Q4 2019 ATU report reflects a mean dosing frequency of 6.7 weeks for dosing Eylea for DME?

A. So for this -- these 200 retina specialists on Q4 2019 ATU study, they are projecting or recalling that the Eylea treatment interval for their patients, the mean frequency was 6.7 weeks.

Q. Okay.

Mike, if we could pull up DX 517.

DX 517 was marked at a prior deposition. The first page has Bates number RGN-EYLEA-MYLAN-705670. You could go to the pages ending in 689. It is page 20 of this PDF.

A. 689. Okay. Thinking. Hold on.

Q. Sure.

A. 689. Okay. I am on 689.

Q. Sure. The slide that -- the page that we're already looking at --

A. Okay.

Q. -- it reflects that the Eylea mean dosing frequency overall is 6.7 weeks; is that correct?

A. So for these physicians recalling their projected dosing intervals for a set of patients which I cannot -- which I have no understanding if they are previously treated or naive

eyes or actually how many eyes -- there we go. Sorry -- of this set of 42,763 eyes, the overall dosing frequency and the mean in the weeks would be 6.7 weeks.

Q. DX 518.

A. DX 518. Okay. It's open.

Q. This is the Q3 2017 ATU report.

A. Okay. Its title page is up.

Q. If you can turn to page 20 of 35 of the document.

A. 20 of 35.

Q. Do you agree that this slide reflects that the overall dosing frequency for Eylea for wet AMD has a mean of 6.7 weeks?

A. So based on this slide from the -- okay -- no source on this. I do not recall which quarter and year this new document is referring to.

The physicians who completed this survey recalled that patients were dosed at different dosing frequency, although I cannot comment if these are treatment-naive eyes or those eyes that have been transitioned from another agent.

And the mean overall dosing frequency for Eylea on -- from this group of physicians recalling based on this number of patients is 6.7 weeks.

Q. So we reviewed ATU surveys -- at least one ATU survey from each of 2017, 2018, 2019, and 2020; is that correct?

A. Yes, I believe that's correct.

Q. And we discussed a number of mean dosing frequencies for Eylea, correct?

A. We discussed the results of ATU surveys from a group of physicians who are recalling their patients' dosing intervals, yes.

Q. And do you agree that of the data we looked at, the mean dosing frequency for Eylea was always less than eight weeks?

A. So for the results of these surveys where the physicians were asked to recall that their projected dosing frequency of Eylea with the patients that they recall and are projecting according to this, in those patients the dosing frequency of Eylea is less than eight weeks.

Q. Sure. It is DX 531a.

A. DX 531a. Okay.

Q. Okay. But you, in your role, cannot speak to off-label uses of Eylea, correct?

A. That is correct. I am unable to -- unable to speak about anything other than the Eylea package insert.

Q. That's because that's what the law states, correct?

A. Yes.

Q. Do you agree that with Dr. Schleifer's comments here that here the availability of Eylea copay assistance is reversing the shift from Avastin back to Eylea?

A. My opinion of -- my opinion is that there are a

number of factors that contribute to a physician's treatment decision and that patient access and copay assistance challenges are factors that do affect physicians' abilities to choose medications.

Q. Ms. Cahn, once they load, DX 807 is going to be a brief video --

A. Okay.

Q. -- that will play, and then DX 808 is a transcript of that video.

(Video played within deposition.)

Q. Once they load, DX 807 is going to be a brief video --

A. Okay.

Q. -- that will play, and then DX 808 is a transcript of that video.

Ms. Cahn, is DX 808 an accurate transcript of the video we watched in DX 807?

A. Yes, it is.

Q. Did you discuss any trend -- a trend of Eylea was utilized more in areas where "A Beautiful Pair" was run than in areas where it was not run?

A. So I can't speak to any trends because I don't have enough information that would make -- that would lead to a trend. But I know from what Mr. Clark told me that in the markets where "A Beautiful Pair" was run compared to in markets

where "A Beautiful Pair" did not run, there was a difference of Eylea utilization in those markets.

Q. Mike, if you can mark as Tab 62 Defendant's Exhibit -- mark Tab 62 as Defendant's Exhibit 811, 811.

This is, as you can see in the top left, pulled from the hcp.eylea.us website, January 16, 2023.

A. Yes, I can see that.

Q. Are you familiar with the hcp.eylea.us website?

A. So I am not familiar specifically on the website. This is the HCP website. I am not responsible for updating or producing content for this website.

Q. The first page, DX 811, at the top it says "Wet AMD: Dosing Flexibility."

Do you see that?

A. Yes, I do.

Q. Okay. And it recites, "Flexibility to choose from three FDA-approved dosing regimens for wet AMD."

Do you see that?

A. Yes, I do.

Q. So do you agree that clinicians have flexibility to choose a dosing regimen for wet AMD, according to the current package insert for Eylea?

A. Yes. According to the package insert for Eylea, physicians may choose the dosing paradigms that are listed in the package insert.

Q. Okay. If we can scroll down to page 4 of 12, on the top it says "DME:Dosing Flexibility."

A. In the same -- oh, I see it, yes.

Q. Okay. So you agree that physicians have flexibility with respect to DME dosing?

A. I do agree that physicians have flexibility to treat their DME patients based on the patient's need for treatment.

Q. Defendants' Exhibit 815 has the Bates number on the first page of RGN-EYLEA-MYLAN-314737.

Ms. Cahn, does this appear to be print advertisements that Regeneron ran in *Time* magazine promoting Eylea?

A. Yes, it does.

Q. And is this a different ad campaign for Eylea other than "A Beautiful Eye"?

A. Yes, this is.

Q. Mike, if you can scroll to the last page of this document ending in Bates Number 707.

Ms. Cahn, does this page of Defendant's Exhibit 817 refresh your memory that this was mailed directly to Eylea patients?

A. So this looks like a direct mail to Eylea patients once patients were enrolled in Eylea4U.

Q. And, Ms. Cahn, if you'd like to review this document, you can ask Mike to page through it at the appropriate pace.

A. Can I see the front cover, please, Mike? I can't

really see it.

So this is another "A Beautiful Pair" print advertisement.

Q. Have you seen -- when you say another version, you mean this is a print ad that was part of the "Beautiful Pair" ad campaign?

A. Yes, that is correct.

MS. MAZZOCHI: And that's the conclusion of that video. And then for administrative purposes, I believe all of these exhibits are agreed to.

The defendants would like to rule in -- move into evidence DTX 514, 515, 516, 517, 518, 520-A, 531-A, 802, 807, 808, 811, 815, 817, and 818.

THE COURT: Any objection to any of those?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, those are hereby admitted.

(DTX 514, DTX 515, DTX 516, DTX 518, DTX 520-A, DTX 531-A, DTX 802, DTX 807, DTX 808, DTX 811, DTX 815, DTX 817, DTX 818 were admitted.)

MS. MAZZOCHI: Great. Thank you, Your Honor.

The next video deposition we have is 21 minutes. And this will be Jennifer Colyer, who is part of Regeneron's finance and marketing, and I believe she was also designated as a 30(b)(6) witness.

THE COURT: Understood.

VIDEO DEPOSITION OF JENNIFER COLYER PLAYED

Q. Mrs. Colyer, could you please state your full name and your home address for the record.

A. Sure. Jennifer Colyer, 37 Shady Lane, Dobbs Ferry, New York 10522.

Q. And the second is a document, "Jennifer Colyer 30(b)(6) Deposition Topics," which will be DX 501.

Do you have both those documents, Ms. Colyer?

A. Yes, I do.

Q. Okay. You can set that document aside.

Do you also understand that you're here testifying today as a corporate representative of Regeneron to speak on behalf of the topics listed in DX 501?

MR. GOLDSMITH: I object to the Exhibit DX 501 to the extent it's not consistent with Regeneron's December 12, 2022, letter. But the witness can answer the question.

THE WITNESS: What my lawyer just said, yes.

Q. Well, factually then, what is driving the sales of Eylea?

A. Successful scientific research.

Q. And what is that research referring to?

A. The research that was done to develop the molecule that became Eylea, aflibercept.

Q. When you say Eylea drug, you're referring to the

active ingredient aflibercept?

A. I'm referring to Eylea.

Q. When you say Eylea, what are you referring to?

A. I'm referring to Eylea, the brand name as licensed by Regeneron.

Q. What is encompassed by the brand name Eylea?

A. I'm afraid I don't fully understand. What do you mean by "encompassed"?

Q. You mentioned that when you used the word Eylea, you're referring to the brand name. And I'm trying to understand what is included, what is different between Eylea and the brand name. Is there a difference?

A. I'm afraid you're trying to make a distinction that I'm not really familiar with. To me, Eylea is a brand name that is licensed by Regeneron somewhere legally, and that is Eylea.

Q. Is the safety and efficacy of Eylea a factor that drives sales?

A. I freely admit I am no scientist. I have not been involved in clinical trial research. The safety and efficacy of Eylea would be considered a benefit absolutely in the use of Eylea.

Q. Are there any other benefits that Eylea imparts to patients?

A. As a finance person, I'm not too familiar with the

detail behind Eylea and the clinical research and what it has proven over the past many years.

Q. Does Regeneron advertise Eylea directly to health care providers?

A. Regeneron advertises Eylea, yes, to health care providers.

Q. And does Regeneron advertise Eylea to the public?

A. Over the years Regeneron has advertised Eylea directly to the public.

Q. Does Regeneron undertake market research for Eylea?

A. Yes, it does.

Q. Are you familiar with that market research?

A. I do not work directly with that market research, no.

Q. Your current job title, is it correct that you're the executive director of commercial finance and business planning?

A. Yes.

Q. Does Regeneron have medical specialists for Eylea currently?

A. Yes, we do.

Q. And what is a medical specialist?

A. That would be a -- I guess layman term, a rep, a representative, customer representative, salesperson.

Q. Salesperson. Do those people have medical degrees? Do you know?

A. I'm not familiar with each and every one of them, but

they certainly can have a medical degree.

Q. Do you know how many medical specialists Regeneron has for Eylea, approximately?

A. I'll stick with roughly 90.

Q. And those medical specialists, do they report to the regional sales directors?

A. Yes.

Q. Does Regeneron have reimbursement and managed market specialists for Eylea?

A. Regeneron has regional business managers.

Q. Are those regional business managers, are any specifically assigned to Eylea?

A. There is a specific team of Eylea regional business managers.

Q. Do you know how many regional business managers Regeneron has for Eylea, approximately?

A. As of today, I believe there are 30.

Q. What is Eylea4U?

A. Eylea4U is the reimbursement support program utilized.

Q. What type of reimbursement support does Regeneron provide for Eylea under this Eylea4U program?

A. Copay assistance.

Q. Any other type of assistance that you're aware of?

A. The core is copay assistance.

COURT REPORTER: Say it again?

THE WITNESS: The core is copay assistance, yes.

Q. What is a regional science manager?

A. That is typically -- how to phrase it? -- a medical science liaison. These are field-based folks that are authorized to speak about the science as opposed to -- separating them from a medical specialist, which would be a rep.

Q. Do these individuals have medical degrees?

A. I assume many of them do. I do not know the composition of the team.

Q. Do you know how many regional science managers Regeneron employs for Eylea?

A. I'm taking a second to recall that because it's not something I work with too frequently.

I want to say mid teens, mid teens meaning somewhere between 12 to 19, give or take. I'm just not recalling exact number.

Q. That's fine. That's fine.

Do you know why Regeneron provides copay assistance?

A. Similar to most other pharmaceutical companies, Regeneron provides copay assistance to help commercial patients pay the copay.

Q. Do you have an opinion whether rebates drive sales of Eylea?

A. Sales of Eylea are derived from the clinical benefit of the drug for patients.

Q. What is the clinical benefit you're referring to?

A. Why doctors prescribe it to patients.

Q. Do you know why doctors prescribe it to patients?

A. To improve their lives.

Q. Are bonuses for Eylea sales representatives related to any sales targets?

A. Field forces are paid bonuses based on achievement of targets.

Q. Do you know why Regeneron is developing a high-dose version of Eylea?

A. The benefit of a high dose would be about a longer dose -- a dosing regimen, greater weeks between injections.

Q. Is that a benefit, a longer dose duration?

A. I think personally, if I could have fewer injections directly into my eye, I would choose to do so.

Q. What has been discussed in terms of how to handle the 8-milligram high-dose version of Eylea?

A. To be fair, it hasn't gone -- it certainly hasn't left any rooms. It's not -- I freely admit, it's not necessarily something I'm comfortable discussing.

Q. Why are you not comfortable discussing it?

A. Because there is no approved plan yet. It's in active -- it's different than a lot of what we've discussed

here, which are things that have gone on in the past. It's not public knowledge. It's up for active what do we want to do? I wouldn't say we have something I could declare is a plan.

Q. What have individuals expressed they want to do with respect to a high-dose version of Eylea?

A. Make an 8-milligram version of Eylea available to the public to hopefully improve the dosing timeline so people would have to get their injections into their eye with a greater time period between them.

Q. Does Regeneron track these sales of Eylea with respect to each indication?

A. You cannot track sales based on indication.

Q. So the sales that Eylea tracks in the financial documents we looked at earlier are independent of what that Eylea is being prescribed for, what condition?

A. That is true from a sales perspective.

Q. In what context, then, have you come to learn about the indications for Eylea?

A. Sales are not tracked by indication, but certainly want -- percentage of the Eylea sales could be allocated to the indications is a separate source of analysis.

Q. Do you know who at Regeneron is responsible for approving the Eylea4U program?

A. There's a chain of approvals, authorized signature levels, and so on. If the budget exceeds a certain amount, as

it typically does with Eylea4U, then Len Schleifer is the final approval, our CEO.

Q. What type of data does your department provide with respect to Eylea4U to this decision process?

A. If it is within the budget that was planned for the year and approved by Len for spend on Eylea, then we would confirm that this is within the approved budget.

Q. I believe you testified -- I just want to confirm -- does Regeneron have to approve all costs with respect to Eylea on an annual basis or is there an annual review?

A. Regeneron approves all budgets for all brands on an annual basis, not specific to Eylea, not specific to Eylea4U.

Q. Does Regeneron today consider Lucentis and Avastin competitors to Eylea?

A. As previously discussed, we talked about Lucentis as indeed competition and Avastin to be an off-label use in the anti-VEGF market.

Q. Have you seen -- are these the ads that ran in *People* for Eylea that you were referring to?

A. Most likely.

Q. If you could turn to the page that says Cover 1 on the bottom left. It's got 535 as the ending Bates number.

A. Yes.

Q. Do you know if this was an insert in *People* magazine?

A. I don't know. This does say at the bottom it was a

cover wrap, but I don't recall. I've read a lot of *People* magazines over the years.

Q. On this page here do you see any discussion of Eylea dosing on this advertisement page?

A. I do not see anything about dosing on this page.

Q. You can go to the next page. It's got Gate 1, lower left-hand corner.

A. Yes.

Q. Does this advertisement page state anything with respect to the dosing schedule for Eylea?

A. As I read through it, I do not see anything related to dosing.

Q. If we can go to the next page, Bates number ending in 537. Do you see the bold heading that's approximately four down in the left-hand column that says "How Is Eylea Given?"

A. Yes.

Q. And this states, "Depending on your condition, Eylea injections are given on different schedules. Consult your eye doctor to confirm which Eylea schedule is appropriate for you."

Do you see that?

A. Yes, I do.

Q. Does that statement state anything concerning an eight-week dosing schedule?

A. It does not use the number eight at all.

Q. Does it talk about how many weeks between doses of

Eylea?

A. It doesn't say anything about weeks.

Q. On the rest of this page is there any other discussion on this page concerning dosing schedules for Eylea?

A. I've not had an opportunity to read every word on the page. I'm happy to do so.

Q. Sure. Go ahead.

A. I'd like a Ctrl-F.

I do not see anything about dosing schedules on my read through this document.

Q. Okay. You can go to the next page, Cover 2.

Is there any discussion concerning Eylea dosing schedules on this page ending in Bates Number 538?

A. No, there is not.

Q. If you go to the next page, Cover 3 is in the lower left-hand corner as Bates Number 539.

If you could take a second and review the text on this page and confirm that there is no discussion of an Eylea dosing schedule on this advertisement page.

A. I do not see anything related to dosing schedules on this page.

Q. And if you could turn to the next page ending in Bates Number 540.

Can you confirm there's no discussion of an Eylea dosing schedule in this advertisement for Eylea?

A. It does not say anything about a dosing schedule on this page either.

Q. If I can have the court reporter mark as DX 529 a document that does not have any Bates numbers. It is Eylea advertisements that ran in *Good Housekeeping* in 2022.

Ms. Colyer, if you could look at pages 2 and 3 of this document. Have you ever seen these advertisements that Regeneron has run in *Good Housekeeping*?

A. I have never read *Good Housekeeping* before.

Q. Have you ever seen these advertisements before?

A. I mean, I've seen similar advertising.

Q. Where have you seen similar advertising?

A. These ads tend to be fairly consistent; so this is a fairly standard set of data.

Q. Does it appear to be the same ad that ran in all three magazines that are included here in DX 529?

A. Without comparing word for word, at a glance it does appear to be a similar ad, yes.

Q. If you could look at the ad that is the -- the first page of the advertisement that appears on page 2 of DX 529. It is entitled "Keep living life through your eyes."

Do you see that?

A. Yes.

Q. Do you see any discussion of the Eylea dosing schedule on this page of this advertisement?

A. I do not see anything on that page related to dosing regimens.

Q. If you could turn to the next page of the ad, it has a picture of a woman in a pink sweater.

A. Yes.

Q. Do you see any discussion of Eylea dosing schedule on this page of the Eylea ad?

A. I do not.

Q. If we could turn to the next page, which is the last page of this advertisement, and if you need to, take a moment to review it.

Does this page include any discussion concerning the Eylea dosing schedule?

A. It does not.

Q. Are you aware that Regeneron won awards for the "Beautiful Pair" ad campaign?

A. Yes, I am.

Q. How are you aware of that?

A. Because it was all over the place for a while. I follow LinkedIn.

Q. It was all over the place; you mean the advertising campaign was very popular?

A. No. Who I worked for, Regeneron at the time, and the team was recognized as having won awards. And I saw it posted on LinkedIn in different ways.

Q. So we looked at some print that Regeneron had for the "A Beautiful Eye" campaign that ran in *People* magazine, correct?

A. Yes, we did.

Q. Are you aware of what other media the "A Beautiful Pair" ad campaign appeared in?

A. Yes, I am.

Q. What are those sources?

A. Television.

Q. I'm going to have the court reporter mark as DX 530 a transcript of an advertisement that Regeneron ran for "A Beautiful Pair".

Do you have that transcript?

A. Yes, I do.

Q. And do you see at the top of this document it has a URL link for YouTube?

A. Yes.

Q. I'm going to play that advertisement for you that's available at that URL. If you can follow the transcript and make sure that the transcript accurately reflects what's provided in the ad.

A. Okay.

Q. Did the transcript track the video?

A. Yes, it did.

Q. And was there any discussion in this advertisement

concerning the dosing schedule for Eylea?

A. The YouTube channel did not talk about dosing schedule, no.

Q. Was the video that I played the type of ad that would have run on TV?

A. Yes, I believe it would have been similar to what would have been on TV.

MS. MAZZOCHI: And, Your Honor, that concludes the Jennifer Colyer deposition.

THE COURT: Understood. Thank you, Counsel.

MS. MAZZOCHI: In association with this, we'd like the administrative matters of entering additional exhibits into evidence. Defendants move into evidence DTX 501, 528, 529, 529-A, and 530.

THE COURT: Any objection to any of those?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, those are hereby admitted.

(DTX 501, DTX 518, DTX 529, DTX 529-A and DTX 530 were admitted.)

MS. MAZZOCHI: With that, then our next topic, I guess, Your Honor, is Ms. Chu.

THE COURT: Yeah. I'll cut to the chase on that.

After giving it some thought, as I indicated yesterday, I do think Mylan's entitled under Rule 32 to play

the portions designated as 30(b)(6) testimony.

Upon further -- I didn't say anything further past that, having wanted to research it additionally. The Court believes Mylan's likewise entitled to play other testimony from Ms. Chu outside of her 30(b)(6) role. Again, she's unavailable under Rule 32(a)(4)(B) in that she is more than 100 miles from Clarksburg, West Virginia. So there would be no limitations under the rules for using that transcript.

I'm aware the parties agreed to something to the contrary in their joint memo applying to this trial, but in all candor, we've blown through that a couple times today -- I'm sorry -- a couple times already. I know paragraph 4 indicates witnesses who are going to testify live, the parties agreed are not be permitted to play deposition testimony. I would not apply that to the 30(b)(6) designations.

But, again, the rules are what they are. The parties can agree as they like, but the rules, in all candor, trump. And from the category of what's good for the goose is likewise good for the gander, paragraph 39 dealt with the agreement that impeachment exhibits not previously disclosed would not be admitted into evidence absent good cause.

So we've already done that once today. Ms. Chu, I understand, is going to testify live as part of -- is it Regeneron's rebuttal case?

MR. GREGORY: Yes, Your Honor.

THE COURT: Rebuttal case. But under Rule 32, I think Mylan is entitled to use that transcript regardless of which hat Ms. Chu is wearing at the time, her 30(b)(6) designee hat or her fact witness personal capacity hat. So they'll be permitted to play it as designated.

I would note, however, given this kerfuffle over it, Regeneron will have some leeway when Ms. Chu is here in person with respect to what areas they're permitted to cover.

So that's how we'll deal with Ms. Chu's testimony.

I'll direct the parties to get together this evening to review and discuss the updated slide deck of Dr. Rabinow to see what remaining issues there are.

Would that be the first witness Mylan anticipates calling in the morning?

MS. MAZZOCHI: Yes, Your Honor.

THE COURT: We'll take that up first thing, but y'all need to get together and talk about that this evening to see what, if any, disputes may remain in light of the Court's granting of Regeneron's motion to exclude those particular -- that particular opinion, I should say, of Dr. Rabinow with respect to obviousness.

Anything else we need to take up at this point of the day, then, from plaintiff's perspective?

MS. OBERWETTER: Not today, Your Honor.

MS. MAZZOCHI: Nothing from us, Your Honor.

THE COURT: We'll see everyone in the morning. Everyone have a pleasant enough evening. Thank you all very much.

(Proceedings concluded at 5:13 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 15, 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 15th 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 5

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 16, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

APPEARANCES:

On behalf of the Plaintiff:

David I. Berl
Ellen E. Oberwetter
Thomas S. Fletcher
Arthur J. Argall, III
Kathryn S. Kayali
Andrew V. Trask
Williams & Connolly, LLP
680 Maine Avenue, SW
Washington, D.C. 20024
202.434.5000

Andrew E. Goldsmith
Kellogg, Hansen, Todd, Figel & Frederick, PLLC
1615 M. Street NW, Suite 400
Washington, DC 20036
202.326.7945

APPEARANCES CONTINUED ON NEXT PAGE

On behalf of the Plaintiff, continued:

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

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

On behalf of the Defendant:

Deanne M. Mazzochi
William A. Rakoczy
Heinz J. Salmen
Eric R. Hunt
Lauren M. Lesko
Neil B. McLaughlin
Lawrence Scott Beall
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

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Transcript produced by computer-aided transcription.

Friday Morning Session,

June 16, 2023, 9:30 a.m.

- - -

THE COURT: We convene for day five then -- it's a casino in here some days -- of trial counsels presence. Had a chance to skim, but I certainly wouldn't say I've read Regeneron's second motion to exclude undisclosed expert opinion.

Would it be fair to characterize that motion as largely based on similar issues as the motion we addressed yesterday?

MR. BERL: Yes, Your Honor.

THE COURT: All right. I need to see Dr. Rabinow's report where this combination of prior art was disclosed and the explanation as to why it would be obvious, then.

MR. HUNT: Your Honor, we will have copies for you here shortly. If I may.

THE COURT: I have -- I do have his report.

MR. HUNT: Very good. Then I would like to take you to paragraph 290 of Dr. Rabinow's opening expert report. There are a number of combinations listed in paragraph 290 of both Dr. Rabinow's opening report, Your Honor. For the Court's benefit and certainly the benefit of everyone's time, we have simplified things a bit for trial today.

Dr. Rabinow, in Number 1, is testifying today

regarding the combination of Fraser with Liu. And in addition to that combination, he will separately be offering opinions today with regard to Number 4, the prior art Lucentis formulations, as evidenced by the Shams and Gaudreault articles, in combination with Fraser.

Now, I expect, Your Honor, that counsel for plaintiff is concerned that, the way that Dr. Rabinow's demonstratives have been organized, that he, they suspect, is going to offer opinions regarding the combination of Lucentis and Liu.

I have assured counsel for plaintiff that that is not Dr. Rabinow's intent, that is not a combination, as we discussed, that is disclosed in his opening report. However, it is important for the Court to keep in mind -- and I think plaintiff may have a response to this -- that prior art needs to be considered in the context of the knowledge of the person of ordinary skill in the art as a whole.

And I suspect that may be where the issue is here, Your Honor. There are certain disclosures in the Lucentis prior art, and there are certain disclosures in Fraser. And the person of ordinary skill in the art, as of June 16, 2006, would have an understanding and a body of knowledge based upon the prior art as a whole that would inform their reading of those references.

So while Dr. Rabinow is not offering opinions as to the combination of anything more than Lucentis and Fraser,

there are certain facts that are known to the person of prior art -- I'm sorry -- the person of ordinary skill in the art that would inform their understandings of the words on the page of Gaudreault and Shams.

So I suspect that may be where the issue is. I'm happy to discuss it a bit more. But if the Court doesn't have any further questions, I'll turn it over to Mr. Berl.

THE COURT: I do not. Thank you.

Counsel?

MR. BERL: Good morning, Your Honor. I think there's some agreement that the only combinations that Mylan is permitted to rely on for motivation, for expectation of success, for meeting each limitation of the claim are the four that are written in paragraph 290 of Dr. Rabinow's report, which they've narrowed today.

The problem, however, is -- and I think this is best seen at Slide 55 of Dr. Rabinow's presentation which we have reproduced on page 6 of the motion that we filed this morning --

THE COURT: One second, please. Thank you.

MR. BERL: I've also shown it on the screen.

THE COURT: Thank you.

MR. BERL: But what this shows is -- here's the way they've organized it, Your Honor. They've organized their presentation so that first they address what they call the

obviousness of Claim 1. Then separately, much later on, they address the obviousness of the dependent claims.

Those obviously aren't two separate inquiries, because the dependent claims include all of the limitations. So when you say Claim 2 is obvious, you're saying everything from Claim 1 and Claim 2 is one claim that includes Claim 1, of course.

THE COURT: Slow down, Mr. Berl.

MR. BERL: Sorry, Ms. Knecht. I did well yesterday, but --

THE COURT: Didn't talk much yesterday. It's 9:45 and --

MR. BERL: The only reference that they cite in the presentation to fulfill the last limitation of the claim, the 98 percent native conformation limitation, is Liu. That's it. They don't have a checkmark for this by Fraser; they don't have a checkmark by Lucentis; they don't have a checkmark for anything else. That limitation is in all of the asserted claims. It's actually narrowed in some of them to get to 99 percent at 24 months. But that's it.

So then when they proceed later to the dependent claims and they say, oh, all we're really running here is Lucentis plus Fraser, pay no attention to Liu, it's already infected because they've already asserted Liu and only Liu with respect to one of the limitations of Claim 1.

So they may make it seem like they're not running Lucentis and Liu together. They admit they're not allowed to do that. But they are. They are. And it's as clear as day. They're not allowed to do it.

So what they're doing is they're kind of merging the two arguments that they say are the two arguments they're now preserving, Fraser plus Lucentis -- sorry -- Lucentis plus Fraser and Fraser plus Liu. They're merging them. And we were concerned about it.

So what we did last time was we sent them a stipulation, a proposed stipulation that essentially says you can't merge your distinct prior art combinations because once you merge them, it's a totally separate inquiry, right? Whether there is a motivation to combine Lucentis and Liu is different than whether there's a motivation to combine Lucentis from Fraser.

Every different combination has different motivation analysis. That's why the whole case is based on what combinations they assert. So we were concerned, and we said how about this stipulation, that just makes it clear you're limited to the four combinations in Dr. Rabinow's report and you can't use art from one combination into the other.

We sent that last night. We've gotten no response. If they sign that stipulation or agree to that stipulation and Your Honor signs it, I think we're okay and they can't do that

and it's clear. But the way they have it now and what they're clearly doing is they are, without making it clear, relying on Lucentis and Liu once you put Claim 1 together with the dependent claims as the law requires. And they're just not allowed to do that.

THE COURT: Is it this single slide?

MR. BERL: No. It's throughout. I mean, we didn't want to reproduce the whole slide deck. I have it for you if Your Honor wants me --

THE COURT: I'll get a copy soon enough.

MR. BERL: But yes. I think it starts at Slide 50 where they matriculate through the limitations of Claim 1, and then what you'll see is, when they get to this final limitation, which they address at Slide 55 which is the 98 percent, it's Liu. It's only Liu.

And then when you get to the dependent claims, which I think they start to tick them off at about Slide 79 or something like that, you'll see starting at about Slide 99 what they do is they start to address the final limitation, and there, actually, they rely on Liu for even more, 40 to 150.

They're allowed to do that for the Liu combination. They're not allowed to rely on Liu for their Lucentis plus Fraser combination. It's different. That's -- Liu's not part of that.

And then when they get to the 98 percent limitation,

they rely for the obviousness -- if we go back to 105 or so, they're relying on Liu for that again.

So the problem is it's Lucentis plus Liu. Everyone agrees -- they just stood up and agreed -- they're not allowed to do Lucentis and Liu together.

THE COURT: Understood.

Counsel?

MR. HUNT: Thank you, Your Honor. I guess my initial point is that we've spent a lot of time looking at slides. Those are not in the record. I suspect they will not ultimately be in the record. What will be in the record is Dr. Rabinow's testimony. I've told counsel for plaintiff the combinations are Fraser and Lucentis and Fraser and Liu. Dr. Rabinow does not intend to offer opinions on the combination of Fraser and Lucentis and Liu.

I don't know how much more clear I can make it. I think maybe we just need to see if we can get the testimony in the record and Your Honor can decide the issue at that point.

With regard to the slides, I will fully admit that there may have been some checkmarks that are missed along the way. It's been -- there's been a number of iterations through the motion to exclude process.

And what will be made clear when Dr. Rabinow testifies is that the person of ordinary skill in the art -- again, through that knowledge that they have, the entire body

of prior art as of June 16, 2006 -- would have a certain understanding when they read the Lucentis references. At that point in June 16th of 2006, the person of ordinary skill in the art would know that Lucentis is in the clinic -- it's in clinical trials -- and, therefore, they would expect and they would understand that the formulations disclosed in those Lucentis references are necessarily stable.

Now, whether that issue is -- carries enough weight at the end of the day to support the obviousness analysis, I think that's for Your Honor to decide, and I'm certain that Mr. Berl will explore on cross-examination. But to exclude prior art references on the basis of the knowledge of the person of ordinary skill in the art to not consider the body of knowledge of the person of ordinary skill in the art, the Federal Circuit has made clear would be error.

THE COURT: But I guess that gets to the point, the Federal Circuit has been abundantly clear, as this Court tried to articulate yesterday, that when we're talking about obviousness, the specific prior art needs to be identified and then an explanation needs to be identified in the expert disclosures. That's the evidentiary basis to support an obviousness defense.

If we can just say, well, a POSA knows everything that is already out there, why then does the Federal Circuit impose that requirement upon someone asserting an obviousness

defense?

MR. HUNT: I'm not disputing, Your Honor, that there is a defined combination. But, for example, the Federal Circuit in *Arioso Diagnostics v. Verinata Health,* 805 F.3d 1359 (2005), made very clear that art can legitimately serve to document the knowledge of that skilled artisans would bring to bear in reading the prior art identified as producing obviousness.

So we can't completely cast away the knowledge of the person of ordinary skill in the art. And Dr. Rabinow, in his report, has articulated that there's -- again, the knowledge of the person of ordinary skill in the art through a reference called Avery discloses that Lucentis is in clinical trials.

So that is part of the knowledge of the person of ordinary skill in the art in this crowded field where you have really just two main players in the area of VEGF antagonists. And so that person of ordinary skill in the art at that June 16, 2006, time frame would be well aware of what's happening with Lucentis.

THE COURT: Yes, Counsel, briefly.

MR. BERL: Very briefly, Your Honor. I think that just gave the game away. I mean, what they're basically saying is we get to rely on any of the prior art that we cited. The report you have in front of you, Dr. Rabinow's report, goes through 46 different references. It starts on page 37 of his

report, goes all the way to, like, page 146. It's, like, over 100 pages.

They can't just later say, oh, I'm going to rely on Avery. What's that? That wasn't one of their four. That's new this morning.

If they're now running a four-reference case, trying to, Shams and Gaudreault -- which is Lucentis -- plus Fraser plus Liu, out of their 46 references, do you know how many possible combinations of four references there are?

THE COURT: We've established I'm bad at math.

MR. BERL: I didn't know either. So I googled it. Google allows you to do it now. 163,185. The notion that they --

THE COURT: Thank you.

MR. BERL: -- can just come in and today say, oh, we're relying on Avery for this or Gaudreault for that, that's not how it works. The cases make that clear.

THE COURT: Understood. I'm going to hold the motion in abeyance at this point. I think counsel's articulated the dance between and among raindrops that they're going to endeavor. The Court ruled on the first motion to exclude yesterday. That holds. Those rules will apply. And we can deal with it as we go as necessary.

I don't think it's necessary at this point. We're talking about demonstrative slides. We don't need to redo

those at this point. We'll note as we go if there are issues that run afoul of the -- what I'll inartfully refer to as law of the case at this point, the Court's position on this, focusing instead on what opinions Dr. Rabinow offers.

So we'll hold that in abeyance and take it up as we go question by question, answer by answer at this point.

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

MR. HUNT: No, Your Honor.

THE COURT: Plaintiff's perspective?

MR. BERL: No. Thank you, Your Honor.

THE COURT: Thank you all.

Mylan call its next witness.

MR. HUNT: Your Honor, with the Court's permission, I've brought an altitude-increasing device for the microphone for the court reporter's benefit and also a little bit for my back.

THE COURT: Understood, sir. Wellness is a focus in this courtroom. Thank you.

MR. HUNT: Your Honor, Mylan and Biocon call Dr. Barrett Rabinow to the stand.

BARRETT E. RABINOW, PhD, DEFENDANTS' WITNESS, SWORN

MR. HUNT: Your Honor, with permission, we have some copies of slides and --

THE COURT: Please.

MR. HUNT: -- exhibits.

THE COURT: Please. Thank you.

MR. HUNT: Your Honor, may I proceed?

THE COURT: You may.

DIRECT EXAMINATION

BY MR. HUNT:

Q. Good morning, Dr. Rabinow.

A. Good morning.

Q. Could you please introduce yourself to the Court.

A. I am Barrett Rabinow.

Q. You are here testifying on behalf of defendants Mylan and Biocon?

A. I am.

Q. Did you prepare some slides to assist with your testimony today?

A. I did.

MR. HUNT: Mr. Gibson, if we could please pull up DDX 4.

BY MR. HUNT:

Q. Are these the slides that you prepared, Dr. Rabinow?

A. They are.

Q. Turning to DDX 4, Slide 2, briefly describe your academic experience, sir.

A. I earned a undergraduate degree in chemistry at Cornell University and then went to the University of Chicago,

where I earned a master's and a PhD in physical organic chemistry.

Q. And after receiving your PhD, did you receive a fellowship?

A. Yes. I had an NIH fellowship that allowed me to learn clinical chemistry at what was then Michael Reese Medical Center in Chicago.

Q. And did your graduate studies involve a particular research or study area?

A. I studied very fast-reaction kinetics, species that lasted maybe a microsecond, studied with a flash photolysis apparatus that I built.

Q. Was your graduate research published?

A. It was published both as a thesis and in the *Journal of the American Chemical Society*.

Q. If we could go to Slide 3, Dr. Rabinow, briefly describe your industrial experience.

A. I went to Baxter Healthcare Corporation where I was there for almost 40 years, eventually earning the title of Baxter distinguished scientist, which is a title earned by less than a dozen scientists in their 50,000-person organization.

Q. If we could go to Slide 4, please, Dr. Rabinow, please tell the Court about your experience as a Baxter distinguished scientist and scientific team leader.

A. I was a -- sort of a chief problem solver for a

number of product problems that Baxter had at the time with issues dealing with, in the case of proteins, adsorption, aggregation, issues.

A number of clients that Baxter had used Baxter products for their proteins and noticed that they were having adsorption issues. So they would contact me, and we would discuss formulation, how to prevent this.

This eventually led to getting involved with manufacturing as well as formulation, studying aggregation and adsorption issues. And I decided to study this.

So I conducted some research in the area of comparing three different proteins -- insulin, albumin, and immunoglobulin G -- and studied their adsorption on a number of different plastics to get an idea of what was the difference in terms of surface adsorption to different plastics and the rate and extent of adsorption.

We eventually published this in the *Journal of Biomaterials* and eventually got a patent on protein adsorption-resistant plastics.

We then -- Baxter had several projects of its own involving insulin. They had a project collaboration with Exubera at the time as well as a company called Epic Therapeutics making nanoparticle insulin dosage forms. So I was an active member of both of those teams.

I also worked on problems that Baxter incurred with

their albumin in factor VIII formulation problems dealing with aggregation, stability, and inflammation issues.

I was also an expert witness involving insulin formulations after I left Baxter.

Q. Now, Dr. Rabinow, you just explained some of your experience with regard to insulin and factor VIII and albumin.

Do you consider that work to be involving the formulating and manufacturing of proteins?

A. Yes. You are essentially under the gun, under time pressures to solve problems, trying to understand what are the issues involved in a particular problem, and then try to understand not only what the scientific basis of the problem is but also develop experiments to come up with a viable solution.

Q. Did your work at Baxter result -- other than I think the publication and patent that you already mentioned -- in any other publications or patents?

A. I have something like 14 patents on various aspects of formulations, nanosuspensions, and antimeres, different sterilization processes, as well as more than 40 publications and book chapters.

Q. As part of your product development experience, do you also have regulatory experience?

A. Yes. I interacted with FDA on many occasions in somewhat rather contentious issues involving product problems and in trying to convince FDA that we understood the problem

and were -- had a viable approach to resolving the issues.

Q. And if we could turn to Slide 5.

Do you have additional specific experience in the field of therapeutic proteins?

A. Yes. After I left Baxter, I became a consultant to pharma, both large companies and small. In this particular case I worked with Dr. Jeffrey Loeb, who is a practicing neurologist and head of the department of neurology at University of Illinois at Chicago.

His group was developing a novel and patented fusion protein involving a decoy receptor to stop disease progression in Lou Gehrig's disease, or ALS. So I prepared the formulation and grant preparation for that work involving the analytical methods, development of the administration procedures for intrathecal and intracerebral ventricular administration, and then I developed toxicity and efficacy protocols to study all of that. So that was my experience with fusion proteins using decoy receptors.

Q. And turning to Slide 6, Dr. Rabinow, how many total years of experience do you have in the field of pharmaceutical formulations?

A. Well, it's at least 25, with four years total in industry altogether.

Q. If we could go to Slide 7.

You have displayed here DTX 7091. Is DTX 7091 your

current CV, Dr. Rabinow?

A. It is.

MR. HUNT: Your Honor, we move to admit DTX 7091 into evidence.

THE COURT: Any objection?

MR. TRASK: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 7091 was admitted.)

MR. HUNT: At this time defendants proffer Dr. Barrett Rabinow as an expert in pharmaceutical formulation science, including the development and manufacture of formulations of therapeutic proteins.

THE COURT: Any voir dire or objection?

MR. TRASK: No, sir, no objection.

THE COURT: Without objection then, motion granted. The doctor is deemed so qualified.

You may proceed, Counsel.

MR. HUNT: Thank you, Your Honor.

BY MR. HUNT:

Q. Dr. Rabinow, let's briefly summarize the opinions that you plan to provide to the Court today.

But before we do, Mr. Gibson, could we please call up PTX 2 on the screen.

Dr. Rabinow, what is the document that appears at PTX 2 on the screen?

A. This is the '865 patent.

Q. And, Dr. Rabinow, you have your own screen, if it's easier for you to reference the screen there.

A. Yes.

Q. Okay. Very good. So this is U.S. Patent Number 11,084,865; is that right?

A. That's correct.

Q. And for purposes of our discussion today, may we refer to this patent as the '865 patent?

A. Please do.

Q. Have you been asked to render an opinion regarding the validity of certain claims of the '865 patent?

A. Yes.

Q. Okay.

Now, Mr. Gibson, if we could please have PTX 3 on the screen.

Dr. Rabinow, what is the document that appears at PTX 3 on the screen?

A. My screen has not changed.

Q. It's possible that it looks very similar. These patents, they all look the same except for that little number in the top right.

A. I'm sorry. It's like an eye chart.

It's Patent 11,253,572.

Q. And for purposes of our discussion today, may we

refer to this patent as the '572 patent?

A. Indeed.

Q. And have you been asked to render an opinion regarding certain limited terms in the '572 patent?

A. Yes.

Q. And do you intend to provide testimony today regarding the invalidity of the '865 patent?

A. Yes.

Q. And, similarly, do you intend to provide testimony today regarding certain limited elements of the '572 patent, including whether a person of ordinary skill in the art would have considered those limited elements known and/or obvious in view of the prior art?

A. Yes.

Q. Dr. Rabinow, do you also intend to provide testimony today in rebuttal to Dr. Trout's opinions regarding the '865 and '572 patents?

A. Yes.

Q. Directing your attention to Slide 8, could you briefly summarize your opinions.

A. My opinions are that one of ordinary skill in the art would have found Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent to have been anticipated by the prior art, that these same claims of the '865 would have been obvious to one of ordinary skill in the art after consideration of the prior art,

that there is no objective evidence of nonobviousness in rebuttal to Dr. Trout and other of plaintiff's experts, and finally that the formulation elements of Claim 6 of the '572 patent were known and/or obvious to the person of ordinary skill in the art.

Q. And were you present, Doctor, in the courtroom for Dr. Trout's testimony?

A. I was.

Q. Did anything about Dr. Trout's testimony change the opinions you intend to provide today?

A. It did not.

Q. Thank you, Dr. Rabinow.

I would like to briefly discuss how you arrived at the opinions you plan to provide to the Court today.

If we could have Slide 9 called up, please.

Dr. Rabinow, do you understand that the Court has construed certain terms of the '865 patent?

A. I do.

Q. And have you set out the Court's claim constructions relevant to the '865 patent here?

A. Yes.

Q. Did you rely on the Court's claim constructions in forming your invalidity opinions?

A. I did.

Q. From whose perspective did you conduct your

invalidity analysis with regard to the '865 patent and the '572 patent?

A. From the perspective of a person of ordinary skill in the art.

Q. And did you bring your experience and knowledge into account in rendering your opinions from the perspective of the person of ordinary skill in the art?

A. I did.

Q. Let's turn to Slide 10, please. Do you understand that defendants and Regeneron have each provided a definition of a person of ordinary skill in the art relevant to the '865 patent?

A. Yes.

Q. And I'd like to look at the top callout on this slide, Dr. Rabinow. This is paragraph 63 from your opening report, which reads, "A POSA, during the relevant time period, would have a fairly high level of education and skill. Here, a person of ordinary skill in the art would have at least a PhD in chemistry, chemical engineering, biochemistry, pharmacology, or a related field, along with one to two years of experience in the development and manufacture of formulations of therapeutic proteins or a lower degree with more practical industrial experience.

"The person of ordinary skill in the art would have access to biologists, biochemists, physicians, pharmaceutical

formulators, and the like with knowledge and experience in the fields such as drug discovery and development and the treatment of ophthalmic conditions."

Did I read that correctly, Dr. Rabinow?

A. You did.

Q. And is this the definition of a person of ordinary skill in the art that you applied in rendering your opinions with regard to the '865 patent claims?

A. I did.

Q. Now, Dr. Trout has also provided an opinion for the person of ordinary skill in the art; is that correct?

A. Yes.

Q. And would your opinions change if the Court were to apply Dr. Trout's definition of the person of ordinary skill in the art?

A. No.

Q. Do you consider yourself at least a person of ordinary skill in the art under both definitions?

A. I do.

Q. Now I'd like to address the '572 patent, sir.

If we could go to Slide 11.

You understand that Mylan and Biocon and Regeneron -- I apologize. Just so the record's clear, defendants Mylan and Biocon collectively and Regeneron have each offered a definition of a person of ordinary skill in the art relevant to

the '572 patent?

A. Yes.

Q. Okay.

Now, Mr. Gibson, if you could please call up DTX 7090 at page 7 to 8. This specifically is paragraph 14 of Dr. Rabinow's reply report.

Dr. Rabinow, is this DTX 7090 your reply report?

A. Yes.

Q. And is this where you discuss the person of ordinary skill in the art with regard to the '572 patent?

A. Yes.

Q. Do you recall that your report contains a number of definitions of the POSA?

A. Yes.

Q. So on the screen do you understand that Dr. Trout provided a definition of the person of ordinary skill in the art with regard to the '572 patent?

A. Yes.

Q. And that definition is "the POSA would have an advanced degree such as a master's in biopharmaceutical science or a related discipline such as chemical engineering and several years of experience in the development of biologic products. Alternatively, the POSA could have a PhD in such discipline and less experience. The POSA may collaborate with others, including a medical doctor, with experience in treating

ophthalmic diseases."

Did I read that correctly, sir?

A. You did.

Q. And for purposes of your testimony today and given the number of definitions that have been floating around for the person of ordinary skill in the art, are you willing to accept Dr. Trout's definition of the person of ordinary skill in the art with respect to the '572 patent?

A. I am.

Q. And you consider yourself a person of ordinary skill in the art under Dr. Trout's definition as it applies to the '572 patent?

A. Yes.

Q. All right. Now, Dr. Rabinow, before we start talking about your opinions in more detail, did you review the literature relevant to the '865 patent as part of your work in this matter?

A. I did.

Q. And did you independently conduct a search for prior art or the knowledge of the person of ordinary skill in the art as of June 16th, 2006, for the '865 patent?

A. I did.

Q. And did you also consider and perform a search for potential disclosures as of January 13th, 2001, with respect to the '572 patent?

A. I did.

Q. Did you prepare a series of slides to help illustrate your opinions regarding the knowledge of the person of skill in the art related to stable protein formulations?

A. I did.

Q. Okay.

If we could please have Slide 12 on the screen.

I apologize. My cocounsel has informed me that perhaps I misspoke. So just so that the record is clear, with regard to your analysis of the scope of prior art for the '572 patent, was that analysis performed as of January 13th, 2011?

A. Yes.

Q. Thank you.

All right. Now, turning to Slide 12, you have DTX 3492 reflected here. What is shown on Slide 12?

A. This is Andya 1 from Genentech published in 1997.

Q. And Andya 1, DTX 3492, is what's reflected on Slide 2; is that correct?

A. Yes.

Q. And did you rely on DTX 3492 in connection with your opinions?

A. I did.

Q. How does DTX 3492, Andya 1 shown here on Slide 13, inform the knowledge of the skilled person?

A. Andya presents formulations of antibodies formulated

with trehalose and Tween 20, which is polysorbate 20, and discusses their stability at 12 months at 5 degrees and shows that there was no change in the percent intact protein for the trehalose formulation using size-exclusion chromatography.

Q. Now, on the next slide, 14, do you present another disclosure you believe is relevant to the art of stable protein formulations?

A. Yes.

Q. And what is shown on Slide 14?

A. This is Papadopoulos from Regeneron published in 2000.

Q. And DTX 3619 is the Papadopoulos reference reflected here?

A. Correct.

Q. Did you rely on DTX 3619 in connection with your opinions?

A. Yes.

Q. Turning to Slide 15, what would the person of ordinary skill in the art find significant in DTX 3619, Papadopoulos?

A. Papadopoulos is a 100-page-long patent that discusses in great detail essentially the generative history of VEGF R1R2 -- or VEGF Trap R1R2 and talks about what the various -- what were the concepts that led to the development of this product. It discusses that it was expressed in Chinese hamster

ovary, or CHO, cells, which would have glycosylated the protein. And it discusses the asparagine sites at which glycosylation occurred as well as the entire amino acid sequence of this protein.

Q. And, Dr. Rabinow, how many glycosylation sites does the Papadopoulos reference inform the person of ordinary skill in the art exist in VEGF Trap R1R2?

A. Five.

Q. If we go to the next slide, DDX 4, Slide 16, how is DTX 3556 relevant to your analysis of the knowledge of the person of ordinary skill in the art?

A. This is Lam from Genentech, a patent published in 2001.

Q. This is DTX 3556. That's the Lam reference, right?

A. Yes.

Q. You relied on DTX 3556 in connection with your opinions?

A. I did.

Q. If we could go to Slide 17, please. What would the person of ordinary skill in the art find significant about Lam, DTX 3556?

A. Lam divulges a monoclonal antibody at a concentration of 40 mg/mL formulated with trehalose and polysorbate 20 and shows the stability in terms of percent monomer by size-exclusion chromatography at several different data points

over a two-year period at 2 to 8 degrees centigrade and shows that it's pretty constant. So there's negligible degradation over that period.

Q. That disclosure, Dr. Rabinow, is at DTX 3556, page 27 and page 30?

A. That is correct.

Q. If we could please turn to the next slide, Slide 18.

What do you show here, Dr. Rabinow?

A. This is Andya 2 from Genentech, a patent published in 2001, DTX 3506.

Q. And did you rely on DTX 3506 in connection with your opinions?

A. I did.

Q. Now, what, if any, disclosure in DTX 3506, the Andya 2 reference, would inform the knowledge of the person of ordinary skill?

A. So Andya --

MR. HUNT: If you could go to the next slide, please, Mr. Gibson.

THE WITNESS: So Andya discloses antibody formulations involving trehalose and polysorbate 20 or Tween 20 and shows the stability at 5 degrees over a period of 12 months and states that there was no change in the percent intact protein for the trehalose formulation.

BY MR. HUNT:

Q. And was there a particular analytical method that was used in the Andya 2 reference to present the stability results that you just discussed?

A. They use size-exclusion chromatography.

Q. And the disclosure of the stability data in Andya 2 is at DTX 3506, page 23; is that correct?

A. Yes. And 22.

Q. Thank you, Dr. Rabinow.

If we could turn, please, to Slide 20, what is DTX 728?

A. This is Wulff from Regeneron, a publication from 2002.

Q. Did you rely on DTX 728 in connection with your opinions?

A. I did.

Q. On the next slide, Dr. Rabinow, how would the disclosures of Wulff inform the person of ordinary skill?

A. Well, first of all, Wulff refers to VEGF Trap R1R2, which, by this point, the POSA would recognize as a specific entity having a known amino acid sequence glycosylation pattern, et cetera, because this was widely discussed in the literature. It would be as common, for example, as when one mentions aspirin. And a POSA would understand that that would envision the structure of acetylsalicylic acid, for example.

He talks about VEGF Trap -- he talks about it's a recombinant chimeric protein or a fusion protein. VEGF Trap was expressed in CHO cells. And he also discusses that control animals in his animal experiments were treated with a vehicle and proceeds to give the formulation of that vehicle consisting of 5-millimolar phosphate, 5-millimolar citrate, 100-millimolar sodium chloride, .1 percent weight per volume Tween 20, and 20 percent weight per volume sucrose.

And a POSA would understand that the formulation used in the control would also be used for the -- what's known as the test arm involving that in combination with the active ingredient, the VEGF Trap R1R2.

Q. And, Dr. Rabinow, the disclosures of Wulff that you've just discussed, that's at DTX 728, page 2?

A. Yes.

Q. If we could please turn to the next slide, Slide 22. Is there an additional reference that's relative to your analysis?

A. Yes. This is Holash, also from Regeneron, a publication from 2002.

Q. And just so the record's clear, DTX 3549 is the Holash reference reflected here?

A. Yes.

Q. You relied upon the Holash reference, DTX 3549, in connection with your opinions?

A. Yes.

Q. On the next slide, Slide 23, what would the person of ordinary skill in the art take away from DTX 3549, the Holash reference?

A. He would take away quite a lot. He would understand from the disclosure that, quote, they were able to engineer a very potent high-affinity VEGF blocker that has prolonged in vivo pharmacokinetics and pharmacodynamics. It lacks nonspecific toxicities and can effectively suppress the growth and vascularization of a number of different types of tumors in vivo.

Q. And that disclosure in Holash is at 3549, page 1; is that correct?

A. Yes.

Q. Moving to the next slide, 24, did Regeneron disclose specifics of the VEGF Trap R1R2 protein in DTX 3549, Holash?

A. Yes. They discussed that it is a fusion protein. It's purified from Chinese hamster ovary cells. And it gave a pictorial which was very illustrative in terms of showing how they combined several different receptor portions of two different receptors of VEGF to combine them to make VEGF Trap R1 and R2.

Q. So by at least 2002 would the person of ordinary skill in the art know the molecular details of VEGF Trap R1R2?

A. He would.

Q. And is that because Regeneron itself published those molecular details and characteristics of the fusion protein?

A. That is correct.

Q. Let's discuss DDX 4, Slide 25. What is shown here, Dr. Rabinow?

A. This is Kaisheva, a patent published in 2003.

Q. And DTX 3610 is that Kaisheva '316 reference, correct?

A. Yes.

Q. Did you rely on DTX 3610 in connection with your opinions?

A. I did.

Q. What does Kaisheva '316, DTX 3610, tell the person of ordinary skill in the art about the protein formulation process?

A. Kaisheva provides a recipe for how you go about developing protein formulations. In terms of a three-step process.

I think you need to change the slide too.

Q. Oh, sorry.

If we could please go to the next slide.

A. So he talks -- the first step is you want to optimize the pH. The pH is a controlling variable, and it's rather easily determined. You would do what are known as accelerated stability tests. In other words, you conduct studies where the

protein is formulated at different pHs and studied perhaps at 40 degrees over a period of weeks. And you select a pH that gives you the most stability. That's known as selecting the optimum solution pH.

After you've locked in the pH, you select the buffer type that will maintain that pH as well as its concentration. There's not many choices here because, for any particular pH, there's only a limited number of options for buffers.

So this is a pretty routine process, if you will. So, again, you would select -- make several different buffers at various different concentrations and study their stability over perhaps 40 degrees over a few weeks and then select the optimum buffer type and concentration which give you the most stable formulation.

So after you have locked in the pH, the buffer type, and the concentration, you're now ready to examine the effect of other excipients for either a liquid or lyophilized dosage form that you're studying. And this is all using a statistical package so everything can be understood to ensure that it has statistical significance.

Q. And these disclosures are found in DTX 3610, including at page 16?

A. Correct.

Q. If we could turn to Slide 27, please.

Is there another Kaisheva reference that's included

in your analysis, Dr. Rabinow?

A. Yes. This is Kaisheva patent published 2003.

Q. And I believe this is a patent application; is that correct?

A. That is correct.

Q. And so this is DTX 3611, the Kaisheva '417 reference, correct?

A. Yes.

Q. Did you rely on DTX 3611 in connection with your opinions?

A. Yes.

Q. Moving to Slide 28, what does DTX 3611, the Kaisheva '417 reference, tell the person of skill in the art about protein formulation stability?

A. Kaisheva discloses a rather high concentration of an antibody that is formulated with a succinate buffer as well as Tween 80, or polysorbate 80, and studies it for a percent monomer, which means he would have done size-exclusion chromatography, and finds that at 5 degrees after 12 weeks, the percent monomer is at 98.25 percent.

Q. And the disclosure of the formulation details in Kaisheva '417 is at DTX 311, page 15; is that right, Dr. Rabinow?

A. Yes.

Q. And the stability results that you have described in

Table 5, that's at DTX 3611, page 15, as well, right?

A. That's correct.

Q. If we could please move to Slide 29.

What reference is shown here, Dr. Rabinow?

A. This is Liu from Genentech, a patent application publication published 2004.

Q. And that is DTX 730, correct, the Liu reference?

A. Yes.

Q. While I think the record may already be clear on this, did you rely on DTX 730, the Liu reference, in connection with your opinion?

A. I did.

Q. Moving to Slide 30, how is DTX 730 relevant to the knowledge of the person of ordinary skill in the art as of June 16th, 2006?

A. The Liu reference discusses high-concentration antibody formulation. So that would be of particular interest. And he discusses protein concentrations ranging from 40 to 150 mg/mL, or milligrams per milliliter. And specifically what is shown on DTX 730, page 35, is a table displaying the stability of an antibody known as E25 formulated at 80 mg/mL with a histidine buffer, a trehalose sugar stabilizer, and a polysorbate 20 component all at pH 6. And stability was monitored by size-exclusion chromatography.

A percent monomer was followed at 5 degrees for 24

months, and the values at 6 and 14 months, for example, were 99.1 and 99.0 percent and at 24 months was at 98.8 percent.

He also discusses turbidity values as well.

Q. Now, before we move on, I want to make sure that the record is clear with regard to a few disclosures that you've referenced in the Liu publication.

Looking at DTX 730, page 35, did the Liu reference disclose a range of protein concentration?

A. Yes. He disclosed the range of 40 to 150 mg/mL; so rather high concentrations. He also discussed ranges of polysorbate of .01 percent to .1 percent and -- as well as sugar ranges, either trehalose or sucrose, ranging from 20 millimolar to 350 millimolar.

Q. And turning to the table that you have depicted on the left side of the slide, DTX 730, also on page 35, what were the concentrations of the protein formulations that Liu tested here?

A. It was 80 -- well, the bottom one that I referred to -- given the stability data for -- was 80 mg/mL in a histidine buffer and trehalose sugar formulation. Above that is an even higher concentration formulation at 150 mg/mL also using a histidine buffer.

Q. And the percent monomer data that's presented in this table, was there a particular analytical method that was used to gather that data?

A. That was size-exclusion chromatography.
Q. And, again, that's at DTX 730, page 35, correct?
A. That is correct.
Q. And, Dr. Rabinow, I apologize if you've already mentioned this, but Liu reported the work of what company?
A. Genentech.
Q. All right.
If we could please turn to the next slide, DDX 4, Slide 31.
Does this disclose an additional relevant reference, Dr. Rabinow?
A. Yes. This is Fraser from Regeneron, an article published in 2005.
Q. And DTX 0729 is the Fraser reference reflected in your Slide 31, correct?
A. Yes.
Q. And did you rely on DTX 729 in connection with your opinions?
A. I did.
Q. Moving to Slide 32, what does DTX 729, the Fraser reference, tell the person of ordinary skill in the art regarding VEGF protein formulations?
A. Fraser discloses VEGF Trap R1R2 would automatically enable a POSA to envision the amino acid sequence of the protein, the glycosylation pattern, and other relevant

information. It is disclosed here that the substance was provided by Regeneron and it was provided at a concentration of 24.3 mg/mL in 2-milliliter aliquots in buffer. That was composed of 5-millimolar phosphate and 5-millimolar citrate at a pH of 6, also including Tween 20 -- that's polysorbate 20 -- with 20 percent sucrose. And this is at DTX 729, page 1.

THE COURT: Sorry, Counsel, not to interrupt. We've got a new word. I don't think I've heard aliquots before or during this trial.

Can you tell me what that is, Doctor?

THE WITNESS: Yes. It's a small volume of a liquid.

THE COURT: It's a unit of measurement?

THE WITNESS: It's not quantitative, more qualitative, suggestive.

THE COURT: Oh, okay. Understood. Thank you very much.

Sorry, Counsel. Go ahead.

MR. HUNT: Problem, Your Honor. Thank you.

Mr. Gibson, could we please go to the next slide, DDX 4, Slide 33.

BY MR. HUNT:

Q. Dr. Rabinow, do you set forth here an additional reference that you believe is relevant to your analysis?

A. I do. This is Gaudreault from Genentech, a publication dating to February of 2005.

Q. And that Gaudreault reference is DTX 2265, correct?
A. Yes.
Q. Did you rely on DTX 2265 in connection with your opinions?
A. I did.
Q. What would the person of ordinary skill in the art note in the February 2005 Gaudreault reference, DTX 2265?
A. He would note that there were preclinical pharmacokinetics -- that means animal studies -- of ranibizumab, which is a vascular endothelial growth factor fragment after a single intravitreal administration.

So he would understand that VEGF was injected intravitreally into the eye of animals and that the substance ranibizumab furthermore was formulated as 10 millimolar in a succinate buffer and 10 percent trehalose and also contained .05 percent Tween 20, or polysorbate 20.

Q. And, Dr. Rabinow, those formulation details you just discussed are found at DTX 2265, page 2; is that correct?
A. That's right.
Q. Now, the ranibizumab that is reflected on DTX 2265, page 2, would that have another name to the person of ordinary skill in the art?
A. Yes. Once it got approved, it was given the brand name of Lucentis.
Q. Turning to the next slide, DDX 4, Slide 35, what is

shown on this slide, Dr. Rabinow?

A. This is Dix '226. Dix is from Regeneron. The date of the patent is 2019, but the priority date tracks back to the provisional application filed on March 25th of 2005.

Q. And, Dr. Rabinow, for purposes of your analysis today, have you been asked to assume that the Dix '226 patent is prior art to the '865 patent?

A. I have been so instructed, yes.

Q. And DTX 13 is that '226 patent; is that correct?

A. That's correct.

Q. And you relied on DTX 13 in connection with your opinion?

A. I did.

Q. If we could go to the next slide, what would be notable to the person of ordinary skill in the art about DTX 13, the Dix '226 patent?

A. It is stated on page 5 that it is, first of all, suitable for injection. On page 7, Example 1, it is stated that it is a liquid formulation containing 10 millimolar of phosphate, 0.1 percent polysorbate 20, 20 percent sucrose, 50 mg/mL VEGF Trap -- and then that is described further as Sequence ID Number 4 -- at a pH of 6.25; and that was stored at 5 degrees centigrade; and samples were tested at a number of time points through 24 months by size-exclusion chromatography; and that it shows that 98.6 percent of this remained intact,

nondegraded, at 12 months; and 98.3 percent remained intact, nondegraded, at 24 months; and, furthermore, that turbidity was measured at OD405. And this was at DTX 13, page 7.

Q. Thank you, Dr. Rabinow.

And you pointed to the suitable for injection piece in DTX 13, and that's at page 5 of that exhibit, correct?

A. Correct.

Q. Is there an additional reference shown on the next slide, Slide 37?

A. Yeah. This is Rudge, also from Regeneron, a publication from 2005.

Q. And the Rudge reference that you're discussing, that's DTX 3592?

A. That is correct.

Q. Did you rely on DTX 3592 in connection with your opinions?

A. I did.

Q. If we could go to Slide 38, please.

What, if anything, would the person of ordinary skill in the art find significant about DTX 3592, Doctor?

A. It's describing the status of what they call a very potent and high-affinity VEGF blocker, termed the VEGF Trap, that may provide the opportunity to maximize the potential of VEGF blockade in cancer as well as in vascular eye diseases. And this is at page 1 of Rudge.

It then goes on on page 4 to divulge "Initial clinical studies in human patients suffering from both AMD and diabetic edema and retinopathy appear quite promising."

Q. And, Dr. Rabinow, the disclosure of AMD at DTX 3592, page 4, would the person of ordinary skill in the art understand that to be referring to age-related macular degeneration?

A. That is correct.

Q. If he could turn, please, to Slide 39.

What is shown on this slide, Dr. Rabinow?

A. This is Ferrara from Genentech in a publication from 2005.

Q. And DTX 4041 is the Ferrara reference, correct?

A. Yes.

Q. Did you rely on DTX 4041 in connection with your opinions?

A. I did.

Q. What did Ferrara 2005 disclose regarding the possible use of anti-VEGF therapies? And if we could please go to Slide 40.

A. He disclosed that in 2004 FDA approved bevacizumab, which is a humanized anti-VEGF monoclonal antibody for the treatment of cancer in conjunction with 5FU, and he talks about very recently data of a controlled Phase III study with ranibizumab is efficacious and maintains or improves vision in

patients with wet AMD, referring to Rosenfeld. And this is located at DTX 4041, page 6 as well as page 1.

Q. Now, the disclosure of a controlled Phase III study with ranibizumab here at DTX 4041, page 6, what, if any, significance would that have to informing the knowledge of the person of ordinary skill in the art?

A. A person of ordinary skill in the art would understand that, by the time you get to Phase III clinical trials, you're talking well into a mature development of a drug. There's a lot of money involved. There's a lot of time involved. There's a lot of additional issues. You're treating patients with your drug there. So that implies that a number of other earlier activities must necessarily have been performed, such as, for example, the development of all the analytical methods, the conduct of the stability studies, all of the preclinical studies to justify this.

THE COURT: Yes, Counsel.

MR. TRASK: Object as outside the scope of his report. There was minimal discussion of the Ferrara reference and no discussion of any stability of proteins in connection with Phase III studies in connection with Ferrara or any other reference in the report.

THE COURT: Counsel, where is it in the report?

MR. HUNT: Dr. Rabinow discusses the ranibizumab clinical trials at, I believe at least, paragraph 174 in his

opening report and 287.

THE COURT: What was the first paragraph, Counsel? 174.

MR. HUNT: Apologies. Yes, 174, Your Honor.

THE COURT: Thank you. That's the Avery article, correct?

MR. HUNT: I believe that Avery is discussed there, yes.

THE COURT: The other paragraph is what again?

MR. HUNT: Apologies. Let me get there, Your Honor.

287, Dr. Rabinow states the published results of the Lucentis clinical trials and then references the favorable data in Shams and Gaudreault.

THE COURT: Counsel.

MR. TRASK: Yes, Your Honor. Neither of these discusses -- neither of the passages that counsel cited to involve the Ferrara reference that he's discussing now. They also don't discuss stability in particular.

THE COURT: I'm going to hold that objection in abeyance consistent with the issues raised in the second motion to exclude at this juncture, but again we want to make sure we stay within the lanes the Court's already identified.

MR. HUNT: Understand, Your Honor. Thank you.

BY MR. HUNT:

Q. If we could please turn to DTX 2264 on the next

slide.

Dr. Rabinow, is there an additional relevant formulation disclosure included here?

A. This is Avery from Genentech, an article entitled "Intravitreal Bevacizumab (Avastin) for Neovascular Age-Related Macular Degeneration," published in 2006, DTX 2264.

Q. And did you rely on DTX 2264 in connection with your opinions?

A. I did.

Q. On Slide 42, what would the person of ordinary skill find relevant about Avery in or around June -- sorry -- June 16, 2006?

A. He would understand that, number one, bevacizumab was commercially available at a concentration of 25 mg/mL, and that it was injected intravitreally into human patients with a volume -- using a volume of .05 milliliters.

Q. And that disclosure, Dr. Rabinow, is at DTX 2264, page 2?

A. That's correct.

Q. Apologies for interrupting, sir. On the second, lower half of the slide, you have included reference to another exhibit. That's DTX 3510, correct?

A. Yes, that's correct.

Q. And is DTX 3510 the Avastin prescribing information?

A. It is.

Q. And did you rely on DTX 3510 in connection with your opinions?

A. I did.

Q. What, if anything, would the person of ordinary skill in the art find of interest with DTX 3510?

A. It states what the concentration of Avastin is, confirming what was in Avery. It states that Avastin consists of a concentration of 25 mg/mL. It further gives formulation details, noting that it is formulated with a trehalose sugar stabilizer, a phosphate buffer, and polysorbate 20.

Q. And the disclosures regarding Avastin that you've just discussed, Dr. Rabinow, are at DTX 3510, page 2; is that correct?

A. Yes.

Q. And what would the person of ordinary skill in the art understand Avastin to mean here? Does it have a different name?

A. Yes. Avastin is the brand name of bevacizumab, which is the vascular endothelial growth factor antagonist protein that was developed by Genentech.

Q. If we could turn to DTX 726 on the next slide, Slide 43, is this an additional reference that you considered, doctor?

A. This is Shams from Genentech. This is a patent publication dating from May of 2006, DTX 0726.

Q. And did you rely on DTX 0726 in connection with your opinions?

A. I did.

Q. Moving to the next slide, what would the person of ordinary skill in the art find significant about Shams?

A. Shams is disclosed to be an example of a VEGF antagonist. Its name is ranibizumab. It referred to its brand name, Lucentis. It is described as a humanized antihuman VEGF Fab fragment for intravitreal administration.

It is supplied in a liquid-filled vial. The concentration is 10 mg/mL for the .5-milligram dose level. And if you divide those two numbers, you learn that the intended volume for intravitreal injection is .05 milliliters; and that the formulation contains a histidine buffer, a trehalose sugar stabilizer, and polysorbate 20; and that the study drug is stored at 2 to 8 degrees.

Q. And that disclosure, Dr. Rabinow, is at DTX 726, page 32; is that right?

A. That's correct.

Q. And if we look at the top of the callout that you have here, again, as of May 4th, 2006, the date of the Shams reference, would the person of ordinary skill in the art have an understanding that ranibizumab and Lucentis are synonymous?

A. Yes, they would.

Q. If you could please turn to Slide 45. What is shown

here, Dr. Rabinow?

A. This is the Lucentis prescribing information dating from 2006 from Genentech.

Q. And DTX 3040 is the Lucentis prescribing information, correct?

A. Yes.

Q. Did you rely on DTX 3040 in connection with your opinions?

A. I did.

Q. Now, why did you include DTX 3040 in your analysis?

A. I included it to show that it essentially confirmed what we learned from Shams that was published earlier.

Q. But you're not asserting that the Lucentis prescribing information from 2006 is prior art; is that right?

A. That is correct.

Q. Looking at Slide 46, what did you find relevant about the Lucentis prescribing information?

A. So on page 4 it states that Lucentis -- ranibizumab -- injection is a monoclonal antibody fragment and that, furthermore, it is provided in a vial and that it is designed to deliver 0.05 mL of a 10-mg/mL Lucentis solution. And, furthermore, it's disclosed that the formulation comprises a histidine buffer, a trehalose sugar stabilizer, and a polysorbate 20 formulation component as well. This is at DTX 3040, page 4.

Q. Thank you, Dr. Rabinow.

If we could turn to the next slide, Slide 47, would the person of ordinary skill in the art have had a particular understanding relating to FDA-approved protein formulations in or around June 16th, 2006?

A. He would. He would be amazed by the apparent routine nature of the ability to formulate all these different antibody formulations with surprisingly few formulation alternatives.

So as we see here, there are half a dozen different antibodies. Some of them -- many of them are fusion proteins. Some of them are not. They all involve a buffer, a surfactant, and a stabilizer for either a liquid or a lyophilized formulation. And within each category of buffer, surfactant, or stabilizer, there are, as indicated here, only two alternatives that are -- that were used.

You could -- for the buffer you can use either histidine or phosphate. For the surfactant you can choose either polysorbate 20 or polysorbate 80. For the stabilizer, you can use either trehalose or sucrose. It reads like a menu in terms of what do you want for soup, salad, appetizer in terms of limited choices here.

Q. And with apologies, Dr. Rabinow, I need to walk through a few exhibits that are referenced on your Slide 47 just for the record.

So is DTX 5036 the Remicade prescribing information

reflected here?

A. It is.

Q. Did you rely on DTX 5036 in connection with your opinions?

A. I did.

Q. Similarly, is DTX 5037 the Xolair prescribing information reflected here?

A. It is.

Q. Did you rely on DTX 5037 in connection with your opinions?

A. I did.

Q. Is DTX 5038 the Raptiva prescribing information?

A. Yes.

Q. And did you rely on DTX 5038 in connection with your opinions?

A. I did.

Q. And, finally -- and there, I believe, is a typographical error on this slide, but DTX 5040, is that the Xolair -- I'm sorry -- is that the Herceptin prescribing information reference reflected in your Slide 47?

A. Yes.

Q. And did you rely on DTX 5040 in connection with your opinions?

A. Yes.

Q. Overall, Dr. Rabinow, what is your opinion regarding

the general scope of prior art that would form the person of skill's understanding of the field of stable protein formulations as of June 16th, 2006?

A. It appears to be surprisingly routine in terms of including three formulation components, each with limited choices for selection and optimization.

Q. Now, Dr. Rabinow, you previously discussed your lengthy experience as a problem solver at Baxter, including on protein formulation issues.

A. Yes.

Q. In conducting your obviousness analysis, did you consider the knowledge of the person of skill in the art in or around June 16, 2006?

A. I did.

Q. Now, in the next few questions, I'd like you to put yourself into that June 16, 2006, time frame and consider the skilled person to be one of ordinary creativity. Okay?

A. Yes.

Q. In that context, let's further assume that the person of ordinary skill in the art is a problem solver developing protein formulations at a biopharmaceutical company. Okay?

A. That's fine.

Q. Now, let's also assume that senior management indicates to the person of ordinary skill in the art that the company is interested in entering the VEGF antagonist space,

including intravitreal administration of protein formulation. Okay?

A. Fine.

Q. Based on your review of the prior art, Dr. Rabinow, what would be apparent to the person of ordinary skill in the art concerning the competitive landscape in the VEGF antagonist space, including intravitreal administration of a protein formulation, as of June 16, 2006?

A. Always of that date, a POSA would realize that there were a pretty small group of competitors. There was Genentech, which had bevacizumab that was being used off label. They had just come out with ranibizumab for the indication involving intravitreal administration. And they would realize that there was Regeneron that had the VEGF Trap R1R2.

Q. Thank you, Doctor.

MR. HUNT: Your Honor, I'm about to switch gears. I'm happy to continue, but I thought I'd offer this opportunity if Your Honor needed a personal comfort break.

THE COURT: Offer accepted, sir.

We're going to call it personal comfort and caffeine break. Let's go ahead and do that. We'll take 15 minutes at this point.

Doctor, as I know you've heard me say ad nauseam this week, you're a man without a country during the break. No one can talk to you because you're midstream.

THE WITNESS: Understand, sir.

THE COURT: Figured you did, but for the record, no one can speak to you during the break because you're midstream on your testimony. You can step down. You can leave everything there.

Otherwise, we'll take 15 and see everyone then.

(A recess was taken from 11:00 a.m. to 11:18 a.m.)

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

MR. HUNT: Thank you, Your Honor.

If I could please have DDX 4, Slide 48. Thank you.

BY MR. HUNT:

Q. Dr. Rabinow, I'd like to now discuss your opinions regarding obviousness, and we're going to start with Claim 1 of the '865 patent. Okay?

A. Yes, sir.

Q. Have you prepared slides to assist with your obviousness analysis with respect to Claim 1?

A. I have.

Q. Okay.

Mr. Gibson, could we please call up DDX 4, Slide 49.

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

A. So I've listed out the claimed elements of Claim 1

for the '865 on the left side of this screen; and on the right side I've indicated for Lucentis, Fraser, and Liu possibilities where we can show where these claim elements may be tracked to.

Q. Okay. Now, is Claim 1 asserted in this case?

A. No.

Q. But do you understand that your invalidity analysis must necessarily include Claim 1?

A. I do.

Q. Now, this slide references Lucentis, Dr. Rabinow. By at least June 16, 2006, were there a number of references published disclosing stable protein formulations comprising ranibizumab?

A. Yes.

Q. But for purposes of your invalidity analysis for Claim 1, are you relying on -- which references are you relying on with regard to Lucentis?

A. I'm relying on those references prior to the June 16th, 2006, priority date.

Q. Specifically, are there two references that you're relying upon?

A. Yes. I'm relying upon Shams and Gaudreault.

Q. Let's go to DDX 4, Slide 50.

What would the person of ordinary skill in the art understand regarding the product presentation of ranibizumab shown here in DTX 726, page 32, as it relates to Claim 1 of the

'865 patent?

A. Shams discloses, first of all, a vial. He discloses intravitreal administration, which would address the ophthalmic formulation suitable for intravitreal administration. So that would all be -- so the entire claim element of a vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises would be disclosed in Shams, DTX 726, page 32.

Q. And also at DTX 726, page 32, does the Shams reference disclose formulation details?

A. It does.

Q. And what are those formulation details?

A. It discloses a histidine buffer, a trehalose sugar stabilizer, and a polysorbate 20.

Q. Apologies. Can we have Slide 50 back? Thank you.

A. And a polysorbate 20 component, which in Regeneron's infringement contention, is considered an organic cosolvent. So I'm relying upon that definition when I refer to an organic cosolvent.

Q. So just so that the record is clear, Dr. Rabinow, you've not taken any position as to whether or not polysorbate 20 is, in fact, an organic cosolvent under the Court's construction; is that correct?

A. That is correct.

Q. So for purposes of your analysis, you have assumed

that polysorbate 20 is an organic cosolvent as Regeneron suggests that it should be?

A. That is correct.

Q. Now, with regards to Shams and Gaudreault, did you have an opinion as to whether the person of ordinary skill in the art would expect the formulations disclosed there to be stable?

A. Yes. Certainly. Of course. They had to be approved by FDA.

Q. Now, if we could please turn to Slide 51.

Dr. Rabinow, can you explain how Fraser, DTX 729, relates to Claim 1?

A. Fraser discloses at DTX 729, page 2, a VEGF Trap R1R2, which the POSA would understand to be a vascular endothelial growth factor, VEGF, antagonist, which is the claim element, one of the claim elements of Claim 1; and, furthermore, by disclosing VEGF Trap R1R2, there is an inherent disclosure of the fact that this is glycosylated and comprises amino acids 27 to 457 of Sequence ID Number 4.

And additionally, there is, for confirmation, a reference made in 21 to Holash who further emphasizes that at DTX 729, pages 2 and 9.

Q. If we could turn to Slide 52.

How is the person of ordinary skill's understanding confirmed if we look at Holash?

A. Holash, once again, refers to VEGF Trap R1R2, which, as in Fraser itself, would signify to the POSA what the amino acid sequence would be, what the glycosylation pattern would be, and explicitly also indicated from the fact that -- of the disclosure purified from Chinese hamster ovary cells at Holash DTX 3549, pages 1 and 2.

Q. Thank you, Dr. Rabinow.

Let's turn to Slide 53, please.

Can you explain how Shams, DTX 726, relates to the excipient limitations of Claim 1?

A. Shams discloses a histidine buffer, a trehalose stabilizing agent, and a polysorbate 20 organic cosolvent using Regeneron's infringement contention of the meaning of that word.

Q. Now, turning to Slide 54, what from DTX 730, the Liu reference, is shown on this slide?

A. This Liu discloses that a stable formulation is important to retain the physical and chemical stability upon storage. He furthermore states that he expects it to remain stable at 2 to 8 degrees for at least two years. And this is at DTX 730, page 15, Liu.

THE COURT: Counsel.

MR. TRASK: Objection, Your Honor. Outside the scope of the report. This is the Liu and Lucentis combination that we heard Mr. Hunt earlier this morning admit is not disclosed

in the expert report.

On the first element of Claim 1 he used Lucentis to check the box for the vial limitation. Now here on the last limitation of Claim 1, he's using Liu to check the box for the 98 percent native conformation limitation.

The combination that's proposed for obviousness is core to the case. We had no chance to respond. Dr. Trout had no chance to respond to the Lucentis and Liu combination. This has come out of the blue. It's not disclosed under Rule 26(a)(2). And we object to testimony on this combination.

THE COURT: Counsel.

MR. HUNT: Dr. Rabinow has not offered an opinion and he will not be offering an opinion that Lucentis in combination with Liu renders Claim 1 obvious.

Dr. Rabinow is walking through disclosures of the reference. There is testimony in the record that the person of ordinary skill in the art would understand that the Lucentis formulations were being used in clinical trials. And to the extent the Court gives that weight, there's also evidence in the record that the person of ordinary skill in the art would expect that the Lucentis formulations would be stable.

We are walking through -- Dr. Rabinow is walking through the disclosures of the prior art and the person of ordinary skill's knowledge. He is not making the ultimate opinion as to obviousness yet. That will come very shortly,

and you will not hear Lucentis in combination with Fraser. I'm sorry. Apologies. Lucentis in combination with Liu.

MR. TRASK: Your Honor, there seems to be a misunderstanding here about background art versus prior art references relied to satisfy limitations of the claims. And what's happening here is not background art. We have Lucentis checking one of the boxes as satisfying the limitation of Claim 1, which, of course, is a limitation in all of the asserted dependent claims. Liu is being used to check the box to satisfy the limitation of 98 percent, which, again, is in every asserted claim.

This is not background art. You can't simply point to general knowledge in the art to satisfy a specific claim limitations under Section 103 for obviousness purposes.

THE COURT: Understood.

Consistent with this Court's rulings of yesterday, I'll sustain the objection.

I understand, Counsel, points you make, that the doctor witness is not going to make the connection between the two; but any invitation to the Court to make that connection will not occur based on the failure to disclose, I think, consistent with the requirements the Federal Circuit has set forth.

On obviousness, the specific prior art must be referenced and reasons articulated -- or the reasons that the