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
Biocon Biologics,
Defendants.

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

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Monday Morning Session,

June 12, 2023, 9:30 a.m.

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THE COURT: Thank you. Please be seated.

Madam Clerk, would you be kind enough to call our next case, please.

THE CLERK: Regeneron Pharmaceuticals, Inc., v. Mylan Pharmaceuticals, Inc., Civil Action Number 1:22-cv-161.

Will counsel please note your appearance for the record.

MR. RUBY: Good morning, Your Honor. Steve Ruby of Carey, Douglas, Kessler & Ruby for plaintiff Regeneron Pharmaceuticals, Inc. With me I have David Berl, Ellen Oberwetter, and Kathryn Kayali from Williams & Connolly in Washington, D.C. And also from Regeneron I have with me Joe LaRosa, who is executive vice president and general counsel; Larry Coury, who is vice president and associate general counsel. I'll note that Mr. Coury is a native of Mercer County.

THE COURT: Welcome home, sir.

MR. RUBY: His father is a WVU alum and his mother Marshall alum. So we're glad to have him back in West Virginia for a little while.

Also Petra Scamborova, James Evans, Andrew Deciare, and Arun Bhoumik, all from Regeneron.

THE COURT: Good morning, everyone.

Good morning, Counsel.

MR. COPLAND: Good morning, Your Honor. This is Gordon Copland, Steptoe & Johnson, appearing on behalf of the defendants Mylan Pharmaceuticals, Inc., and Biocon Biologics, Inc. Also appearing this morning is William O'Brien of Steptoe & Johnson; William Rakoczy and Deanne Mazzochi, both with the Rakoczy Molino Mazzochi & Siwik firm.

THE COURT: Good morning, everyone.

All right. Here for day one for trial slated to start opening statements, but word was there was a request to seal the courtroom during a portion of plaintiff's opening. Is that correct?

MR. COPLAND: That's correct, Your Honor. The motion's not opposed by the plaintiff. We did prepare a brief just in case, which I'll hand up if I may, Your Honor.

THE COURT: Sure. Which slides are we talking about?

MR. COPLAND: It's 14 through, I believe, 45, but may I double-check that, Your Honor, when I get back to my seat? And there are about 142 slides, maybe a little more. So only the portion between the first slide, which is 14, and the last one that has an issue, 41, would we request sealing. And, of course, that would not apply to anyone already under the protective order, only to third parties present in the courtroom.

We do have an agreement that certain counsel for Regeneron may attend even though outside-counsel-eyes-only material will be some of the material, and we just ask that their counsel confirm that they're agreed to be under the protective order pursuant to the parties' prior agreement.

THE COURT: Understood.

Counsel?

MR. RUBY: We agree to that, Your Honor, yes.

THE COURT: Understood. And note that we have a spectator or two today. I'll leave it to counsel to police who is permitted to attend -- remain in the courtroom under the Court's protective order and who is not.

MR. COPLAND: If Mr. Berl will just give us notice before he hits Slide 14, and we can pause.

THE COURT: Understood.

A couple housekeeping matters for everyone. There are additional restrooms. Since we've got a bigger crowd than we had for naturalization on Friday, the line will back up quickly here. There are additional restrooms up on the third floor and either the elevator or stairs at the end of the hall will get you there.

As folks may have noticed, in addition to our looming asbestos abatement project, some preliminary work is ongoing on the roof of the building. So please continue to refrain from trying to park immediately adjacent to the courthouse, those

spots abutting the building. One, it'll save your cars or rental cars some damage -- potential damage, I should say -- and we need whatever slots they randomly let us have on any given day for the court personnel.

With that, Mr. Berl, sir, the floor is yours.

MR. BERL: Good morning, Your Honor. David Berl for Regeneron. This case is about Eylea, a product that made Regeneron what it is today. More specifically, this case is about the discoveries that made Eylea what it is.

Before the discoveries at issue in this trial, Regeneron was a small fledgling company with virtually no products or revenues. The discoveries of the patents-in-suit led to Eylea's groundbreaking treatments for diseases that are the leading causes of blindness.

Eylea is responsible for a majority of Regeneron's revenues. It funds Regeneron's research and development into the hardest diseases to treat, from cancer to Alzheimer's. Regeneron had and has a culture of innovation.

To take just one example, when COVID struck and most of the world shut down, its scientists, led by George Yancopoulos, its cofounder, sprung into action immediately and quickly developed a treatment that saved many lives, including possibly the then-president of the United States.

That's who the plaintiff is.

The defendants in this case are Mylan and Biocon.

Mylan filed an abbreviated biologic application to FDA to sell a biosimilar version of Eylea. Mylan then transferred that application to its successor in interest, Biocon, in Bangalore, India. Biocon will be selling this product if the defendants succeed in this case.

In order to understand the issues a little better, some background on the anatomy of the eye will be helpful. This is a diagram of a healthy eye. It's not drawn to scale. It's intended to show in two dimensions what's obviously three dimensions in real life.

The important components here are the retina, shown in pale yellow, which is supplied by blood vessels, that are shown in red; and the vitreous, which is a gelatinous area of the area that abuts the retina. In between the vitreous and the retina is a barrier called the ILM, the inner or internal limiting membrane.

There's also a protein in the retina, shown in green here in the little dots, called VEGF. And when VEGF is present in the right amounts, it supplies the healthy blood vessels of the retina and everything is fine.

But when there's too much VEGF in the eye, things go wrong. The blood vessels increase, and the blood vessels get too thick, and blood and fluid starts to leak. That creates significant problems and diseases, including macular edema, shown here, and other diseases that cause blindness.

Regeneron developed Eylea to try to solve that problem. The active ingredient in Eylea, aflibercept, shown in purple here, blocks VEGF -- two hands on the football -- and thereby inactivates it.

Now, Eylea is administered into the eye through a needle, so-called intravitreal injection. When it's administered into the vitreous, however, it must get into the retina to do its job. It must pass through that barrier, get into the retina, and inactivate the VEGF there, where there's a disease state. And when it does that and inactivates much of the VEGF in the retina, the VEGF essentially goes away and the disease recedes. You can see the blood vessels come back to their healthy state and vision is restored.

Now, Eylea has a VEGF inhibitor called aflibercept, but there were lots of VEGF inhibitors out there, not just one, for many different companies. This is the story of why a product with one of those inhibitors, from a sea of potential inhibitors, won out. This is the story of the two inventions that made that happen.

There are two inventions here. One on the left is directed to the product that is administered. Because of witness schedules, we'll start with that one this week. And it came first in time. The second invention is treating using aflibercept, the VEGF inhibitors in a particular way that has been proven to be very successful.

Now, starting with the product patent, the '865 patent, you will hear from two of the inventors of the product patent, Dr. Furfine and Graham, about their invention and the research that led to it.

The products they invented, one example of which was Eylea, were transformative. They bucked the conventional wisdom to invent a stable formulation with a high concentration of aflibercept, 40 milligrams per milliliter, required by all the asserted claims through incorporation of the independent claims. And that high dose and formulation of Eylea facilitated the product's eventual success.

Now, in order to market a biosimilar version of Eylea that copies from the patent the 40 milligrams per milliliter of aflibercept as well as the organic cosolvent it uses of polysorbate, Mylan and Biocon advanced various defenses of noninfringement and invalidity. I don't think you'll hear in detail about many of these defenses given how many there are, but Mylan has not narrowed what it proposes to present at trial; so I'll try to cover them all this morning.

The first dispute is whether Mylan infringes the organic cosolvent limitations of the claims. And they do.

And this is the point where I'm going to hit material that I think they want the courtroom sealed for.

THE COURT: Understood.

The Court would then seal our proceedings. Those not

specifically permitted to be here in the Court's protective order, if I could ask you to depart, please.

(The following proceedings (10/3 to 20/7) were sealed and are filed under separate cover.)

THE COURT: Thank you.

If I could ask court security to unseal our courtroom and extend an invitation to those out there to rejoin us if they'd like. Thank you.

Welcome back, everyone.

Mr. Berl, go right ahead, sir.

MR. BERL: Next are Mylan's invalidity defenses, and we'll start with anticipation.

The patents at issue in this case were issued after substantial examination by the US Patent and Trademark Office, and they were duly issued and entitled to the presumption of validity.

Mylan bears a heavy burden -- clear and convincing evidence -- to prove the facts necessary to show invalidity. It can't do so. Anticipation requires that a single record, just one, disclose each and every limitation of the claims expressly or inherently arranged as in the claim.

The first of Mylan's two anticipation references called Fraser doesn't even come close to meeting that

requirement. It's mincing lots of limitations from the claim. This argument of theirs reminds me of the old Coffee Talk Joan Rivers skit on Saturday Night Live. The Holy Roman Empire is neither Holy nor Roman nor an empire. You may remember that. That's what this is.

Fraser discloses neither an ophthalmic formulation nor intravitreal administration nor glycosylated nor aflibercept nor 98 percent native conformation nor 40 milligrams per milliliter. It's got none of it. And it has to have everything.

Mylan tries to plug at least some of the holes in the dam by suggesting that anything written in an article that Fraser cites or, in fact, anything written in an article cited by an article that Fraser cites somehow magically becomes part of Fraser because anticipation, they have to have only one reference.

First of all, that's implausible; but second, it's contrary to consistent federal circuit precedent, that the host document -- here Fraser -- must identify with detailed particularity what specific material it incorporates. Simply adding the footnote and citing a reference isn't close to enough. You've gone from Joan Rivers to Six Degrees of Kevin Bacon in one article.

Now, the second anticipation argument that they advance is this, and the assertion of Dix requires the Court to

address a subsidiary question, which is whether Regeneron is entitled to a priority date of March 21, 2006, or earlier because that's before the time that Dix was filed.

Now, the answer to that question is yes. In fact, the invention here was made far earlier in the fall of 2005, but for present purposes, because Mylan has only asserted Dix, we only need to show priority back to March 21, 2006, or earlier.

If Regeneron is entitled to that date -- and we think it's clear that it is -- then Dix simply is not prior art. Everything you hear about Dix the next two weeks -- and I suspect you'll hear quite a bit -- is totally and blessedly irrelevant to this case because it's not prior art.

But even if Dix were prior art, then it would still not anticipate the claims because it too, like Fraser, is missing at least one limitation, in fact, several, including intravitreal administration and an ophthalmic formulation. It has none of that.

Now, for the 40 milligrams per milliliter formulation, which is a very important limitation in the claim, what they rely on is a disclosure of 10 to 50 milligrams per milliliter in Dix.

First of all, that disclosure is not about aflibercept in particular; so it's not arranged as in the claim. But more importantly, the federal circuit repeatedly

has been clear, including earlier this year, that the disclosure of a range, like 10 to 50, is not a disclosure of discrete points within that range like 50, like 40. 10 to 50 does not anticipate 40. It can't do that under controlling law.

Now, with that, I'll move to obviousness, which is their backup prior art argument. And the first problem with Mylan's obviousness argument is their selection of references. They pluck out of prior art various references, most of which have nothing whatsoever to do with the issue here, which is intravitreal injection that can treat diseases in the retina. But that's not allowed under the law.

The question is not whether the so-called person of ordinary skill, or the POSA, with the two prior art references in front of him could combine them and arrive at the patent-in-suit, which, by the way, it couldn't even if they had them in front of them.

Mylan and Biocon don't even get to that question because the question, as the federal circuit said in the WBIP case, is whether the skilled artisan would have plucked one or more of those references out of the sea of prior art in the first place. And Mylan's experts skip over that analysis and choose their references without any contemporaneous justification or basis.

There were many VEGF inhibitors in the prior art. It

was a sea of VEGF inhibitors. And Mylan just assumes without basis that the POSA would have chosen one of them, aflibercept. Not so.

As I mentioned earlier, there's a barrier between the vitreous, where the drug is injected, and the retina and other associated tissues where it needs to go. And whether the molecule would get from the vitreous to the retina was understood to depend on its size. And aflibercept at the time was considered too big.

Now, the prior art taught -- and this is the Gaudreault reference from Genentech in 2005. And we'll hear a lot about this reference. It taught that penetration of ranibizumab -- that was Genentech's product at the time. They were developing a different product called ranibizumab that later became Lucentis, which is a product on the market. They were ahead of Regeneron; so they were publishing already.

And what they said was penetration of their molecule, ranibizumab, into the retina is critical for its credible use. You've got to get to the retina. Or as people in the field often say, the tissue is the issue. So you've got to get to the right tissue. And why do they say their product gets to the retina? Because of its small molecule size, 48 kilodaltons. Kilodaltons is just a measure of weight like pounds or kilograms.

And they contrasted it with what they called a

full-length antibody, something that was 148 kilodaltons that they said was not able to penetrate the retinal layers of the monkeys. So 148 was too big; 48 was good enough. And what the art said -- not just Genentech but others -- is that things that are over about 70 kilodaltons or about 76 kilodaltons were too big.

Now, we all know that aflibercept, in fact, did end up penetrating the eye into the retina. If it didn't, none of us would be here today. Okay? We'd all be somewhere else. But that's not what matters for obviousness. What matters is what everyone thought and knew at the time of the invention about 16, 17 years ago. And at that time aflibercept was simply considered too big.

This is ranibizumab, what we just saw, 48 kilodaltons. Aflibercept was 115. And it actually behaved like it's even bigger because of its unusual size. The idea of using aflibercept via intravitreal injection straight into the eye was actually tried in mice in the prior art, and it didn't work very well.

The figure on the left is subcutaneous injection. That's systemic injection that Your Honor is used to, less scary than intravitreal injection. And what you want to look for here is does the problem go down. You want the numbers to go down. This is golf, not bowling.

And when you did this systemic administration, what

we see is the bar goes way down. That works well. But when you do intravitreal administration straight into the eye, the bar doesn't go down very much. And what people at the time said -- and not just people. This on the right is an article by Genentech and in particular someone called Napoleone Ferrara. He's the godfather of VEGF. He actually discovered VEGF. And he, while at Genentech, developed the first two anti-VEGF therapies: Avastin and then Lucentis. And what he said is he looked at these data and he said there's limited efficacy, despite the high binding of the molecule. And it may be due at least in part to the existence of a barrier to penetration of large molecules such as the VEGF Trap.

That's what people were thinking and saying at the time. It's too big. And without showing that you want to do intravitreal administration of aflibercept, that claim can't be obvious because all of the claims require it.

But the claims actually require more. Mylan has to show much more than that. They have to show that the person of skill would have wanted to use 40 milligrams per milliliter of aflibercept, this high concentration of aflibercept. They have to show that by clear and convincing evidence.

And the presentation from them that you'll see in a moment has all sorts of prior art showing all sorts of buffers and organic cosolvents and stabilizing agents, almost nothing about 40 milligrams per milliliter. That was never done in the

prior art for aflibercept. And they can't meet that burden, including because people thought that increasing concentration increases aggregation. That's the problem I discussed earlier.

In fact, Genentech in this same Gaudreault article tried 40 milligrams per milliliter, and it went poorly. What happened when they did 40 milligrams per milliliter was that they got ocular inflammation that was moderate to severe. Bad news. You don't want inflammation. It resolved after eight days, but keep in mind this is a product that's administered every month. No one wants their eye to be inflamed for one week out of every month, let alone inflamed potentially with particles that can hurt your vision and cause real problems.

So Genentech, the leader in the field, ditched the 40 milligrams per milliliter idea and instead pursued lower doses, 6 milligrams per milliliter or 10 milligrams per milliliter, which is what they ultimately used in Lucentis.

The argument based on Fraser of obviousness fails for this reason alone. Not only does it fail to disclose aflibercept or intravitreal injection, it has only 24.3 milligrams per milliliter, and the claim requires 40. The skilled artisan would have used less than 24, not more, and certainly wouldn't have gone all the way up to 40 when Genentech, the prior art, was teaching away from it.

Now, the second prior art reference for obviousness

that Mylan advances is Dix. And the assertion of Dix would require the Court to answer a second question in the event that the Court does not believe that Regeneron is entitled to an earlier priority date.

If we are entitled to an earlier priority date, as I said, Dix goes out the window completely. But if you answer that question no, Your Honor, then you have to answer a second question. Is Dix subject to the safe harbor of 103(c) in the statute so that it cannot be used for obviousness?

And the answer to that question is that Dix is subject to the safe harbor. The statute is very clear. You can't use as an obviousness reference a reference owned by the same person as the patent or subject to an assignment of -- to an obligation of assignment to the same person. Your own prior art can't be used against you for obviousness under 103(c).

There is no question but that Dix shown here on the right and other such references and the product patent at issue were owned by the same person, Regeneron Pharmaceuticals. And all of the scientists working at Regeneron at the time, of course, had an obligation to assign their inventions. That's how pharmaceutical companies work. If you work for them and use their labs, you don't get to keep your invention. It belongs to the company, of course.

Now, even if Dix could be used for obviousness, it doesn't really help Mylan and Biocon. It does not disclose

40 milligrams per milliliter. And based on the prior art that we've seen, the skilled artisan never would have used that high a concentration. It would have used a much lower concentration for the intravitreal injection, just as the prior art repeatedly taught.

In any event, even if Mylan could show motivation to make the claimed invention, it cannot show expectation of success, an independent requirement of the obviousness inquiry. And moreover, the objective indicia of nonobviousness, including commercial success, demonstrate clearly that the invention was not obvious, as you'll hear from Dr. Richard Manning, our expert economist.

Now, Regeneron did not succeed because it had a molecule that inhibited VEGF. Lots of companies had that. But consider what happened with Genentech. They were the big 800-pound gorilla in the field, the leaders in the field of biotechnology in general and VEGF in particular. They had a big first mover advantage with their product, ranibizumab.

And there were lots of companies out there trying to compete with Genentech, who had the leader in the field, Dr. Ferrara, leading their program. None of the other competitors succeeded, none of them. Only Regeneron succeeded. And Regeneron succeeded wildly with a product Eylea that ended up being the market leader and, in fact, overtaking Genentech's ranibizumab.

Now, because the prior art does not invalidate the patent, Mylan next turns to Section 112 defenses. Now, these defenses, as I pointed out at the pretrial conference, are so blatantly inconsistent with their prior art references that Mylan actually has to bring two separate experts in order to advance these arguments -- prior art on the one hand and Section 112 on the other -- because one person couldn't possibly keep them straight, let alone testify lucidly as to both.

They start with enablement, but their theory on enablement suffers from a repeated fatal flaw. Mylan runs enablement in the alternative in saying if the patent is not obvious, then it must not be enabling because it's either hard to do, in which case it's not enabled, or it's easy to do because it's obvious.

The problem with that argument, as the federal circuit repeatedly recognized, including in the Allergan case, is that enablement and obviousness are different because, for obviousness, you don't have a patent. You don't have the benefit of what the inventors did and taught the world. For enablement, you do. And the question is, whether reading the specification, then you can practice the invention without undue experimentation.

The Supreme Court addressed enablement last month in the Amgen v. Sanofi case. And what they said, among many other

things, is that enablement is a problem where you have to do as much work without the patent as you do with the patent, where the patent doesn't really help you in any way. That manifestly is not the case here.

The claims here require 40 milligrams per milliliter of aflibercept, not taught for intravitreal injection in the prior art. Taught in the patents. They require organic cosolvents disclosed in the patent. They require stabilizing agents disclosed in the patent. The patent tells you what pH to use so that you can choose an appropriate buffer.

The notion that the skilled artisan is in the same position with or without the patent, respectfully, is not plausible. And the prior art does not disclose all of this, including and especially 40 milligrams per milliliter of aflibercept. But the patent does.

Mylan's argument is premised on the very notions that the Amgen supreme court decision rejects, that it's about the cumulative time and effort it takes to make all the embodiments or that enablement is about exhausting the genus, making every single embodiment in the claim. That's not what we have here.

In the cases where nonenablement is found, each and every embodiment of the claim must be made and tested. So you've got a big research project of making absolutely everything. But in this case, as their own Section 112 expert explained repeatedly, the skilled artisan wouldn't need to make

every formulation in order to practice this claim. You'd be able to eliminate a lot of candidates and narrow yourself down to acceptable candidates and then do some experimentation. So the premise of cases like Idenix and others from the federal circuit -- you have to make each and every one; therefore, it's not enabled -- is simply not present here.

Now, Dr. MacMichael says for enablement that it would be really hard to make these formulations of the claim. He's wrong. The POSA could have made the formulations with the patent in hand quite easily. But you don't have to take it from me. You can take it from Mylan's other expert, Dr. Rabinow.

When we asked him, in your view, the POSA could have made and used the formulations within the claims even without the specification with one hand tied behind his back. And he answered quite simply yes. It is impossible on this record to find that the claims are somehow not enabled when their own expert agrees you can make the formulations even without the help of the specification.

Now, finally, Amgen is a mismatch for this case. Justice Gorsuch said the problem is where a patentee seeks sovereignty over an entire kingdom. You claim everything that works, which is what they did in Amgen, without limitation as to what particular structures should be used to practice the claim.

Our claim, unlike Amgen's and all the others that go down, is full of structural limitation. It has to have aflibercept. That's a structure. Organic cosolvent. Buffer. Stabilizing agent. Those are all structures that limit what formulations are in the claim. If you don't have an organic cosolvent or a buffer, you're out of our claim. Whether it works or not, it's structurally limited. And, therefore, enablement cannot -- nonenablement cannot be found.

Mylan's written description argument is advanced on the same basis as its enablement argument, and it's wrong for similar reasons. The federal circuit in Alcon made clear that all that matters for written description is whether the skilled artisan can recognize what was claimed. It's not about whether the patentee has proven that it will work.

So Dr. MacMichael's enablement -- the written description argument that there aren't enough examples, you haven't proven enough, simply isn't required. He's looking for something that the law does not require.

And written description is present where claims are limited to known sets of structures. And he admitted over and over in his deposition, and will admit it again at trial, that the claims are limited to particular structures that were known. Nonwritten description is present where a skilled artisan doesn't know what structures to use and so can't visualize what was claimed. When it's clear what structures

can be used, the written description requirement is met.

The last invalidity argument on the treatment patent is indefiniteness. And Mylan asserts that the terms "suitable for intravitreal administration" and "measured by SEC" are somehow indefinite. They appear now only to be running one of those arguments, but both of them are wrong. And they're wrong including because their own experts were able to understand and use that term repeatedly.

And so if their experts understand what it means and skilled artisans understand what it means, then the claims simply are not indefinite, as the federal circuit has held.

And, with that, I'll move to the treatment patents.

You'll hear momentarily from Dr. Yancopoulos, the sole inventor of the treatment patents. There are two sets of claims at issue in the treatment patents. The first is Claim 6 of the '572 patent. It claims treating an angiogenic eye disorder with an extended eight-week dosing regimen, that you dose every eight weeks, with an isotonic solution of aflibercept. And isotonic refers to the amount of substance dissolved in the formulation.

The other claims at issue relate to treatment of specific diseases: diabetic macular edema, DME, and diabetic retinopathy, DR, using a specific dosing regimen that requires five monthly loading doses. In the claims called an initial loading dose and then four secondary doses, one plus four being

five. That five loading dose regimen was never disclosed, never suggested in the prior art.

These claims do not involve any of the terms that the Court construed in its claim construction order, and none of them were asserted or admitted to be invalid by stipulation, as Mylan misleadingly asserts in its slides.

Now, a little background about how this works. The claim in the patent discusses initial doses and secondary doses. And those together are called loading doses. Loading doses is loading the patient up with initial doses to try to get the disease under control. And then the patent talks about maintenance doses, which are also called tertiary doses. And what we see here is an every-eight-week dosing regimen. Every eight weeks, a dose is administered. An extended dosing regimen of eight weeks rather than four weeks, which was typically used in fixed-dosing regimens of the prior art.

Now, the number of loading doses in the patent can change. It can move back and forth. And, in fact, in the DME and DR claims, as I just mentioned, five loading doses are required. The claimed dosing regimens were nothing short of transformative. Everyone agreed that you wanted fewer injections. Obviously, everyone wants injections into the eye less often.

But Regeneron was the only one who figured out how to made that happen. And they did so with a particular

fixed-dosing regimen that was disclosed in claims in this patent and that are at issue in this case. They did that by going against the conventional wisdom which taught going in a different direction, and they did something different.

Now, Mylan has again a host of defenses, throws up everything against the wall, but none of the defenses are meritorious. Somehow, Mylan and Biocon still continue to assert noninfringement. But the expert testimony as to the two inquiries that underlie the infringement analysis will be uncontested.

That is because, even though Mylan insisted that its noninfringement expert, Dr. Russell, would testify when it submitted the pretrial order on May 18, it reversed course a week later and agreed that no expert would testify about noninfringement. Dr. Russell vanished.

Our expert, by contrast, Dr. Karl Csaky, a renowned retinal specialist who practices in Dallas, Texas, will address both validity and infringement. And as to infringement, it's no mistake that Dr. Russell capitulated. Mylan and Biocon do not seriously dispute that their label teaches each and every limitation of the claimed dosage regimens. And as a result, under the federal circuit's law, that is dispositive of the induced infringement inquiry.

Now, they then move to invalidity, to excuses for why they should be able to sell their product anyway, starting for

anticipation, which again requires a single prior art reference to each and every limitation in the claim. And the problem with their anticipation theory here, based on the prior art Dixon reference, is that it never discloses the isotonic solution required by Claim 6 of the '572 patent.

Instead, it discloses something different, the suitable -- suitable for the comfortable, nonirritating direct injection into the eye. That doesn't say isotonic, and Mylan knows it. So what Mylan does instead is rely on the doctrine of inherency to prove anticipation, but inherency is a tall standard. That's a tall hurdle to meet. It requires that the missing material -- here, isotonic solution -- is necessarily present in the prior art, necessarily present in Dixon, not there by probabilities or possibilities.

In his report, Mylan and Biocon's expert said that it is inherent because you have Dixon, and comfortable, nonirritating injection into the eye must be something that is not -- must be something that is isotonic. But that flimsy opinion did not survive even moderate cross-examination.

We asked him quite clearly, "Do you think that even a hypertonic solution, one that's not isotonic, nonetheless could be comfortable and nonirritating to the patient?" It could still be within Dixon so that Dixon could include isotonic and nonisotonic.

And he said, "I don't know. I'm not sure." Anything

but clear and convincing evidence that the isotonic solution necessarily and always must be present in Dixon.

He further testified, not shown here, that the skilled artisan would want to administer intravitreally nonisotonic solutions in the prior art. Now, remarkably, based on the deck we got yesterday, Mylan and Biocon intend to resuscitate this argument at trial. But they cannot succeed in doing so given the testimony.

So Mylan and Biocon shifted to a different anticipation theory in summary judgment argument. And it is equally wrong. Their new theory is that Dixon, which discusses a clinical trial, is somehow to be conflated or combined with the clinical trial itself shown here on the right where people actually were injected.

But these are two different references. Dixon is just a publication. It's a piece of paper. It's not actual injections that happened. Mylan could have relied on the actual clinical trial saying that those uses of aflibercept somehow anticipated the claim, but it can't really do that because the clinical trial itself was confidential and not prior art.

So what they've done is suggest that, because the clinical trial, unbeknownst to anyone in the field at the time, used an isotonic formulation, that must have been present somehow in Dixon. But that's not so because that isotonic

formulation and the trial itself is not part of Dixon. It's part of something else.

And the issue of inherent anticipation for Dixon is whether someone practicing Dixon necessarily and always -- always -- would practice the claim. It's not enough that they could practice the claim, as in the federal circuit's Glaxo v. Novopharm case; they have to do it every time. And Dr. Rabinow agreed that you could practice with isotonic; you could practice with something that's not isotonic.

Now, on obviousness, they've also made a fundamental legal error. The Court's Markman decision held that various language here in the claims is not limiting. However, the Court did not rule that the longstanding principles of obviousness jurisprudence somehow magically do not apply to this case. They do. And Mylan asks the Court to cast them aside improperly.

First, it is black letter law that obviousness must consider the claim as a whole. It's right in the statute. And it's improper to disaggregate the claim piece by piece -- A plus B plus C, as the federal circuit says -- and say, well, this was here and this was nonlimiting and this was here, and so, therefore, because I can find something everywhere or it's not limiting, the claim is obviousness.

That's not how obviousness works. You have to look at the claim as a whole and assess whether it's obvious. And

their approach, crossing certain things out because they're not limiting and finding isotonic formulations somewhere else, is wrong.

Now, second, let me be clear about the effect of the Court's claim construction. We understand that the Court held those limitations about certain eye improvements to be nonlimiting. And so they don't need to show those limitations in the prior art. They don't need to be shown.

But that does not mean that the inquiries about motivation to practice the invention and expectation of success get thrown out the window. The skilled artisan is not somehow lobotomized and all the sudden doesn't care about treating patients and improving their vision just because language is not in the claim.

The federal circuit has been clear that whether those goals of the POSA are in the claim or out of the claim or, in this case, in the claim and not limiting under Your Honor's construction. It doesn't matter. There's still relevant motivation and expectation of success.

They have to show someone would have been motivated and expected to succeed in practicing the claim, and they can't do it because the prior art simply did not disclose that this every-eight-week regimen would be successful. What they do instead is rely on disclosures of people trying -- of Regeneron trying this eight-week regimen, which, of course, we were. We

were doing clinical studies with it. But not that it would succeed. In fact, people thought it was a bad idea in the prior art, which forecloses a finding of obviousness.

The prior art shown here was moving in an entirely different direction, towards so-called pro re nata, or prn, dosing, which is evaluate a patient and then dose if you think he needs it rather than a fixed dosage regimen where there's a prescribed amount of time between each dose.

Mylan's own expert agrees that individualized assessments, this so-called prn dosing, is what most people were doing at the time. And those who tried extended fixed dosing, including Genentech, failed spectacularly, including in the important peer trial in the prior art, where patients lost a whole lot of vision with extended fixed dosing.

The prior art was clear here. Extended fixed dosing was a bad idea. It provides less benefit to patients. And, in fact, Genentech tried and failed with every-eight-week dosing as well.

Regeneron at first tried prn dosing too. That's the way the wind was blowing. I want to explain the nomenclature for just a moment. You'll see often a number followed by a Q followed by another number in connection with these documents. The first number is the dose. That's how much of the drug people are getting.

THE COURT: The solution itself? That's not

reflecting how much aflibercept is in the solution?

MR. BERL: That's how much aflibercept is in the solution, not the solution itself. So the solution itself has other things, and they usually get up to 50 microliters into the eye. And so that 50 microliters can either have a lot if it's really concentrated, or it can have a little if it's less concentrated.

THE COURT: So the first number is actually the active ingredient?

MR. BERL: That's the amount of the active ingredient. Exactly right.

THE COURT: Thank you.

MR. BERL: .502. And the -- after the Q is how often it's given, every 4 weeks, every 12 weeks, every 8 weeks, et cetera. And in this trial, which is in the prior art, the CLEAR-IT 2 trial, they did every four weeks, for example, with .5. And in all of these cases followed by prn dosing. They were doing this pro re nata dosing too, just like everyone does.

But then Dr. Yancopoulos shifted course contrary to the conventional wisdom and chose to pursue a fixed-dosing regimen at every eight weeks rather than prn as in the prior art View 1 and View 2 trial.

The difference between what Regeneron did and what the prior art previously did before the invention is stark and

important.

The prior art trial did not disclose every week -- every eight-week dosing, did not use three loading doses before that, did not compare aflibercept to ranibizumab -- Genentech's leading product -- in order to see whether it would work as well, and switched to prn rather than having extending fixed-dosing.

Now, quite surprisingly, Dr. Yancopoulos's invention worked, and he showed that dosing aflibercept and Eylea every two months, extended fixed-dosing will work as well as the ranibizumab, Genentech Lucentis, treatment every four weeks.

As you'll hear, this was enormously consequential for patients and caregivers alike, and it helped drive the success of Eylea.

Claim 6 reflected in this invention here is not obvious as a whole. But even if obviousness inquiry were limited improperly, as Biocon and Mylan urged, to the isotonic aflibercept limitation added by Claim 6, they still would fail. Their clinical expert, Dr. Albini, has no opinions about formulation. He defers to their formulation expert, Dr. Rabinow, on this.

For his part, Dr. Rabinow in his report relied on the Hecht prior art reference for a motivation to use an isotonic formulation. But then at deposition he agreed in no uncertain terms repeatedly -- and this is his word, not mine -- that

Hecht is inadequate -- it's inadequate -- to motivate the POSA to use an isotonic solution for intravitreal administration. It's not good enough. It's not even close. And Mylan should not be able to advance a new theory of obviousness here now that its experts crumbled under oath as to the theory they actually advanced.

Now let me turn to the DME or DR dosing, which require five monthly loading doses. An initial dose and four secondary doses make five.

No prior art disclosed that regimen. Zero. It's a big goose egg.

The published dosage regimen for the Phase II trials shown here had a lot of different regimens but never, never five loading doses followed by every eight weeks.

Now, Mylan's anticipation theory is actually based on the prn arm of this published trial, of this published regimen. What they say is that with prn dosing, it's possible somehow that someone could have gotten a fourth and fifth dose at weeks 12 and 16 and then possibly, magically, could then have gotten doses every eight weeks pursuant to his pro re nata treatment appropriate after UR-inspected regimen.

But that potential treatment by happenstance is exactly what inherent anticipation is not. The furthest their expert would go is that this prior regimen could easily result in the claimed regimen. But of course "could easily result"

isn't good enough. That is probabilities or possibilities. The law requires that it necessarily must result, and not even their expert thinks that.

So their main argument here is obviousness. And the argument that they propose is contrary to what the inventor actually did.

Dr. Yancopoulos chose a different regimen, never disclosed in the prior art, and he used it in the ensuing trials, called VIVID and VISTA. Mylan must prove that it was obviousness to do this, with an expectation of success. And it can't.

But, briefly, in order to evaluate what's prior art and what's not, Your Honor will have to decide what the priority date is for this invention, whether it's 2011, based on Regeneron's claim to its initial application filed with the patent office, or only 2013, if the initial application does not support the claims.

Mylan and Biocon disputed this issue, unlike in the product patent where they agree that the 2006 application supports the provisional application and never fought it and asserted the 2006 date in its expert reports.

But the 2011 application here supports the claim. It discloses the exact treatments that are in the claim, the diseases of diabetic retinopathy and DME, the initial dose, and four loaded doses. That's five loading doses and then every

eight weeks.

Mylan's argument, essentially, is that Regeneron disclosed too much in the 2011 application, that along with five loading doses, it also disclosed three or four or six or seven or eight.

But that doesn't work under the law. If you disclose the invention and more, you still describe the invention and you get priority, as the federal circuit explained in the Streck case where the disclosed priority application disclosed the particular molecule and a bunch more. That's good enough. You don't have to disclose only your invention; you just have to disclose your invention.

Now, on obviousness with the 2011 date, Mylan pretends that it's really easy to go from three loading doses to five. They say you just add a box here and you add one treatment. But while it might look like that on a piece of paper that you do that, that's not actually the intellectual exercise one must go through in order to get the five loading doses. Rather, if one starts at three -- and let me be clear.

There's nothing in the prior art showing a problem with three. No one ever would have said they used three in the prior art; that's a problem; I want to change that. No reason to do it. And if you're going to do it, you actually want to use fewer not more injections.

But even assuming that one considered it, it's not

just adding one treatment. If you add one loading dose, there you are, there is treatment at Week 12, and then you've got to push out the ensuing every eight-week doses because, if you keep that dose where it was before, at the 16-week point, you're not doing every four weeks any longer -- every eight weeks any longer after the four loading doses; so you push it out.

And then the skilled artisan would have said four isn't good enough -- even the prior art doesn't say go to four -- I'm going to double down for some reason -- who knows why? -- and go to five. And then people dose at five, again push out the ensuing treatments off the board, and change the regimen entirely.

Mylan pretends here, and in its presentation today, that whether you treat at these time intervals of 12 weeks, 16 weeks, or 20 weeks, it's just a simple coin flip exercise -- yes; no. Do I do it? Do I not? That's not what's going on here.

These are physicians and scientists actually trying to make a decision about a dosing regimen. They're not doing it by law. They're doing it based on analysis, based on the prior art. And the prior art told over and over fewer doses, not more, relieve patient discomfort. Don't make it worse, especially for DME, where you don't need to use as many loading doses, the prior art taught.

Indeed, Dr. Albini, their sole expert on this point, agrees that there was a move toward reducing the number of injections, not increasing them, flatly contrary to the theory that Mylan must prove in order to go from three loading doses to five.

In fact, the prior art itself, which is what matters rather than coin flips that Mylan is conjuring in its demonstratives, talked clearly -- and this the Lalwani article, PTX 703 -- that treatment of DME will be more of an art form with the tailoring of individual treatments for individual patients, prn, treat each patient individually, not a fixed extended dosage regimen like is claimed in our trial.

Now, with a 2013 priority date, there's one additional piece of prior art that Mylan asserts, which is the Do 2012 reference, which shows the initial data from the three loading dose trial, and the every-eight-week regimen with three loading doses is shown here in pink.

And what Mylan says, with classic impermissible hindsight, is that these data somehow would have motivated the skilled artisan, of all things, to add two loading doses.

That's not true. The contemporaneous evidence will show otherwise, including the fact that Regeneron, with all of the assembled experts together staring at the data, never thought that these published data tell you to use five loading doses rather than three. No one said it at the time, only

someone who comes in 12 years later and says it would have been obvious.

The objective indicia of nonobviousness, including commercial success, further confirm nonobviousness. No one would have wanted to use this regimen. No one would have wanted to do it or expected that it would work.

Finally, we get to Mylan's dog's breakfast of different 112 defenses that it asserts. There are, like, eight of them. It's not clear what they're actually running, but I'll address a few that they actually mentioned in their pretrial briefing.

The first is that somehow the patent doesn't disclose treatment of angiogenic eye disorders in general.

Now, again, these arguments are so contradictory, they have to bring two different experts in to advance them, which they'll do again, because they're saying you wouldn't have any idea, even with the specification, how to disclose, how to treat these diseases. But the specification tells you how. It tells you very clearly which diseases to treat, and it tells you how to treat them, the extended eight-week dosing regimen with different numbers of loading doses.

Now, this is sufficient as a matter of law. Mylan's complaint is that we didn't treat enough diseases in the specification using actual clinical data that we said what we should treat, but we had to prove somehow with clinical trials

that each disease would work, that more diseases would work.

But there is no requirement in the law of written description that the disclosure contain either examples or an actual reduction to practice. On the contrary, Alcon v. Barr again, the patent need not guarantee that the invention works and efficacy data -- exactly what Mylan asserts is missing here -- are generally not required -- not required -- in a patent application. And we do have clinical data in our specification. We meet this requirement easily.

Finally, Mylan and Biocon assert that the term "approximately," which appears in the claim, somehow is indefinite.

Now, first of all, that's wrong because their experts know exactly what it means. So it has to be reasonably certain for people because it's used frequently in the art. But more importantly what we see on the right is the proposed label that Mylan and Biocon would send if their product gets approved to doctors. This is what they're telling doctors to do with their product. And they use the word "approximately" in their instructions to doctors.

Mylan and Biocon surely aren't trying to confuse doctors by using a word that doctors have no idea what it means so they'll have no idea how to use Mylan and Biocon's treatment. The real Occam's razor answer here is that everyone knows in the field what "approximately" means and would have no

difficulty implementing this patent claim. In fact, the federal circuit, time after time, has clarified that words of approximation -- "about," "substantially," and what we have here, "approximately" -- are perfectly fine in patents in order to provide some breadth to the claim rather than numerical specificity. And they are not here, and they never have been indefinite.

With that, I thank Your Honor for patience. We look forward to presenting the case to Your Honor, and at the end we'll ask for a judgment that the patents-in-suit are both valid and infringed. Thank you very much.

THE COURT: Understood. Thank you, Counsel.

As a housekeeping question, how long do you anticipate opening statement to take?

MR. RAKOCZY: Probably an hour, Your Honor. Do you want to take a quick break?

THE COURT: Yes, let's take a quick break. That will give you all a chance to set up, and then we'll roll from there. We do have -- as I promised, we do have a proceeding that's set for noon. We can -- they can wait a few minutes, but I'll give everybody a heads-up at noon we do have a criminal hearing that we had to tend to. So I'll ask everybody to, as best you can, move some stuff back a row. That shouldn't take all that long, but this will all flow nicely. If we can do that, we'll take a lunch break at that point.

So 15 minutes enough for you guys to switch?

Let's take 15; then we'll resume with defendants' opening statement.

(A recess was taken from 10:45 a.m. to 11:01 a.m.)

THE COURT: Counsel, are you ready to proceed?

MR. RAKOCZY: I am, Your Honor.

THE COURT: The floor is yours, then.

MR. RAKOCZY: William Rakoczy on behalf of Mylan and Biocon. I will briefly address the '865 formulation patent, after which I'll turn it over to my colleague Ms. Mazzochi to address the dosing patent.

I'd like to start by hitting the reset button, Your Honor. Suffice it to say you're going to hear quite a different perspective from me than what you just heard. In short, the evidence will show that the asserted claims of the '865 patent are not infringed and they are invalid. Before I preview that evidence, three quick introductory points.

Number one, in simplest form, the case on the '865 patent breaks down like this. The Court finds that the polysorbate 20 in the Yesafili accused formulation is not an organic cosolvent as construed by the Court and as we believe the evidence will show. There could be no infringement, and judgment should be entered for the defendants. But if that polysorbate 20 is, in fact, a cosolvent, despite what we

believe the evidence will show, then if it is, the claims are anticipated and obvious.

Beyond that, the Court will hear additional evidence demonstrating that the claims of the patent are invalid under another section of the patent statute, Section 112, including lack of enablement, written description, and indefiniteness.

Point two, I think we can step back and talk about what the '865 patent is not about. It is not about a groundbreaking new drug or use. Aflibercept and its use have been in the art for years. Aflibercept is the subject of a different patent not at this current trial, a patent that's about to expire. They've enjoyed their over 20-year monopoly on that aflibercept patent.

The '865 patent is not about that. It's about taking the old drug and putting it into an old prior art formulation. Tried and true blueprint using excipients known in the art, which I'll get to more in a moment.

Point three, I think we heard more accusations of copying, that somehow Yesafili is a copy of the '865 patent, or Eylea, in a word, nonsense. Regeneron's the me-too that copied the prior art blueprint for a stable protein formulation in the '865 patent. Yesafili practices that prior art blueprint as well. It's not a copy of Eylea or the '865 patent.

So let's start with the art of protein formulation to provide some context.

As Your Honor can see here on DDX 1, Slide 4, protein formulations go back many decades, to the late 1990s at least. And in this area, Genentech was the trail blazer. They had formulated a number of stable protein formulations, starting with Herceptin in 1998, up to the VEGF antagonist formulations, some of which you heard about -- Avastin in 2004, Lucentis in 2006.

And these all had one thing in common. They had used the blueprint -- a buffer, a surfactant, and a stabilizer that you can see here on Slide 4 highlighted in blue, yellow, and purple. Those were the tried-and-true known excipients in the art for making a stable protein formulation.

And one ingredient you're going to hear a whole lot more about is the surfactant polysorbate 20.

Here on Slide 5 I have a snapshot from the literature. This is the Randolph and Jones reference. This is one that Regeneron and its expert relies on. And as you can see, the Randolph reference teaches that surfactants are used as, quote, stabilizing agents, end quote, in protein formulations.

I'm going to pause and emphasize that terminology. Stabilizing agents. Not cosolvents, not solvents, not some other agent used to dissolve the drug, but stabilizing agents.

Randolph goes on to teach that Tween 20, which is another name for polysorbate 20, is often added to formulations

due to its ability to protect proteins from the surface-induced denaturation. That's the exact use of surfactant in these protein formulations, and it had been used for decades to do that as a stabilizing agent.

So let's talk about a couple of those prior art VEGF antagonist formulations. We can start with Genentech Avastin here on Slide 6. This is the VEGF antagonist bevacizumab, a powerful VEGF antagonist, just like the drug at issue here, and I might say an even larger molecule than aflibercept.

You heard some argument that somehow no one thought aflibercept would work because it was too big. This molecule is even bigger, and it worked. And the skilled person would know from this drug that if you used the blueprint from the art -- a buffer, a surfactant, and a stabilizer -- you would get a stable protein composition that could be used for intravitreal administration. Avastin, case in point, models approved for treating cancer in 2004; by 2006 this had been used in the eye by intravitreal administration.

The art didn't stop there, nor did Genentech. Here on Slide 7, you have Lucentis, another VEGF antagonist called ranibizumab. Your Honor will note the common blueprint from the art -- using a buffer, a surfactant, and a stabilizer to get a stable protein formulation for intravitreal administration.

So the art had evolved considerably before the '865

patent, and the blueprint was known and was simple. Use these tried-and-true components -- the buffer, a surfactant like polysorbate 20, and a stabilizer -- and the skilled person knew they could get a stable composition for intravitreal administration, just like the '865 patent purports to claim.

So knowing that, knowing that, Your Honor, what did Regeneron do when it formulated Eylea, the alleged commercial embodiment of the '865 patent? No surprise, they followed the prior art blueprint. Why wouldn't they? Why reinvent the wheel?

Here on Slide 9 we have a snapshot from the Eylea BLA. That's the biologic license application submitted to the FDA. The BLA is when you seek approval for the stated effective use of a drug in humans. BLAs are supposed to be truthful and accurate. They are checked over by many folks, and they are representations to the FDA to get approval. You have to tell them what the drug is, what the ingredients are, and what their functions are.

So two take-aways from the Eylea BLA, you see here on Slide 9. Number one, Eylea uses that same prior art blueprint -- the buffer; surfactant, polysorbate 20; and a stabilizer. No question about it, following that prior art blueprint from Genentech and others.

Point two, I want to pause and focus, what did Regeneron tell the FDA regarding the function or the role of

polysorbate 20 in the formulation? They said, quote, stabilizing agent, end quote. Say it again, stabilizing agent. They didn't say cosolvent. They didn't say solvent. They didn't say an agent used to dissolve the drug. Why? Because you don't need something else to dissolve the drug.

The solvent, as you can see, Your Honor, is water. Aflibercept is fully soluble in water. It doesn't need anything else to help dissolve it or increase its solubility. That's why Regeneron told the FDA polysorbate is a stabilizing agent, not a cosolvent.

That's perfectly consistent with the art and the literature, but it's a far cry from their litigation-inspired theory they're running with here where they want to rewrite not only history but the science and somehow call polysorbate 20 in a protein formulation a cosolvent. It's not, as the evidence will show.

So what did Mylan do when formulating the Yesafili, the accused formulation or product here? No surprises. Mylan is also practicing that prior art, that blueprint -- the buffer, the surfactant, and the stabilizer.

And here on Slide 11 we have a snapshot from the Mylan BLA. And again, you see the buffer; the surfactant, polysorbate 20; and the stabilizer. And what did Mylan represent to the FDA regarding the function and role of polysorbate 20?

We can see it right here in yellow in the red box. Just as Regeneron represented to the FDA, Mylan represented polysorbate 20 functions as a stabilizing agent. Again, stabilizing agent. Not a cosolvent. Not a solvent. And, again, it's not used to dissolve the drug or increase its solubility.

That's what the water is for. Water is the solvent. Aflibercept is fully soluble in water alone. Doesn't need anything else. Doesn't need a cosolvent. Polysorbate 20 is a stabilizing agent, just as the art identifies, just as the literature says, just as Regeneron represented to the FDA.

Nor did Mylan or Yesafili copy Eylea or the '865 patent. This is a very quick comparison table of the prior art VEGF antagonist, Avastin and Lucentis versus Yesafili and Eylea. Your Honor can see Yesafili follows the prior art blueprint, but it doesn't use the phosphate, the sucrose, or the sodium chloride from Eylea.

Yesafili practices the Lucentis prior art. We can see it right here, uses the same histidine buffer, the same polysorbate 20 surfactant, the same trehalose stabilizer. That's classic practicing the prior art.

If the '865 patent somehow covers Yesafili, then it also covers that prior art. It would be invalid.

That illustrates what's going on here. Regeneron followed that prior art blueprint from Genentech and others,

then went out and filed their own patent on it, and they now want to prevent others from using those tried-and-true known excipients.

So let's get to the infringement position. Before we do, I think we need to recap the claim construction and the Markman again.

I want to repeat the construction, Your Honor. "'Organic cosolvent' means 'an organic substance added to the primary solvent to increase the solubility of the solute, here a VEGF antagonist.'"

Now, Regeneron paid lip service to that construction, but they left out some of the underlying rationales and context for it from the Court's opinion.

Simply put, quote, cosolvents are used to dissolve another substance, end quote. It's that simple. As the Court also observed, cosolvents work in conjunction with a primary solvent, quote, to better dissolve the drug substance, end quote.

The Court also noted that polysorbate's role is as a surfactant, which is not interchangeable with cosolvent.

So what does it mean to be a cosolvent to increase solubility? It's simple. It's something you're using to help dissolve the active ingredient or the drug substance.

Now, why are we here on these particular claims, then? Why these claims? Why not others? What is this patent

about and not about?

And the Court provided some context for that in its opinion as well, as we see here on Slide 16. This patent does have claims or embodiments to the so-called polysorbate embodiments. To those formulations, like Eylea, it used polysorbate 20 as a stabilizing agent. That would be unasserted Claim 51 and its dependents. As the Court noted, Claim 51 corresponds to embodiments like Example 3, which is the Eylea fingerprint.

But that's not -- that is not the claims asserted here. Regeneron instead, they can't use these because Yesafili doesn't use all the components here, doesn't use the phosphate buffer or the sucrose stabilizer. So they're trying to stretch other claims that were never designed to cover a polysorbate embodiment like that. They're using all the claims that depend on Claim 1, which require the organic cosolvent.

And as the Court noted in its opinion, Example 2 is an embodiment of Claim 1. That's a formulation using a cosolvent like polyethylene glycol or PEG. That's a far different animal than the polysorbate embodiment like Eylea or even Yesafili that uses polysorbate 20 as a surfactant and stabilizing agent.

So let's get to it, then. What is the noninfringement case? Just to recap, the asserted claims are 4, 7, 9, 11, and 14 to 17. They all depend in one fashion or

another on Claim 1. They all require an organic cosolvent.

We see here on DDX 1, Slide 20, our noninfringement case is simple and straightforward. Evidence will show that there's no organic cosolvent in Yesafili. None. The only solvent we can see in this formulation is water. And there's no dispute that aflibercept is fully soluble in water. It doesn't need anything to help dissolve it.

The evidence will show polysorbate 20 is not a cosolvent. It doesn't increase the solubility of the active ingredient, doesn't work in conjunction with water or anything else to dissolve the active ingredient. Not at all. And the arguments you just heard from Regeneron are unfounded.

You heard Regeneron talk about -- I have it right here on Slide 32 -- somehow the most important document in the case, some data they cite from the Mylan BLA, some so-called DLS testing. What they didn't mention, Your Honor, is that testing was not on the Yesafili formulation. They rely on testing on a formulation that is not Yesafili.

They also left out that other data in the BLA shows and undermines their aggregation theory, that the Yesafili formulation, even without polysorbate 20, isn't subject to aggregation.

So when the evidence is in, Your Honor, it will show that their arguments are unfounded and they make no sense. They're premised on this circular idea somehow that

polysorbate 20 is increasing the solubility of something that is already in solution and soluble in water. They will not be able to carry their burden of proving that there is an organic cosolvent in Yesafili.

Now, this issue, the Court will hear from our expert, Dr. Gregory MacMichael. He's an expert in biopharmaceutical formulation and development, over 38 years of experience. Your Honor may recall Dr. MacMichael from the claim construction proceedings. His declaration evidence was unrebutted. He will testify consistent with those opinions and explain why polysorbate 20 is a non -- is a surfactant stabilizing agent, not a cosolvent.

So as I began, Your Honor, when the evidence is in, the Court should find Yesafili does not contain an organic cosolvent and, therefore, Yesafili cannot and does not infringe.

Now, as I began, if polysorbate 20 is a cosolvent, the evidence will show the claims are invalid as anticipated and obvious.

On anticipation, one quick note. It doesn't matter the prior art expressly discloses every element verbatim of the claims. That's not what anticipation is about. If the prior art discloses the elements expressly or inherently, as understood by a skilled artisan, not by laypersons or lawyers, as understood by the skilled person, then the claims are

anticipated, and that's what the evidence will show here.

The evidence will also show, if not anticipated, the claims are obvious. And I won't belabor this point, Your Honor. I'm not going to go through every single reference, every piece of art disclosing the supposed claimed embodiments or formulations, but I've got a timeline here, DDX 1, Slide 25. And it looks very busy and for good reason, because the art was very crowded. It was chock-full of stable protein formulations, starting with VEGF antagonists like Avastin and Lucentis that we see here and the Gaudreault, the Avery, and the Shams references.

And beyond that, there were actual references, like Fraser in Dix '226 that actually disclosed aflibercept, the molecule in question here, in a formulation using that prior art blueprint, the buffer, the surfactant, and stabilizer. The bottom line, as our expert Dr. Rabinow will explain, the skilled artisan knew from all this art exactly how to achieve a stable composition suitable for intravitreal administration, and that was using that buffer, surfactant, and stabilizer.

The evidence will show that the claims are anticipated by the Fraser or the Dix reference. And, again, these references disclose, expressly or inherently, all of the composition and the functional stability elements of the claims. But even if not anticipated, the evidence will show that the claims are obvious over Fraser or Dix, over other

references.

But let's not forget Lucentis. Lucentis kind of got short shrift in Regeneron's opening. This is the VEGF antagonist that Yesafili practices, a drug just like the one here, a formulation with all the elements of the claims -- the buffer, the surfactant, and stabilizer -- that the skilled artisan knew was stable, the skilled artisan knew could be used for intravitreal administration.

It's an understatement to say the skilled artisan would have been highly motivated to use aflibercept, with references like Fraser and others, in the Lucentis formulation. That's exactly what Yesafili and Mylan did practicing that prior art. That claims would also be obvious over the Lucentis art in combination with other references.

On these issues the Court will hear from our expert Dr. Barrett Rabinow. He's an expert in pharmaceutical formulation and development with over 25 years of experience. And, again, he will explain much better than I can how all of this art and more renders these claims anticipated and obvious.

Now, I also mentioned the other evidence will demonstrate the claims are invalid under Section 112, including for lack of enablement. I want to start there with nonenablement and focus on Slide 29 because recently the Supreme Court in the Amgen decision made absolutely clear if a patent claims an entire class of compositions, just like the

patent here, the specification has to enable the skilled person to make and use that entire class, all of the compositions, without exception. In other words, the specification must enable the full scope of the claims.

I'm not even sure I heard the word "full scope" from Regeneron's opening. That's the requirement. And the Court made clear that the more a party claims, the broader the monopoly it demands, the more it must enable.

The problem for Regeneron here is it claimed very broadly; it disclosed very, very narrowly. Now, this issue our expert Dr. MacMichael will testify these claims cover countless -- millions of formulations, but the specification provides very little guidance, very few working examples beyond a few.

He will testify this specification can't possibly enable the skilled person to practice countless numbers of formulations, millions of formulations, without undue experimentation. And this is a classic nonenablement case. As a matter of fact, in one of the last cases tried in this court before Judge Keeley, the AstraZeneca v. Mylan case, Judge Keeley found very similar claims invalid for lack of enablement precisely because the specification was far too thin to enable the skilled person to make all of the claimed compositions.

Now, that decision was vacated pursuant to a

settlement of all things --

THE COURT: I may have heard about that.

MR. RAKOCZY: But it's quite a decision. And it illustrates exactly how the Amgen decision and enablement works when you try to claim the world, when you try to claim all of the compositions, countless numbers, but your specification can't carry the water necessary to enable the full scope. And there is nothing inconsistent or contradictory about our obviousness and our nonenablement theories, nothing.

In a case like this, the specification discloses no more than the art, and, in fact, even less. The claims can't be both nonobviousness and enabled. If that art doesn't render the claims obvious and if the specification has no more than the art, then the specification can't possibly enable millions of other compositions. It's just not possible.

Another way to look at it is like this: To prove obviousness, we don't need to show that a single formulation in the prior art falls within the scope of the extraordinarily broad claims here covering countless formulations. That would render the claims obvious.

But those same claims would be equally invalid for lack of enablement precisely because of their extraordinary breadth because they claim countless formulations. So there's nothing inconsistent about these theories. The only inconsistency may come from Regeneron and its expert.

On the one hand on obviousness, they may say there would be no reasonable expectation of success in achieving the claimed formulations based on the teachings of Shams. That's the Lucentis article that you saw he was practicing. Yet in the same breath on enablement, they may say that a skilled person could have used that exact same art to make a formulation with the histidine buffer which is not even mentioned in the patent. That makes no sense.

If Lucentis art can't render the claims obvious, then it certainly can't enable. And I apologize. My cocounsel here said I may have misspoken. What I meant to say -- if I didn't say it, Your Honor, I want to make it clear.

To prove obviousness, we only need to show a single formulation in the art is obvious and falls within the scope of the broad claims. But that broad claim, because of its breadth, would also be invalid for lack of enablement. So nothing inconsistent about our positions here.

The evidence will also show that the asserted claims lack written description. Written description is just like it sounds. The written description or the specification itself, the four corners of the patent, have to show that the inventors actually possessed and invented the full scope of all of the formulations claimed.

As Dr. MacMichael will testify here again, these claims are directed to a broad genus of formulations, countless

numbers. But the specification shows possession of only several very narrow formulations, a phosphate buffer and a sucrose stabilizer, if that. That is inadequate written description.

And on written description, Regeneron can't point to the art and try and fill in the holes in its specification using the prior art. It is based on the written description itself. And here it is very thin.

Lastly, on 112, Your Honor, the evidence will show that the asserted claims are indefinite precisely because of the use of purely subjective language like "suitable for intravitreal administration."

The federal circuit has cautioned on using subjective language like that. And as Dr. MacMichael will explain, the guidance here -- the specification here provides very little guidance on what components would and would not be suitable for intravitreal administration. And, again, I expect Regeneron to come and point to the prior art and say, well, the prior art teaches you all kinds of things about what's suitable and not suitable.

Again, they don't get to fill in the gaps in their specification with the prior art. And here the zone of uncertainty based on this specification renders these claims fatally indefinite.

Finally, Your Honor, I wasn't sure if I had to

mention this or not, but we heard more complaints and attempts by Regeneron to somehow disqualify the Dix art as prior art. It sounded a lot like rearguing the summary judgment motion that was denied. And we think that is better argued in posttrial briefing. So I'll be very brief; two quick points.

Number one, on this so-called 103(c) safe harbor theory, Regeneron continues to ignore the fact the entire theory is based on them being able to claim priority all the way back to this June 16th, 2006, application. There were ten intervening applications between that provisional and the issued '865 patent.

Regeneron is supposed to come forward with evidence showing written description with support in every single prior application all the way back to the provisional for every single limitation in its asserted claims in the '865 patent. They have not done that, and they cannot do that.

A simple comparison of the issued patent and the provisional shows that they added all kinds of new matter to the '865 patent, likely to try and provide that written description support which is missing from the prior applications. So they won't be able to carry their burden of production. They won't be able to show they're entitled to that June 2006 priority date.

Lastly, Your Honor, apparently they're not content with this argument, this 103(c) argument; so now they're also

saying, well, forget about the June 2006 date. We actually invented this well prior to that. We submit they won't be able to show that either. They won't have the evidence to show that they invented anything covered by the claimed patent.

So, with that, Your Honor, I will end as I began. When the evidence is in, the Court should enter judgment of noninfringement and invalidity for the defendants on the '865 patent. And, with that, with Your Honor's permission, I'll turn it over to my colleague Ms. Mazzochi to address the dosing patents.

THE COURT: Understood. Thank you, Counsel.

MS. MAZZOCHI: Thank you very much.

Good morning, Your Honor. Pleasure to see you again. Deanne Mazzochi for Mylan and Biocon to discuss the '601 and '572 dosing patents.

Now, with Regeneron, the invalidity concessions -- and they were concessions -- we're down to four claims. For the '601 patent, Claims 11 and 19, which are boxed here in red. But because we are going to be looking at the claims as a whole, we also have the underlying independent claims, Claims 10 and 18, respectively, that are incorporated into Claims 11 and 19.

Now, before we go on, you heard Mr. Berl talking about the extended fixed dose and how this was a big part of the invention. Let's be clear about what these claims are

actually requiring on their face. 2 milligrams approximately every four weeks for the first five injections followed by, in Claim 18, 2 milligrams approximately once every eight weeks or two months. Ask them, as they try to start pushing this new theory on some type of super extended eight-week dosing regimen, where that actually appears in their claims.

Now, when we get to the '572 patent, you're also going to hear about two claims boxed in red, Numbers 6 and 25. Here again, some of the invalidity defenses are tied to the underlying independent claim and some of them are actually within the asserted claim.

So for Claim 6, isotonic solution, for -- dependent Claim 25, four secondary doses, has to tie back to the single initial dose that's part of Claim 15 so that we get the five loading doses all together.

So with that framing the claims, let's now go first with what the evidence will show when it comes to anticipation and obviousness.

Our expert Dr. Thomas Albini is going to put a lot of this science together for you. He is an expert from the renowned Bascom Palmer Eye Institute with the University of Miami which is rated the best in the nation for ophthalmology. He has incredible experience in the design and use of dosing regimens, how to treat patients, how clinical trials work, and what those of ordinary skill in the art knew and understood,

particularly in the relevant time periods here.

Now, if we start with the '572 patent, again, Regeneron has accepted summary judgment of invalidity of a bunch of claims. That's because what these claims discovered undisputedly is not new. A method of treating an angiogenic eye disorder in a patient is not new. The drug aflibercept is not new. Administering by intravitreal injection was not new. A 2-milligram dose was not new. A dosing regimen with three loading doses followed by eight-week dose intervals, also not new. And then the last part of the claim is not going to confer patentability under the Court's claim construction.

So after we've looked at the drug, the dose, and the schedule, what actually becomes left in Claim 6? Just this, the aflibercept formulated as an isotonic solution. That's all that Regeneron has pointed to.

Now, when it comes to Claim 25 of the '572 patent, Regeneron points to the method of using this single initial dose followed by secondary doses, which Claim 25 specifies it for, for a total of five doses before starting eight-week dosing. And that's the identical issue that we see for the '601 patent, Claim 11, and then for another disease state called diabetic retinopathy that we see in Claim 19. Again, all they're focusing on is the existence of five loading doses in the regimen.

So as we go forward, let's talk first about Claim 6,

the doses formulated as an isotonic solution. Then we'll talk about the loading doses. You'll hear from Dr. Albini as well as our formulation expert Dr. Rabinow to explain how and why the prior art taught that an isotonic solution was not new and also obvious. And they are going to defend that position in testimony, notwithstanding Regeneron's doing what it's done a lot through this case in trying to cherry-pick some things and give incomplete quotes to try to say they said something that they didn't.

When we get to invalidity, you're also going to hear that one of our main prior art references continues to be the Dixon publication. Now, Regeneron is taking the position in this case that Dixon does not, quote/unquote, disclose any isotonic solutions, usually because it doesn't use the word "isotonic" itself.

Of course, the evidence will show that they will never find the word "isotonic" itself appearing in the Yesafili labeling that they say infringes. So as we go through trial, we want to be clear -- and I think the Court will make sure Regeneron is clear -- that when they and its experts are talking about the term "disclose," are they using it to mean is a particular word actually written there verbatim or are they looking at disclosure in terms of what a person of ordinary skill in the art would understand?

Because what the federal circuit has stated is that,

when it comes to what's actually in the reference, it's not just what is expressly said; it's also what is inherent within the reference.

Inherency means that we're going to look at how things can be known or understood from the perspective of that person of ordinary skill in the art. And the way in which I would like to think about it, Your Honor, is like this.

Let's say I were to write home today and say I used the elevator to get to Judge Kleeh's courtroom today. Now, Regeneron would say I only disclosed in that letter there's an elevator in the courthouse. In reality, from the perspective of someone like you, who is certainly the person of skill when it comes to this courthouse, you are going to know that there are features and properties and behavior that's inherently a part of this existing elevator. You know that it has buttons to three floors, it has a motor, cables, hopefully a maintenance schedule, a door that automatically opens, and that it travels to all three floors.

THE COURT: There are a lot of assumptions about our elevator in that statement, Counsel, but go right ahead.

MS. MAZZOCHI: But the person of ordinary skill in the art, Your Honor, knows that's what's going to be part of a working elevator in this courtroom.

THE COURT: "Working" being the operative term.

MS. MAZZOCHI: I am not relying on that for

inherency.

Now, when the prior art does, however, reference a real thing that exists, that person of ordinary skill in the art can use their knowledge and their skill sets to figure these inherent properties out. And that's really all that Dr. Albini and Dr. Rabinow have done here.

They've looked at how a person of ordinary skill in the art would see Dixon. They applied the skill and knowledge from their respective fields. And they can assess things like what's in the composition, what's in the dose, and then follow -- also follow what are some of the steps involved in the dosing regimen and how these Phase III clinical trials even work before the FDA. So with that framing, with that background, let's now apply it to the Dixon reference.

The evidence will show here that Dixon did describe an isotonic solution inherently, as required by the '572 patent's Claim 6, and has happened through two independent and, yes, inherent disclosures. Now, here's the first one.

The description in Dixon of the VIEW 1 clinical trials. Now, we agree that it expressly describes that there's a VIEW 1 Phase III clinical trial going on. A 2-milligram dose was being given to patients for three monthly dosing intervals then followed by an eight-week dosing interval after that. What does a person of ordinary skill in the art know is happening, just like we know there's buttons in the elevator,

they know that there's a dose there that actually exists and which is being given to patients while the trial is underway.

So we just need to look up what were the inherent properties of that 2-milligram formulation dose that actually existed and was actually used in the VIEW 1 clinical trials.

The evidence will show that it was the Eylea formulation. So all of the features and properties of Eylea that were inherent in the Eylea formulation is also inherent in this disclosure of the prior one VIEW 1 uses of the 2-milligram dose in the existing regimen.

And since Regeneron does not dispute that Eylea was isotonic, that's why we will meet our burden on inherent anticipation.

But that is not the only description of aflibercept doses in Dixon. Dixon tells us another thing, which is our second inherent disclosure. Dixon expressly taught that VEGF Trap-Eye, aflibercept, was formulated with buffers to be suitable for the comfortable, nonirritating direct injection into the eye.

The evidence will show that a person of ordinary skill in the art understands that this description is using signal words like "buffered to be comfortable" and "nonirritating," which is part of the whole goal of an isotonic formulation.

Now, Mr. Berl accused Dr. Rabinow of abandoning his

positions. He didn't. And, again, the context of the deposition will make that clear. But let's also make clear that Regeneron's own experts for anticipation purposes never disputed that this aspect of the inherent disclosure in Dixon was actually going to be inherent disclosure of isotonicity. So that's why, when it comes to the isotonic formulation that we see in Claim 6, it's inherently anticipated and not new.

However, Your Honor, let's assume in Regeneron's favor that the person of ordinary skill in the art does want to know more about these buffered ophthalmic formulations that are suitable for the comfortable, nonirritating direct injection into the eye. What are they going to want to make?

The evidence will show -- and this is the thing that formulators like Dr. Rabinow knows -- that it would have been obvious for the person of ordinary skill in the art to prepare an isotonic formulation. And how do we know that? Because it's basically textbook, Your Honor.

Remington Science and the Practice of Pharmacy is the go-to resource when it comes to drug formulations. The evidence will show that Remington's has been described as the formulary which is known to all pharmaceutical chemists. Dr. Rabinow will explain that the Remington's textbook does have a whole chapter authored by Gerald Hecht, PhD, senior director of pharmaceutical sciences, who explains the fundamental basis of what is in these ophthalmic formulations.

And, again, Mr. Berl citing deposition testimony asking Dr. Rabinow about a formulation for the cornea in the context of irrigation of surgical wounds is not going to somehow change the fact of what a person of ordinary skill in the art would learn from the context of Dixon or also learn from Hecht.

Dr. Rabinow is going to also explain that the term "isotonic" is right there in the Hecht chapter when talking about Remington's. He says that there are things --

You can go to the next slide.

-- that things -- formulators are required to consider, and one of them is tonicity. When you look at the buffer system, that also must be considered with tonicity and comfort in mind. And Hecht didn't just say this as a casual mention. And when it came time to pick what type of tonicity he wanted to talk about, he said ophthalmic solutions are formulated to be sterile, isotonic -- not hypertonic, not hypotonic -- and buffered for stability and comfort.

Again, that's exactly how Dixon described their aflibercept formulation. Buffers. It was going to comfortable and nonirritating to the eye. So an isotonic formulation would be the conventional and known thing to do. And it also wasn't just a known choice. The evidence will clearly and convincingly show that, given a choice, isotonicity is always desirable in the context of injections like this. And it thus

would be reasonable to use, make, and expect success as a consequence.

Thus, the evidence will show that, not only were isotonic formulations of aflibercept not new, they were also obvious, including for use in the claimed dosing regimens.

So with that, Your Honor, let's now turn to this issue of the five loading doses. And I'll put up Claim 11 here as one of our illustrative claims which again depends on Claim 10.

So when it comes to what the evidence is going to show here, Your Honor, the aspect of the claimed method, what Regeneron calls five loading doses, not three, for DME, that also was not new and also obvious. And Regeneron has been emphasizing these five loading doses in the DME regimen and that you see the number 3 and you don't see the number 5.

But, first, I think we should take a look at what it actually means in practice in the context of these types of dosing regimens when you're going to actually go from three loading doses based four weeks apart to five loading doses spaced four weeks apart.

It means -- and you can see this in the bottom regimen here with the red arrow. It means that there's one extra dose in there. You don't have to shift everything else down; you've still got an eight-week schedule at every single point from 16 weeks forward on this chart. You just have to

keep putting in one extra dose at the four-week mark.

So was this really anticipated? Was it obvious? The answer to that question, the evidence will show, is yes. And, for example, to illustrate this, we're going to take a look at a reference that the evidence will show specifically talks about diabetic macular edema, DME, which is one of the specific disease states called out in several of the claims.

This is a press release from Regeneron. And they specifically confirm that VEGF Trap-Eye, aflibercept, was being used in Phase II DME clinical trials. So here again, we have the use of the drug aflibercept; we have the specific indication, DME. So those two things, not new.

How about the dose and the schedule? Dr. Albini will explain that in this September 14th, 2009, press release we've also got the dose. And we actually have several schedules. So, again, dose is not new. And now let's talk about the schedule.

Now, here again, Regeneron says that only says three. We agree that there's a minimum of three loading doses that are required for the every-eight-week dosing regimen and for what's described as the 2 milligrams on an as-needed regimen. But this again is why you have to read these references, not just superficially, but as a person of ordinary skill in the art understands how they are applied in practice. And Dr. Albini is going to walk you through these schedules.

So on Slide Number 60 here's an illustration of what these dosing regimens look like. Now, in the yellow box, in the first one, the 2 milligrams, so 2q4, 2 milligrams being dosed every four weeks, that's effectively the monthly schedule.

The next one in the box, 2q8, has the specified three loading doses denoted by the black boxes. Then they skip a week -- I'm sorry. Then they skip a box, which is another four weeks later. And then they dose again at week 16. Then they skip another one at week 20. Then they go again at week 24. So black box, white box, black box, white box, that's how you're getting the eight-week dosing interval.

Now, what about the prn dosing schedule? So a person of ordinary skill in the art, again, is going to read what -- the dosing regimen that Regeneron was talking about in the press release. They're going to see that there were required three black boxes at the start. So 4 weeks, 12 weeks, et cetera -- I'm sorry -- baseline zero, then 4 weeks, then 8 weeks.

But when it comes to the gray boxes, again, the context of this press release, having a primary end point at the 24-week mark, the person of ordinary skill in the art knows they've got very limited options. They've got a limited number of dosing and a limited number of options in terms of how to fill the box. Now, those boxes are put there in gray because,

in a prn dosing regimen, the doctor does have some discretion to decide are you going to make it black? Are you going to make it white?

But that doctor is still going to necessarily know and envision that you've only got one of two options there. So, you know, if we look, for example, at the treatment needed, if we're looking at weeks 12, 16, and 20, it's going to be yes/no week 12, yes/no week 16, yes/no week 20.

So then when we actually apply -- once the doctor is then thinking what are these dosing regimens going to look like for my patient, well, for those gray boxes in the prn dosing they're going to know that if their patient needs dosing at weeks 12, 16, and 20, all the boxes are going to be filled in black. That's going to be effectively just like what you're seeing with the monthly dosing.

If the treatment is not needed at Week 12 but their patient does need it at Week 16, their patient doesn't need it at Week 20, does need it at Week 24, that's actually the same thing as what Regeneron has described as three loading doses plus eight weeks.

If the treatment is needed at Week 12, not at Week 16, then your patient slips so you need it again at Week 20, that is going to give you four loading doses plus an eight-week interval.

That leaves us with the next set of yes-or-no options

that a doctor is going to envision for their patients when it comes to Weeks 12, 16, and 20. And guess what it is. Week 12, yes; Week 16, yes; then your patient is good enough that you can skip a dose at Week 20; and then you go back to a dose at Week 24. That is going to be the five loading dose option. I've circled the five loading doses in red on Slide 63.

And then when you skip a dose because your patient actually got them to where you needed them to be, then you dose them again at Week 24; that's your eight-week dosing regimen.

So this is also, by the way, why we will fit the cases relating to disclosure of -- in the prior art of either a genus or a range, is that this is a very limited number of things to envision. The person of ordinary skill in the art understands how these dosing regimens work. They understand what the treatment choices are going to be at each of these approximately monthly intervals with regard to whether it's Week 12 or Week 16. And they're going to be able to carry out the dosing. And when they do, this is absolutely 100 percent going to be a dosing regimen, they will understand, is on the list in the context of this prn dosing for DME.

So that's why we say these two other dosing regimens, the one, for example, with four loading doses or this one with five, they may not be expressly disclosed, but the person of ordinary skill in the art understands that they are necessarily a type of regimen that can be envisioned because those are two

options for the gray box -- yes or no, black or white. And Dr. Albini will explain why this is readily easy for a person like him of ordinary skill in the art to envision. So the regimen, again, is not new.

But, again, let's talk about obviousness, and let's assume that Regeneron maybe is right, the person of ordinary skill in the art somehow just can't envision how to pick something in the range of three to six doses, they can't understand if those boxes should be black or white when they're outlining their treatment regimen.

The federal circuit has said the choice is still obvious. In Galderma v. Tolmar, 737 F.3d 731 at 738, Federal Circuit, 2013, the federal circuit explained that, if a range is disclosed and a claim falls within the range, then the patentee has the burden to produce evidence that there was teaching away, unexpected results, or some other kind of secondary consideration tied to this deviation or this particular species within the range.

This Galderma case is why you're going to hear from Regeneron their theory that somehow a person of ordinary skill in the art would be terrified to have five loading doses and instead would only want to limit themselves to three.

Frankly, Your Honor, we don't even think that that evidence is credible, especially, you know, their concerns that it's going to be dangerous to have more than three maybe having

four or five. It's not credible when their own press release specifically said they were also running a monthly dosing regimen. A monthly dosing regimen for a -- for six months is going to give you six doses, which is greater than five.

So if there was really something that was going to actually inhibit someone of ordinary skill in the art from using five, the press release and the fact that this trial was actually running with six monthly doses would certainly put that to rest.

And, furthermore, as for the question of whether there is a trend towards fewer injections overall, what the evidence is going to show that doctors do want to treat their patients to get their retinas dried out. They try to actually get their patients' retinas dried out, get rid of the fluid on the eye, bring down that inflammation, then they'll move to the extended dosing period.

So when Mr. Berl was quoting Dr. Albini saying, hey, is there a trend to reduce the number of doses? Of course it is. But as a general rule, the way in which doctors like to think, particularly today, is they want to get the macula dry, they want to get the retina dried out, and then they're going to move to their extended dosing regimens.

So there was nothing new about this. This was a theory that was already known in the prior art about how to get the patient's macula dry. So to suggest that somehow there's

anything new or novel or nonobvious about what's being done here as opposed to just optimizing a treatment regimen for patients, the evidence is going to show that this was not new and it was also obvious.

Now, also, for secondary considerations, Dr. Albini is going to explain why there's no teaching away, why there were no unexpected results, why there's not other secondary considerations that show nonobviousness.

Much of Regeneron's secondary considerations evidence, for the reasons we stated in our motions in limine, is utterly irrelevant. A lot of the things that they've identified, well, somebody else didn't extend the regimen for Macugen or Lucentis, but number one, it's not actually accurate, but even so, the fact that there was already data and information about the VIEW 1-VIEW 2 clinical trials going on already indicated that dosing regimens that could be extended were underway.

Furthermore, it also doesn't matter to claims like Claim 10, Claim 11, Claim 19, Claim 25 because those are involving a different disease state than AMD.

The praise for the VIEW 1-VIEW 2 wet AMD clinical trials likewise has nothing to do with their claims that are limited to DME and diabetic retinopathy. Their claim that it was unexpected that a fixed extended dosing regimen worked is not supported by the evidence.

And they've also got a really interesting commercial success position here. Now, Mr. Berl, I believe, indicated that there were only two inventions that were driving success. I would argue that that concession is actually fatal because what he's basically saying is that there's two completely distinct and different patent families that he's trying to tie to the commercial success.

Well, the federal circuit has said you have to have a nexus that is actually tying what is in the claims to what you're claiming is the source of your success.

So the sheer fact that they're trying to split it amongst two families actually undermines the whole premise that they've demonstrated a nexus between the alleged success and the claims.

And the other big thing that they have forgotten about in our economics expert, Mr. Ivan Hofmann, who is a CPA and certified licensing professional who has looked at the family of patents that Regeneron has, he's also going to point out, by the way, you also have this patent to a little molecule called aflibercept, which has also kept all kinds of competition out of the market. So, yes, you've managed to get some success, but you've been able to do it because you're a monopoly with no competition.

When that aflibercept molecule patent is protecting their entire franchise, on the verge of expiring, which is one

of the reasons why we're here, that is also a problem for them in terms of establishing nexus because what they haven't been able to show is that what doctors really like about their product isn't the property's intrinsic to the molecule as opposed to something about the dosing regimen itself.

If I can, Your Honor, let me switch gears to another part of the patent statute, 35 U.S.C. Section 112. Now, you heard Mr. Berl earlier. I think he said that nonenablement depends on whether you're better off with or without the patent.

The evidence here is going to show that every single thing they complain about with the prior art -- too many options, no clear teaching in this direction versus that direction -- their own specification doesn't resolve most of those problems.

Now, Dr. Jay Stewart has looked at a lot of these issues. Dr. Stewart is the head of ophthalmology and a full professor at the University of California San Francisco Medical Center. He has gone through this specification in depth, and he's going to be able to explain to Your Honor, particularly from the perspective of the dosing and disease treatment issues, why the claims do not comply with Section 112.

In addition, we're going to have Dr. Rabinow talk about some of the formulation-related issues for Claim 6, isotonic.

Now, when it comes to the claims here, a claim like Claim 6 which claims a lot but enables very little, is exactly the type of claim where the inventor claims a lot, enables a little, and the public does not receive the benefit of the bargain.

But here's another part of Section 112 that the federal circuit has discussed. And the federal circuit has also discussed this question of written description. The federal circuit have also said, if you have a disclosure in your specification that's very broad with lots of choices, then you try to get claims that are very, very narrow. You can't say "Here's the forest, and now I claim the tree. Here's the haystack, and now I want to claim the needle." You've got to give blaze marks that are going to direct a person of ordinary skill in the art towards that particular tree, and it's got to be in your originally filed disclosure.

So here's how this is going to play out for Claim 6. Dr. Stewart will discuss the dosing issues, and Dr. MacMichael will discuss the formulation -- I'm sorry; this is Dr. Rabinow. Dr. MacMichael will be discussing the formulation issues.

So what does the specification do when it came to some of the -- what I'm calling -- broad terms, like angiogenic eye disorder and secondary doses?

Well, first of all, I think Mr. Berl brought up the sovereignty of the kingdom. Well, look at that first line

there when it comes to angiogenic eye disorder. They said can be used to treat any angiogenic eye disorder. That is trying to cover the kingdom, any angiogenic eye disorder.

But even for this list that they then follow, which I think has, like, over 18 different indications, even today doctors don't use aflibercept to treat those indications. They don't even use VEGF inhibitors to treat those indications because the drug class just doesn't work for those indications. So they claim broadly, but they cover things that don't work. That's classic nonenablement.

Similarly, while they like to put the little circle around the number four when it comes to the number of doses you're going to use in these regimens, look at what they actually said. When it comes to the number of doses at any particular phase of these regimens, two or more, e.g., two, three, four, five, six, seven, eight, or more. That's not a narrow disclosure. That's an incredibly broad disclosure. That's something too that they have not enabled.

And even with all of their patent examples, it doesn't provide the requisite support that would be needed so that the person of ordinary skill in the art can read the specification and be confident that it's actually going to work.

And, ultimately, Your Honor, what we see here in the specification, we are not seeing blaze marks towards four or

five loading doses. What we are seeing is a CYA memo, where they're trying to cover the universe until their hindsight data allow them to pick something later on.

Now, when if comes to the term "isotonic," there is nothing in this specification saying this was a key part of invention, that this was something that Dr. Yancopoulos invented, and then that's one of the things that Dr. MacMichael is going to be talking about as well.

Now, when it comes to the loading dose claims, here we're in the situation where they're trying to claim something very narrowly, but here again, as we saw, they disclose the forest. So Mr. Copland was very insistent that I pronounce the forest name. The Monogahela forest.

THE COURT: Close enough, Counsel. Close enough.

MS. MAZZOCHI: He told me if I got it wrong, you would catch it and I would be humiliated forever. But that being said --

THE COURT: It's a little harsh, but probably closer to accurate than inaccurate.

MS. MAZZOCHI: I'll make sure he schools me during the break.

But that being said, you know, they basically disclosed in their patent specification we want the entire forest; but then when it comes to those claims, they're saying, Well, what we really want is the ten-foot holly tree with a lot

of berries that's at the end of the trail that's over by the waterfall.

If you want to do that, you have to actually have some guidance in your patent specification that's going to help the person of ordinary skill in the art follow that path. And so if we take a look at the next slide, what we see is what the federal circuit wants to see is some clear blaze marks down the middle, but what we actually have are a bunch of twisted paths going in all sorts of different directions. That's why these claims fail under the written description requirement.

Dr. Stewart will also be explaining why the term "approximately" is indefinite. And this is not a question of Regeneron being able to find some context where somebody actually knows how to use the term "approximately" to mean some type of variability.

Part of the problem is is that Regeneron isn't even using the term "approximately" consistently within its own claims. So that's part of what leads to the difficulty here when it comes to indefiniteness, is that their inconsistent internal use within their own claims is what's not apprising the public as to what's available to them.

Likewise, to the extent there's going to be a priority fight on this, Your Honor, I want to be clear and give you a heads-up. We are going to be challenging whether Regeneron has actually done the work that they needed to do

during fact discovery to actually put us on notice of what their claims and theory was going to be, let alone whether they actually have the evidence to back it up.

So when we're done, though, reviewing claims as a whole, the evidence is going to show these claims are not valid and they are, for a whole host of reasons, anticipation, Section 103 obviousness, as well as Section 112.

Now, let's finish up on explaining why Regeneron will not be able to meet its burden of proof on infringement. Mr. Copland told me I got two minutes left; so let me roll into it.

THE COURT: I don't know why Mr. Copland became in charge in this courtroom.

MS. MAZZOCHI: I think he's trying to make sure you are served and your interests are served, and that is what local counsel is supposed to do.

THE COURT: Understood, Counsel.

MS. MAZZOCHI: So Mylan concedes that Regeneron and Biocon do not directly infringe. They're say it's the doctors who infringe. But the problem is they're not going be able to meet their burden of proof to even show that they've got a requisite direct infringers here.

Now, Your Honor, they gave you the label, and that label has a very rigid schedule. But after five years of this rigid label being on the market, their so-called wanted

extended fixed-dose regimen doesn't even make the list of what ophthalmologists who are surveyed say this is how they actually treat their patients when it comes to this drug class.

So we're not disputing that doctors really like Eylea. The problem is they're not actually using it the way in which the label instructs. And when we know that doctors aren't using it the way that the label instructs -- and Mr. Berl seems to actually admit that Dr. Albini thinks that we should be custom-tailoring these treatment regimens to the patients -- they're not going to be able to meet their burden of proof, they're not going to be able to prove that you should infer an intent that we want doctors to use the rigid schedule as opposed to what's actually happening in practice, and with that, Your Honor, they're not going to ultimately be able to meet our burden of proof of infringement.

And in terms of why we don't need to bring our expert, when that particular fact does not appear to be in dispute, I don't need an expert to tell you something duplicative about a fact that's not in dispute.

With that, Your Honor, that's why the evidence is going to show that Regeneron cannot meet their burden of proof, Mylan and Biocon will meet their burdens of proof. And we do very much thank the Court and your staff for your time and attention. We look forward to working together with you over the course of the next two weeks as the evidence comes in. And

we respectfully submit that, once the evidence is in, the Court can and will enter judgment for Mylan and Biocon on all claims and defense.

Thank you, Your Honor.

THE COURT: Thank you, Counsel.

All right. We'll take -- from your-all's perspective we'll take an hour for lunch. If I could ask trial counsel, we do have to take up one hearing here in a few moments. It won't take all that long. If you wouldn't mind, as best you can, sort of moving your stuff back a row for us, that would be tremendously helpful. Then we'll resume with the first witness at 1:05 or so.

We'll take a break. We'll see you all at 1:05 or so. Like I said, our 12:05 shouldn't take all that long; so we should be ready for you then. Thank you.

(A recess was taken from 12:05 p.m. to 1:14 p.m.)

THE COURT: At least a few moments behind schedule. With that, plaintiff may call their first witness.

MR. COPLAND: Your Honor, one housekeeping matter. The Court usually wanted demonstratives filed with the Court. If that is the operative rule, then Mylan and Biocon request that the public filing of demonstratives be redacted so they can file a full under seal and redacted in public.

THE COURT: Any objection to that, Counsel?

MS. OBERWETTER: No, Your Honor.

THE COURT: Thank you, everyone. Without objection, so ordered.

Also, any objection to the Court ordering filed the bench memo on sealing that portion of opening statements?

MR. COPLAND: They've already been filed, Your Honor, by Mr. O'Brien.

THE COURT: I withdraw my question, then.

MS. OBERWETTER: Your Honor, the parties have had discussion about moving into evidence as a whole exhibits used during the course of direct. If that meets with your approval --

THE COURT: It does, absolutely.

MS. OBERWETTER: Thank you, Your Honor.

In that case, Regeneron calls its first witness, Dr. George Yancopoulos.

GEORGE YANCOPOULOS, PLAINTIFF'S WITNESS, SWORN

THE COURT: If I could trouble you to adjust that mic so everyone can hear you clear. Don't worry; you can't break it.

Counsel.

MS. OBERWETTER: Thank you, Your Honor. We're just making sure the witness has a binder. Thank you.

DIRECT EXAMINATION

BY MS. OBERWETTER:

Q. Good afternoon, Dr. Yancopoulos.

A. Good afternoon.

Q. As you know, my name is Ellen Oberwetter. I'm here on behalf of Regeneron.

Could you please introduce yourself to the Court.

A. My name is George Yancopoulos. I'm cofounder, cochairman, president, and I guess most relevant and important, chief scientist at Regeneron.

Q. And in your role as chief scientist at Regeneron, what have been your general responsibilities in that role?

A. To oversee all aspects of research and development at Regeneron.

Q. Okay. And can you describe briefly what kind of company is Regeneron.

A. Yeah. We like to think that we're a very different kind of company. I know everybody says it, but we do have a lot of things that I think can objectively attest to that.

We're the only major biotech/biopharmaceutical company that was started and still run by physician scientists. We think that keeps our focus uniquely on the science, and that is our goal, to use science to change the practice of medicine. As you know, most companies are headed by commercial or business people.

We had started over the years with this focus on

science, and for many years we were viewed as a failure. My partner, Leonard Schleifer, likes to say we became a success after 20 years of failure, an overnight success after 20 years of failure. What we were actually doing during those 20 or 25 years was really building the technologies, the break-through technologies that allowed us to then become very successful as a company.

So in the first 20 to 25 years we were not profitable. It's amazing that we actually survived, but we used those technologies eventually to start developing and creating and inventing new medicines. And over the last ten years or so, many have recognized us as one of the most successful biotech or biopharmaceutical companies in the world.

We've invented out of our own laboratories ten important new medicines, and it is worth putting that into perspective. You may or may not know there's over 5,000 biotech and biopharmaceutical companies in America alone, and there's only 20 to 40 new drugs approved every year, and most of those are actually me-toos. They're not really new, innovative medicines.

So as you might think, 5,000 companies, 24 years -- it's rare that one company even invents one new medicine, but over the last ten years or so, we've invented ten new medicines and most of them really break-through new medicines.

And so that makes us a real outlier in the industry.

Even the biggest companies, what they do is they -- they don't generally invent their own medicines; they license them from one of these rare companies that has come up with something. So that puts us in a really unique position, and we've been recognized for that.

So, for example, many times over the last ten years we've been on Forbes list of the 10 most innovative companies in the world, often the only biotech or biopharmaceutical company on the list.

So we like to think we're a very special kind of company, one of the most innovative biotechnology companies on the planet. And we have our focus on R&D, as reflected by the fact that over the last ten years, we've had one of the highest percentage of our revenue spent in research and development trying to come up with new medicines. So in addition to the ten FDA-approved or -authorized medicines, we have over 60 medicines that are in the clinical stage of testing right now.

Q. Thank you. And we'll, obviously, talk more about one of those in particular today as we go through this.

First, just briefly, where is Regeneron based?

A. Regeneron is located in Tarrytown, about a half hour north of New York City.

Q. And how many U.S. employees does Regeneron have?

A. We now have about 10,000.

Q. And how many did it have when you started the

company?

A. There was just a couple of us when we started, and we built up slowly. And as I said, for the first 10 and 20 years, we were struggling. And we slowly built up. It's only been in the last five to ten years that we've really ramped up to the levels that we're at now.

Q. And, Dr. Yancopoulos, are you the named inventor on any patents?

A. Yes, I am.

Q. Approximately how many U.S. patents are you the named inventor on?

A. Over 150.

Q. Okay. And you understand that this trial includes two of your patents; is that right?

A. Yes, I do.

Q. I'm going to hand you a copy of two documents --

MS. OBERWETTER: If I may approach the witness, Your Honor.

THE COURT: You may.

BY MS. OBERWETTER:

Q. -- which we've marked as demonstratives PDX 1-1 and PDX 1-2.

A. Do I take them out of these folders?

Q. Yes, if you would, please, sir.

And you can just take those one at a time, but what

do you recognize --

A. This chair is --

THE COURT: We've already talked about our elevator, Doctor. Add the chair to the list.

Go right ahead.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, can you identify those two documents that I just put in front of you, please.

A. Yeah. These are two patents about the use of a VEGF antagonist to treat angiogenic eye disorders.

Q. And do you see that one of those is the '601 patent and one of those is the '572 patent?

A. Yes, I do.

Q. Okay. And you should have a binder in front of you, sir, with the direct examination exhibits. If you take a look at PTX 0001 and PTX 0003, and if you could let us know if those are copies of those same two patents that you just looked at in official form.

A. PTX 001 and PTX 003.

Q. That's correct.

A. Yeah.

Q. Okay. Thank you. You can put those aside, and we'll come back to the patents.

I'd like to talk briefly about your work and your background. First of all, if you could describe briefly for

us, what are some of the scientific awards and recognitions that you have received for your work at Regeneron?

A. Well, I've been recognized as one of the top scientists in the world based on what they call citation index, how often other scientists refer to your work. I was among the top ten in the world at various points.

In large part based on that, I was elected to the National Academy of Sciences, which is an organization that has the top scientists in the country and in the world.

I was elected to the Biotech Hall of Fame. I was selected by Ernst & Young as entrepreneur of the year. And --

Q. Did you receive any recognition for your work in connection with the pandemic?

A. Yeah. I was recognized by Forbes magazine as one of the heroes of the pandemic.

Q. And we'll touch on that, but if you could also tell us, approximately how many publications are you an author on?

A. Over 500 or about 10 a year over my long career in science.

Q. And if you could just tell us briefly how you first got interested in science.

A. Yeah. Well, I was born into an immigrant family. My parents were refugees from northern Greece, which had suffered through both World War II but then subsequently a war against the Russian-supported communists.

So my parents never got -- never finished their education. But they had the -- I don't know how they did it, but they had the courage to just come on a ship to America. And they believed very much in America, and they believed that education was the route to success in this country. So they pushed their kids into education and education.

And what they wanted, like many immigrant families, they wanted me to become either what they called a real doctor or a lawyer. Since English was not my first language, and I'm still struggle a little bit -- you guys might be able to tell -- I was not going to become a lawyer, but I was always very good at math, and I was always one of those kids who was playing with gadgets, making electric motors, ham radios, and so forth when I was a kid. So I was always interested in the sciences.

And when I was in -- I was going to the New York City public school system. When I was in what they call junior high school, 7th and 8th grade, the teachers there -- I remember Mr. Shackle and Mr. Michaels said, "Hey, you know, in New York City, there's a public high school for science called the Bronx High School of Science," and that "You should consider taking the test and seeing if you can get in."

So I did that, and I got into the Bronx High School of Science. It literally changed my life because I met a whole bunch of other science nerds and geeks just like myself, and it

really sort of opened my eyes into what could be done. But the other really special thing about the school was that the heroes -- or the students who were really looked up to in the school were the kids who won what they called the Science Talent Search.

It was sponsored by a company called Westinghouse at the time. And it was like the American Idol for science geeks. And as I said, the school would have, occasionally, winners in this competition. They would encourage everybody to enter. And the winners were looked at as stars and heroes. So that became a goal of mine. And I had to come up with a science project to work on so that I could eventually enter into the Westinghouse Science Talent Search.

And, tragically, at around that time my grandmother -- in immigrant families, you're often raised largely by your grandmother -- she had early onset Alzheimer's and was dying, clearly. And so I decided I was going to -- for my high school science project I was going to cure Alzheimer's disease. And I worked on a project initially called regenerating neurons to try to help her.

And though I did not save my grandmother, my project -- I ended up being a winner of the Westinghouse Science Talent Search. Getting that recognition and that award just made me believe that I could become a scientist. And that was really the start of my commitment and devotion to try and

become a scientist.

Q. Okay. And after your experience at Bronx School of Science, where did you go next for your education?

A. I went to Columbia College in New York City, because, these immigrant families, we want to stay close. Never really left that area because all of my family is in that area.

Q. And what was your experience at Columbia?

A. It was a great experience. I continued to try to work on becoming a scientist.

Q. Did you graduate with any honors?

A. Yes, I did. I graduated as valedictorian of Columbia College. I was also a two-sport athlete, and I was selected as the top student athlete at Columbia for two years in a row.

Q. What did you do next after Columbia College for education?

A. Then, once again, stayed close to home. I went to Columbia for my MD and my PhD degrees.

Q. And why did you end up getting both an MD and a PhD?

A. Well, because, as I mentioned, my parents -- my father particularly wanted me to become a real doctor -- sorry -- I think of my dad; it gets me -- wanted me to become a real doctor. And so it was sort of a compromise or a negotiation that I could pursue my interest in science in getting a PhD, but I would get the MD so I could become a real doctor.

Q. And when you worked on your PhD at Columbia, what was your area of study? And let me know if you need a break.

A. Yeah.

It was in the early days of cloning genes. I became an expert at cloning genes. I worked for one of the world leaders in that field at the time. And particularly we were using cloning genes to understand how the immune system worked and how genes came together to form the immune system.

Q. Okay. And did you end up with a lab at Columbia?

A. Yes, I did. I was given a faculty position.

Q. What ultimately caused you to leave Columbia?

A. Well, when I got my faculty position, I applied for grants. And I received a very large grant at the time. This was in, like, 1987 and -- or so. And it was for $2.5 million, which was a lot of money back then. It still is. And I thought I could finally make my father proud of me.

So I went up to Queens where they lived to share the news. And instead of being super proud of me, my dad was a little disappointed. And though he had no education, he was a pretty smart guy. And he was challenging me about why this was so great. And I said, well, I really think that I have the ability to make -- understand how a disease works. And I might be able to actually someday cure some disease, maybe even Alzheimer's. And he said, well -- he was a very big believer in America. I'm sorry. This whole thing is unusual and

emotional for me.

But he said in this greatest country in the world, if you really believe what you just said, that you can understand and cure a disease, you can get a lot more resources to do that instead of -- he considered getting -- you know, no matter how poor we were, he never took money from the government. So he said you don't have to be a beggar from the government getting grants. You can go to the private sector. You can raise a lot more money, get a lot more resources, and really live your dream.

Q. What happened after that conversation?

A. So remarkably, within a couple weeks of that conversation, I got a call from the man who is now my long-time partner at Regeneron, Len Schleifer. And he was trying to start a company. And it turns out that he had a son who was born with severe growth disorder in his brain. And his dream was actually to regrow his son's brain, but he didn't have the skills. And he thought that somebody like me bringing my skills from what I was doing in gene cloning, since I was one of the world's first gene cloners to clone genes for the brain, we could together regenerate neurons.

And we were both interested in regenerating neurons, me from my first science project, him now with his problems with his son. And our company was called Regeneron, which actually stands for regenerating neurons.

Q. And when did you form Regeneron with Dr. Schleifer?

A. In the late '80s.

Q. Dr. Yancopoulos, do you want to take a second?

A. No. That's okay.

Sorry. This is ridiculous.

Q. All right. Families are emotional.

Dr. Yancopoulos, what was Regeneron's focus in the early days?

A. Our focus was on regenerating neurons. We actually did clone some of the world's first nerve growth factors with the goal of using nerve growth factors to grow neurons in the brain. We were young and inexperienced and didn't know a lot about how things like clinical trials worked and so forth.

And I guess this is a rule in the industry, this is why there's 5,000 companies and less than 20 to 40 approvals every year. Most things fail. The estimates vary between 95 to 99 percent of things that enter clinical trials. And that was the case for our whole first series of work and clinical trials that were all in the neurodegenerative field. We were working on Lou Gehrig's disease and Parkinson's and Alzheimer's disease. And all of our trials over our first 10 to 15 years failed.

Q. Okay. Are some of those diseases you just listed things that Regeneron is still working on?

A. Yeah. They are some of the things that we are still

most intensively working on. My dream is, you know, before I'm done, to make a difference for Alzheimer's disease still. And so we're still working incredibly hard on these neurodegenerative diseases.

Q. And a couple of other questions. Can you describe, at Regeneron today, what are some of the drug development projects that Regeneron has underway?

A. Well, as I said, we spend a lot, from the outside world's perspective without that much to show for it, in neurodegenerative diseases, including Alzheimer's, Lou Gehrig's disease, Parkinson's, and Huntington's, though I hope, just like we came out of nowhere in other settings, we'll do so here as well. But we also have major efforts and approved drugs for various forms of cancer, lymphoma, myeloma. We have efforts in asthmatic disease, emphysema, allergic diseases, and also in infectious diseases.

Q. We touched briefly on the heroes of the pandemic award. What was Regeneron's contribution during the pandemic?

A. Well, as I said, we had spent our first 20 years without outward success in terms of getting drugs approved and so forth. But we invented some of the world's leading technologies for developing drugs known as biologicals, which is what we're experts in. And we realized -- well, actually, we realized it first during the Ebola breakout in the Congo a few years earlier, that we could apply our technologies. And

we came up with the world's first treatment for Ebola.

And then when the COVID pandemic broke out, we realized we could take advantage of these same breakthrough technologies. And we came up with the first monoclonal antibody cocktail treatment for COVID. We supplied millions of doses to the U.S. government. And it saved many, many lives, including one of the first people who was actually treated was the president at the time. In fact, the effort was done under the auspices of Operation Warp Speed, which had been supported by that prior administration.

Q. As you know, Dr. Yancopoulos, the drug at issue in this case today is Eylea. So we're going to turn to talking about that part of Regeneron's history in particular.

What is the name of the active molecule in Eylea?

A. Well, the scientific name is VEGF Trap. And then when you work with the FDA, they assign a technical name or a generic name, which is aflibercept. And then the brand name is Eylea. So there's three names -- I know it's complicated -- VEGF Trap-Eye, aflibercept, or Eylea.

Q. And if we use aflibercept mostly for today's purposes, that will work fine for you?

A. Sure.

Q. How would you describe what aflibercept is?

A. Well, the way the cells inside your body communicate is they literally throw signals to each other. And then one

cell throws it; the other cell catches it using what is known as a receptor or a -- it could be viewed -- it sort of looks schematically like an antenna. It receives the signal that's thrown by the other cell.

And VEGF is a signal that's thrown by one kind of cell to act on what are known as -- VEGF stands for vascular growth factor blood vessels. So it's received by blood vessels, receptors on blood vessels, the antenna on blood vessels. And the cells respond by growing. And in certain environments like the back of the eye and so forth, the last thing you want is to start growing new blood vessels. All hell breaks loose. And the retina is supposed to be this totally pristine -- like a photographic film, you don't want blood vessels growing and leaking and bleeding all over that. Otherwise, you can lose vision.

So I had the idea to essentially make a new kind of blocker. We cut off these receptors that are normally found only on the blood vessel cells. And we made a form that literally floats around. And so the VEGF signal, before it can actually find the receptor on the blood vessel cells, there's these -- called soluble decoy receptors floating around.

They can literally intercept the VEGF before it hits the cell. And that's how it blocks the signal. So basically it's a soluble decoy version of the normal receptor found on the cell surface. We give it so that it floats around, and it

intercepts the VEGF before it gets to the blood vessel cell.

Q. Okay. And at this point let's actually take a look at a document to talk about some of this.

If we can please pull up PTX 3333.

And you should have a copy of that there in your binder in front of you as well.

So we've put this PowerPoint up on the screen, Dr. Yancopoulos. Can you please describe what this document is that we're looking at.

A. Yeah. This is a PowerPoint presentation that I personally prepared back on February 16th, 2007. We had invented Eylea under two prior partnerships, one in the mid-1990s with Procter & Gamble. They lost faith in the molecule, and they actually did a commercial assessment. And they said that it would never be an important drug, that the total worldwide sales for it would be less than $100 million a year. So they gave it back to us. We were a small company. We couldn't afford to develop it on our own.

We developed a second partnership with a company that was known then as Aventis. It's now Sanofi. They came to the same conclusion. They also gave it back to us. This is why we think it's important to put physician scientists in charge of companies instead of these people making commercial and business-type decisions because we believed in the science here.

So finally we found a third company Bayer. So BSP stands for Bayer Schering Pharmaceuticals, now known as Bayer. And they had agreed to become our third partner for the VEGF Trap. And they would help us fund the clinical trials because we were a small company at the time and we needed help funding these things.

And when we finally got together this -- we were going to have a kickoff meeting where I was going to describe to my new Bayer collaborators and colleagues the basic science behind the VEGF Trap, or aflibercept, and how I thought that there might be some ways to turn it into an important drug. And by this time -- by this time Lucentis had just been approved. And so there were concerns about that.

We had gone from being on our own to now being behind here and -- but in the presentation I talked about how there was still room to maybe come up with a way to show that maybe we could even be better than Lucentis, which was truly a miracle drug.

Q. And we will come to that, Dr. Yancopoulos.

I'd like to look first if we could look at page 16 of PTX 3333. There is a slide here that's got a title at the top "Regeneron's Traps." And then there's a diagram on the left-hand side of the page.

Can you please explain the diagram and what that's -- that was meant to illustrate.

A. So this thing on the left is a schematic diagram of the so-called VEGF Trap. Okay? And what you can see here in red, that oblong thing, that is VEGF. It's sort of pictured sort of like a football. Okay?

The green and the purple here are one side of what you can think of as a VEGF receptor. And the green and the purple on the other side are another VEGF receptor.

And so the magic of what we came up with was a way to essentially hold onto the football on both sides. I used to use the analogy of holding onto the football with two hands. You know, every coach tells you, when you start playing football, not to run around holding to the football with just one hand but hold it with two.

Well, that's what the VEGF Trap does. And this is why it's such a potent blocker. It binds so tightly that the argument could be made that we had invented the most powerful potent blocker of VEGF ever described.

Q. Okay. And once you arrived at the VEGF Trap or aflibercept molecule, how did you realize that aflibercept might have some promise?

A. So when we first started testing it in what we call in vitro, in a dish or in a test tube, it was, as described on the slide here, hundred- to a thousandfold more potent than anything else that had ever been described that could bind and block VEGF.

Q. Once you had a molecule that you thought had some promise, what else did you have to do to try to get it to market eventually for an ophthalmology indication?

A. Right. So as I said, this is a business of failure. Most things fail because there's so many steps involved and you need to get almost every one of them right in order to ultimately succeed.

And so, of course, you would have to start with the world's greatest blocker. But that's not enough. You have to be able to just manufacture it. That's a major process. Manufacturing can make enough for all the patients.

There's millions of patients that are being treated now with this drug. But you not only have to manufacture it, you have to purify it to a degree because any -- particularly if you're going to inject it in the eye, it has to be incredibly pure. And many drugs in this space have failed because they've caused what's called inflammation or other side effects leading to actual blindness. So the cure can be worse than the disease if you inject something that can almost immediately cause blindness. So you have to purify it.

And you can only put tiny amounts in the eye without disrupting the eye. So you have to concentrate it into a very, very small volume. As we all know, it's very hard sometimes to concentrate things. Like, if you put in, like, sugar in your coffee, you can only put so much before it starts falling out.

It's the same thing with proteins. If you put a lot of it into small amounts, it can clump and fall out, and that would cause bad reactions in the eye.

So it's called concentrating and formulation, coming up with a formulation that is suitable and allows for high enough concentration in the eye. That is a major challenge.

And then, of course, you have to come up with the right clinical trials, which is a whole art and science form. How you do inclusion, exclusion criteria, how you design the regimen and the dosing schedule and so forth that you're going to use.

So there's a myriad of steps, and history shows us by just looking at the failure rates in the industry, it's very, very hard to get it all right, starting from a great molecule, finishing with a great clinical trial that actually shows what you want to show.

In this case, it's even harder because there was already a competitor that was now ahead of us that was really good. So in order for it to really make a change in the practice of medicine, we had to actually show something not only that it worked but that it actually worked in some way better than what was already out there.

MS. MAZZOCHI: Your Honor, if I may, I understand that Dr. Yancopoulos has a very significant role at Regeneron and he has a quite intricate -- storied background. However,

Regeneron did not present Dr. Yancopoulos under Rule 26(2)(C) as someone who would be offering expert testimony in this case. And it seems like a lot of these answers are starting to get into more what I would consider to be the realm of expert testimony as opposed to what he did and who he talked to.

So I just want to be careful that we're actually focusing on the relevant facts here to the patents at issue as opposed to veering off into expert testimony because Dr. Yancopoulos is just here as a fact witness.

THE COURT: Understood. Overruled at this point.

Counsel.

MS. MAZZOCHI: Thank you.

MS. OBERWETTER: Thank you, Your Honor.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, how did you get to the decision that aflibercept would be administered through an intravitreal injection into the eye?

A. Well, it's much harder to consider treating directly into the eye. In fact, I was the first person to consider treating into the eye with growth factors back in the early 1990s. Those efforts actually failed, like all of our efforts did in the 1990s.

And so, in fact, people told us that people would never accept direct injections into the eye. So our first approach, probably five or ten years before I made this

particular slide, is we started by trying to inject the VEGF Trap or aflibercept under the skin -- it's called subcutaneously -- and hoped that it would float around and get to the eye and do its business.

In some ways you didn't need as important a focus. You still needed it but not as important a focus on the whole formulation and all of those aspects that are so special for the eye. It was a lot easier. And so our first formulation was more easy to get into the body subcutaneously.

In very early studies, the studies suggest that it worked that way. On the other hand, since it blocked VEGF, it also caused constriction of blood vessels through the whole body, which is not something that you want. Constricting blood vessels causes increase in blood pressure, or hypertension. And many of these people suffering from these diseases are older people that you wouldn't want to cause high blood pressure to and increase their risks of disease of strokes and heart attacks and so forth.

So then it took us a couple of years to pivot from our first studies that were subcutaneous administration to developing the formulation and moving on to eye administration.

Q. Okay. And I want to touch on the concept you mentioned earlier about developing a usable formulation of aflibercept. If we can take a look at page 36 of the same PowerPoint that we've been looking at.

There's a slide now up on the screen with a title that says in part "VEGF Mini-Trap." Can you please describe what was the Mini-Trap idea?

A. So schematize on the left is the original VEGF Trap. But then for a couple of reasons we thought about making a smaller version of it. So what you can see here is the part that I described, this is -- the colors are different; it's a little different. The left side is one receptor; the other side is the other receptors; and the middle is the VEGF, here shown as a double football. Okay?

This is the business end of the molecule. This is the part that is not really the business end of the molecule. It's required for sort of putting it together and manufacturing.

So we thought that we could maybe cut the molecule in half, literally, get rid of the nonbusiness end of the molecule and now have something that was about half the size that was just the business end of the molecule.

Why would we want to do it? The first, the parental VEGF Trap was bigger, and there were some theories and some signs, though we had evidence, actually even in this presentation that I put together, that suggested we didn't have a problem getting into the back of the eye, penetrating into the back of the eye; but there was a lot of people and there was a lot of signs and there were concerns.

And so this was a backup. In case this did make it to the back of the eye, we would make this as a backup that had a better chance of penetrating in back of the eye.

The other thing is, as I said, one challenge is getting enough protein into a tiny small volume that you could inject into the eyeball. The theory was, if you cut it in half, you could get twice as much of the business end in there into the same volume.

So we started working on this shortly after we invented the VEGF Trap. We're actually, unbelievably, still working on this. We have not yet gotten a successful formulation of it that has the advantages that I wanted but luckily -- shows how hard this business is -- but luckily, as we all know now it turned out, there was no problem with this penetrating and, due to our formulations efforts, we were able to concentrate this sufficiently.

So the parental molecule ended up penetrating, and it ended up getting formulated to a high enough concentration that it would work. So we spent a lot of time, and we're still working on this, but we haven't gotten a satisfactory formulation yet.

Q. If we look just very briefly at the next book, page 37 of this document, there's a box of text up at the top. And what does that refer to?

A. These are the two problems that I talked about. At

the top is there was concerns that the full length, the original VEGF Trap, couldn't penetrate deep enough into the retina to do its business and that a smaller molecule would penetrate deeper. And that was one of the two reasons that we developed the Mini-Trap or tried to develop the Mini-Trap.

Q. Thank you.

And we can take that slide down.

Approximately when did aflibercept enter into preclinical development?

A. Well, I don't know the year exactly, but it would have been under the Procter & Gamble collaboration in the mid-1990s.

Q. And after coming up with the aflibercept molecule itself, what was your role going forward in the development of Eylea?

A. Well, I continued to lead all of the science and clinical development efforts for the molecule.

Q. Did you have a role in the clinical development program?

A. Yes. So I headed both the research, the science, and the clinical development.

Q. And over the course of your work, did you educate yourself on angiogenic eye disorders while working on Eylea's development?

A. I certainly did. I immersed myself in the field. As

I said, I'd already been interested in the eye and was involved in clinical development of other programs that didn't work in the early '90s, and I continued to further immerse myself in the field during this whole experience.

Q. Okay. During the early clinical development of aflibercept, were there other anti-VEGF agents that were under development?

A. Yes. I'd already mentioned Lucentis, but the first one that was approved was Macugen. It was quite a game changer when it came out, but it was a rather poor VEGF blocker. So when, a few years later, Lucentis came along, it completely displaced Macugen, and Macugen sort of disappeared because the Lucentis was better. And then we were hoping to do to Lucentis what Lucentis did to Macugen.

Q. During the time period of the development program, was Regeneron paying attention to what was going on with those other drugs?

A. Yes. Certainly, we were constantly looking at everything that was coming out and was known about those programs.

Q. Okay. If we could, I want to go back to the PTX 3333 PowerPoint slides that we were looking at, and in particular if we pull up page 42.

There's a section of the PowerPoint that says "VEGF Trap-Eye in the clinic," and it has a reference there to

"Lucentis sets a high bar," and you should feel free to refer to this page and the following two pages.

But what was the purpose of referring to Lucentis here?

A. Yeah. So this was in my presentation to Bayer, and as I said, we acknowledged that Lucentis was a real game changer, really provided a lot more benefit to patients in terms of gaining and maintaining vision in these otherwise blinding eye diseases, but we thought, just like Lucentis was an improvement over Macugen, that there was reasons why maybe with a better molecule, with a better program, and so forth that perhaps we could even improve on the Lucentis.

Q. And if we pull up pages 43 and 44 of the PowerPoint deck, what were these two pages signifying?

A. Right. There was two ways to improve on Lucentis that I acknowledged in this presentation more than 15 years ago now. One was maybe we could be better than Lucentis in terms of, when you give Lucentis, you gain vision and then you maintain it. But in order to do that, you need to give Lucentis on a monthly level. We thought that maybe because our molecule was better, at least in the test tube, you might actually gain more vision -- so that is beating it on its visual acuity efficacy -- that it would be better.

The other way we could beat Lucentis, even though it was a, really, miracle drug that now, for people who would

otherwise go blind, it actually restored vision and maintained it, the problem was was all sorts of studies, that are referred to in the text below, show that once you deviated from the monthly interval -- you had to give Lucentis every month; otherwise the gains that you initially got would disappear.

And so since we thought we might have a better molecule that we formulated to a higher concentration and so forth, that we could design a clinical program that might be able to show that the treatment burden, getting monthly injections --

You have to understand these are all drugs for generally elderly patients. My own mother had macular degeneration. I would take her to the doctor all the time. This is a big burden on patients and their caregivers. You essentially have to take a whole day to bring them in, and this is a whole procedure and so forth.

So we thought that, if we could reduce the very significant onerous treatment burden of monthly treatments, that could provide a very, very important benefit to patients as well.

So we thought that Lucentis set a high bar, but the opportunities were we could either restore more vision or we could do exactly the same as Lucentis but perhaps, as it turns out, cut the number of treatments by half, which would really be game-changing for these patients and their caregivers and

the doctors and so forth.

Q. And we'll talk more about that in a moment.

On the left-hand page there's a couple bullets I want to touch on briefly. The first, if you could go down to the fourth bullet on that page, that bullet refers to "Genentech was limited to max dose of .5 milligrams because of inflammation arising from unoptimized early formulation."

Do you see that bullet?

A. Yes.

Q. What were you referring to there?

A. This is exactly what I was talking about before. It's very hard to cram in a lot of protein into a very small volume so it can safely be injected into the eye. And with Genentech, they couldn't come up with a formulation beyond this ability to put in .5 milligrams into a single suitable injection of the eye without causing damage and inflammation into the eye. And we thought -- well, we did have an incredible formulations group that was able to much more highly concentrate our drug. So in addition to the fact that we had a better drug, we could actually deliver more because we could more highly concentrate it in a form that we thought was safe.

Q. And if we just look briefly at the last bullet on that page, what is that last bullet, "We can deliver 4 milligrams," in reference to?

A. Already by that time we had done early studies to

show that we could highly concentrate it into a purity that, in early small studies, we could deliver up to 4 milligrams or eightfold more than Genentech was actually delivering.

We have to say, though, that when you're dealing with these things, we were a little nervous that in large studies, even though in very small studies it appeared safe, we were very worried about the formula gram dose that maybe it was too much; it might cause locally problems by trying to put in too much or, because some of it would leak out and could work on the rest of the body, it might show side effects in the rest of the body as well.

So even though we were able, and in early studies, to deliver 4 milligrams, we actually backed off at a certain point and only in the major studies delivered 2 milligrams because of this concern that maybe too much of a good thing might cause problems.

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

What was the first eye disease for which Eylea was eventually approved?

A. What is known as the wet form -- because that's the form that's due to excess blood vessel growth and leak -- the wet form of age-related macular degeneration, or AMD, wet AMD.

Q. And very briefly, what are the -- what are some of the symptoms or consequences of wet AMD?

A. As I said before, blood vessels start growing and

leaking --

MS. MAZZOCHI: I'm sorry, Your Honor. Again, I'd like to object to some of this, and here's the reason why. I realize that this is the first day of trial, Your Honor, but we have the benefit of their expert reports and knowing some of the issues that they're trying to do. And I'd just like to reiterate again to the extent he's talking about his own personal knowledge or experience, but a lot of the questions and the answers that are being given are being framed very broadly on this is what other people know, this is what -- trying -- either counsel needs to represent that she's not going to try to argue this is reflective of the state of the art, persons of ordinary skill in the art, then go to town. Otherwise, I think it's really not appropriate because this is, again, bringing in new expert testimony that we had no notice of in through a back door.

THE COURT: Understood. The witness is not called as an expert. His testimony won't be treated or received by this Court as such, regardless of the witness' credentials or the rest.

So let's stay on target, Counsel.

MS. OBERWETTER: Yes, Your Honor.

THE COURT: To that extent, sustained, but also understanding a lot of this is background and context.

MS. OBERWETTER: Yes. Thank you, Your Honor.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, we were just talking about what are some of the consequences of wet AMD.

If you could please go ahead and finish your answer.

A. So when you disrupt the normal pristine anatomy of the back of the eye, it swells, it gets distorted by the blood vessels, and vision gets fuzzy, and in fact, you can go legally blind.

Q. Okay. And when it came to clinical development of Eylea, did you have goals for Eylea vis-a-vis Lucentis?

A. Yeah. As I said, that was on my presentation from 15 years ago. We wanted to try to do better than Lucentis. Lucentis was a real advance, a real miracle drug. We wanted to either get even better vision or we wanted to get to the same point and maintain it but with a less onerous treatment burden.

Q. I'd like to turn briefly to some of the approaches that you were familiar with in the 2006 to 2007 time period that other people were using.

If we can go back to your PowerPoint PTX 3333 and go back to page 42. And then if we can scroll forward a couple of pages to page 45.

There's a slide up on the screen that says "Lucentis Phase III MARINA and ANCHOR."

What were you conveying with this slide, Dr. Yancopoulos?

A. May we just blow up on this one because it's hard to see. Perfect.

So what this just shows is the results in a clinical trial with Lucentis. And on the vertical axis is number of letters gained or lost from the beginning of the trial. So the beginning, everybody at their baseline is at zero. And you see the horrific consequences of this disease. Basically, patients, over the course of months -- this is 12 months -- they're losing vision. They lose about 12 letters in 12 months, a letter a month. That's two to three lines on an eye chart. This is why many patients go legally blind just in one year.

The miracle of Lucentis was you give it and immediately you see a gain in vision. The patients are gaining, as you can see here, significant amount of vision, and then it's actually maintained.

But this is done using a monthly regimen.

Q. Okay. Let's advance to the next slide, page 46 of PTX 3333, and there's a reference at the top of this page to the PIER study.

Can you describe what you were trying to convey here?

A. Right. Well, this was the beginning. I believe that I was the first person to try to come up with understanding what is the interval at which Lucentis fails? That's what I want to know, because if we knew when Lucentis failed, we knew

what we had to beat with our VEGF Trap or with aflibercept.

And what I indicated here, I actually just took this figure from the label, but then I mocked it up and I put this box to make my point on the right side.

So what you can see in the red arrows that I added to the figure is every time you give an injection of Lucentis, you gain vision; but then in this so-called PIER study, because of the treatment burden, they switched to every-three-month injections instead of every-month injections. And what you can actually see very clearly on the figure is with monthly injections, they're gaining vision, and then they maintain it for a bit; but then as soon as they go to every-three-month injections, they start losing vision almost at the same rate as the untreated people.

What this clearly showed was that Lucentis fails as an every-three-month drug. It just can't sustain the initial vision gains you get with monthly treatment.

This was approved and made in the label that proved how important the treatment burden was, that the FDA would actually approve such a suboptimal treatment where patients gain but then lost their gains. But it's showed to me what the room for improvement was, that, for sure, they couldn't work every three months. In my mind, though this made it into the label, this was really a failed study.

Q. And let's go on to the next slide of this slide deck,

and this one says at the top -- this is page 47 of PTX 3333 -- on the top says "Lucentis DME Study."

What were you trying to convey here?

A. Once again I don't know if you would cut out just the bottom one here. But it's the same point. But now I had narrowed the point to where Lucentis failed at two months. I mean, it's very clear on this figure. And once again, I used these brackets of where I say 1M for one month, 1M for one month and two months and two months. And the red arrows that I drew in here show when you're giving the actual Lucentis injections. And when you give them once a month, the month after the first injection, you gain vision. You gain vision. But then as soon as you go to two months after that injection -- you see that first asterisk at two months? -- you actually go up, and then you lose vision. So it's not even -- and then you do it again. You give one injection, gain vision, and then you lose vision. You do it a third time, you gain vision, you lose vision.

So Lucentis couldn't even last two months. So I had found -- so I was convinced, in my own mind, that I had found the weakness. Lucentis was a great drug, but you had to give it every month. If you didn't give it every month, you were going to lose the gains that you were making.

And that, to me, identified where we could do better, and that's what set me on this path of devising a clinical

strategy that was built on giving our drug every two months. And if our drug could magically work every two months, it would halve the treatment burden and it would provide a major advance. Instead of decreasing this onerous treatment burden, it could cut it by half.

Q. And if we take this slide down, another question about this general time period, were people at this time also using an approach called pro re nata, or prn?

A. Yeah. I believe it's a Latin term that means "as needed."

Because of the treatment burden and bringing in patients every month was so onerous, what doctors were doing is they were literally waiting for patients to fail before they treated them. And at the time this was -- the so-called other experts in the field were all moving towards this. They thought this would be the way to get patients treated and decrease the treatment burden, by waiting for them to fail.

I thought -- I'm sorry. I thought it was just the dumbest thing that you could be doing. It would be like saying you got an infection, and you know what we're going to do? We're going to treat it with an antibiotic, and then you're going to get better. And then when you start getting worse again, then we're going to give you more antibiotic. And then you're going to get better -- and it was just a regimen that just seemed so clear to me that it would be destined to fail.

So I was a speaker at major ophthalmology meetings and so forth where I was considered an expert, where I was railing against this, where I thought that prn was just a way to cause systematic loss of vision across the entire nation. Millions of people were being subjected to this. And, subsequently, I was validated by later studies that came out, like CATT and HARBOR, that showed that indeed this was a formula for losing the benefits of Lucentis by deviating from the monthly regimen.

Q. Ultimately, were you able to achieve for Eylea a fixed extended dosing interval in wet AMD?

A. Yes. This was ultimately proven in the two large VIEW trials, Phase III trials.

Q. And you're referring to trials called VIEW 1 and VIEW 2?

A. Yes.

Q. And what was the regimen that you arrived at?

A. So we had this notion of doing intense dosing for a short while, and then could we maintain it with a less intense dosing regimen? And that's what we designed. And, you know, you had to -- in this world of clinical trials where so many things fail, you had to just get everything right. And what we settled on was three monthly doses, then followed by a switch to every-other-month dosing. That was one of the three arms in the trial.

We had three arms in the trial because -- in both trials because, of course, this was sort of a bet. It was based on my best guesses and thinking. And I was hoping it would work, but as I said, most of things that you do in clinical trials failed.

So we had two other arms where we were sticking to the monthly paradigm because, as a small company, just getting a me-too. So most drugs that people invent are me-toos. They don't really have big advantages. So just getting a me-too as a small drug -- as a small company at the time would have been a big advance. But we had this third arm which was a bit of a reach where, if it really worked -- and there was reason to think it would work but, obviously, no guarantees -- if it would work, it could really change the practice of medicine.

Q. And we have prepared a demonstrative to help walk through the arms of the VIEW trials.

If we could pull up PDX 3.001.

And, Dr. Yancopoulos, have you had an opportunity to review this in advance of today's testimony?

A. Yes, I have.

Q. And can you just put briefly in context with reference to this demonstrative exhibit what the arms of the VIEW trials were.

A. Right. So on the bottom is ranibizumab, which is the generic or technical name for Lucentis. And here, this arm,

it's given at its every monthly regimen, which was the gold standard at the time that had been shown in the ANCHOR and MARINA studies that you already showed which were the ones that showed the best way to get the best visual outcomes in patients and what was in the FDA label. So this is Lucentis monthly with a .5 milligram dose.

We used three doses. We wanted to try our high dose. But once again, we didn't do the 4 milligram because we were too worried that there might be some toxicity that we hadn't seen in early trials. Once you go into large trials, you see things that you don't see in smaller trials. So we stuck with two milligrams as the high dose, but we also kept a .5 milligram arm because we worried that these two might have some sort of toxicity that we hadn't been able to see in the small trials. So this arm was pretty much a me-too, just showing that it was just like Lucentis.

This was an arm where we used our higher dose monthly. So this the same dose as Lucentis monthly, a higher dose like Lucentis monthly. This one we hoped maybe would see better vision gains, but this was really the reach and the one that could really change everything, which it ultimately did, which is 2 milligrams. After three monthly loads, you then switch to every-eight-month dosing after that.

And if you could really do with this what Lucentis does with monthly dosing -- as I showed you already in the

earlier slides, Lucentis fails as soon as you go from monthly. If this could work, it could literally half the onerous treatment burden on patients.

Q. Okay.

THE COURT: Counsel, I don't mean to interrupt.

But I think you said, Doctor, every eight months. I think you meant every eight weeks.

THE WITNESS: Eight weeks. I'm sorry.

THE COURT: No, it's fine. I just wanted to make sure our record is clear.

THE WITNESS: So I should say it's either every two months or -- I asked you guys to put "every two months or every eight weeks" on there because I do get confused. But it's every eight weeks or every two months, yes.

THE COURT: Sorry, Counsel.

MS. OBERWETTER: Thanks very much, Your Honor.

THE COURT: Hey, you're welcome.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, I think we have the terminology from the left-hand down, but can you explain what the -- can you remind us what the q is for on the left-hand side?

A. Yeah. Once again, you know, Latin. I don't really know what it means but q means every. 0.5 refers to the dose; q means every four or first week. So 0.5 q4 means 0.5-milligram dose, q means every, four means four weeks, and

then 2 milligrams every four weeks, 2 milligrams every eight weeks.

Q. Dr. Yancopoulos, who came up with the three loading dose every-eight-week regimen?

A. So I was the initiator and the driver of this strategy.

Q. And how did you arrive at the concept of doing a three loading dose eight-week fixed-dosing interval regimen?

A. It was based on what I showed you before, and it was exactly the rationale that I had developed over the preceding years, which I showed to Bayer at this kickoff meeting. I had come to the realization that Lucentis could not work every two months, which meant that if we could work every two months, it would change everything.

But I also knew and saw that I didn't want to endanger those early gains, and the early gains seemed to sort of maximize it around after the third monthly injection.

So I said let's give them these three injections. Let's get to the maximum point. And then if we could just maintain it with this regimen, we would really be changing the practice of medicine.

Q. Okay. Prior to the VIEW trials, had Regeneron ever tested the three loading dose 2q8 regimen?

A. No.

Q. Did Regeneron's inclusion of the 2q8 regimen in the

VIEW trials mean that you expected that it would work?

A. Well, we certainly hoped and dreamed that it would work, but the whole --

MS. MAZZOCHI: Sorry. Your Honor, here again, you know --

THE COURT: State the objection.

MS. MAZZOCHI: Yes. My objection is that, again, he's starting to get into this area -- the issue of expected results and unexpected results, which, again, he was not designated as an expert to talk about.

THE COURT: He is the inventor. It's his experience and belief. Overruled.

Repeat your question, please, Counsel.

MS. OBERWETTER: Yes, Your Honor.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, did Regeneron's inclusion of the 2q8 regimen in this trial mean that you expected it would work?

A. The reason we designed this trial exactly as is -- or I designed the trial exactly as is because I was afraid that it wouldn't work and I wanted to have these backups as I just explained.

So at worst, we were a small company. As I said, we had been losing money every year. We would have been -- at a minimum, we needed to have at least a me-too that could be like Lucentis. Okay? That was our minimal -- if we had gotten

that, we would have been happy with that.

But these were reaches over here. And the reason we have three arms is we didn't know, frankly, if any of them would work. The one that had the highest chance of working was the top one, and the bottom ones were real reaches.

Q. Okay. We can take that slide down.

I want to talk briefly about another aspect of the Phase III trials, which was the formulation that was used.

If we can pull up briefly PTX 0003 and take a look at Claim 6.

Dr. Yancopoulos, do you recognize this as Claim 6 from the '572 patent?

A. Yes.

Q. Okay. And if you look at the language in Claim 6 referring to formulated as an isotonic solution, why did your method of treatment include an isotonic formulation of aflibercept?

A. Well, so as I said, there's a million decisions that have to go into how you design your experiment. And as I said, unfortunately in this world of clinical trials, most experiments fail. So you have to try to get everything. You think of everything, and you hope and you try to get everything right. And you don't have all perfect data at that time.

But we had a formulations group. I was not an expert myself, and I was not the one who was doing the formulations.

But our formulations group said that they had developed this very concentrated but pure form of what is known as an isotonic solution.

Isotonic means it has the same tonicity, the same concentration of molecules, as the normal fluid in the eye. You want to have something as natural as possible because what we're deathly afraid of and what has killed many drugs in this field is a reaction because what you're injecting is not natural.

So isotonic, in our minds, was something that was giving us a formulation that might be as natural as possible, has the decreased risk of seeing adverse events, even in a small percentage of patients.

Remember, what you're looking for, if you have side effects in just a few percent of the people, which you will only see in large Phase III trials. So we want to increase our chances that we were going to get something without even relatively rare side effects that could kill the drug. So that's why we chose the isotonic solution for our regimen.

MS. MAZZOCHI: Your Honor, I'd like to make an objection for the record. We had asked Regeneron, both during discovery as well as in interrogatory responses, to identify any conception of the invention story that they were going to present at trial.

This is nowhere in those discovery responses. So if

I may, what I'd like to do is have an objection to this line of questioning. We'll brief it for you, and then you can decide whether you're going to strike it from the record or not.

THE COURT: Understood.

MS. MAZZOCHI: Thank you, Your Honor.

MS. OBERWETTER: For the record, Your Honor, obviously we disagree that our disclosures were inadequate, and we will brief it accordingly.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, were there other formulations of aflibercept available to you?

A. Yeah. The formulations group came up with dozens, if not hundreds, of distinct formulations.

Q. And who chose to use the isotonic solution of aflibercept in Regeneron's Phase III trial?

A. Well, like I said, it was in consultation with my team of experts. They're the ones who came up with it. But based on their recommendations, I was the one who made the decision.

Q. I'd like to talk a little bit more about Regeneron's earlier Phase II trial in wet AMD. We talked about the VIEW 1 and the VIEW 2 trials.

If we can pull up PDX-3.002.

Dr. Yancopoulos, have you had a chance to review this demonstrative in advance of today's testimony?

A. Yes, I have.

Q. And does this slide summarize aspects of the Phase II study that Regeneron conducted in wet AMD?

A. Yes, it does.

Q. That was also called the CLEAR-IT 2 trial?

A. Yes.

Q. Can you just briefly describe the arms of this trial from the earlier Phase II trial.

A. This goes from the lowest dose, 0.5 milligrams, the same dose as Lucentis, to this eight times more concentrated dose, the 4 milligrams. And then we tested it in a variety of ways. We gave it every month to see how it would do when given every month, and we also gave it just once and then repeated the dose again at Week 12. But we were mostly interested in what the results would be at this point. So monthly dosing versus a single dose.

Q. Did this trial have any arms that used three loading doses of aflibercept?

A. No.

Q. And did it have any arms that used fixed extended-interval dosing?

A. No. Obviously, you couldn't test that in the short early trial; so no.

Q. And what was the strategy instead tested here after 12 weeks?

A. Well, at the time, as I said, most of the experts in the field believed in this prn dosing. And in order to engage all the sites and all the investigators that we needed, we agreed that after they did this dosing, it would be followed by this so-called prn dosing, which I personally felt was going to be proven to be suboptimal.

Q. Did the Phase II data that came out of the CLEAR-IT 2 trial tell you what visual acuity gains you would then get from a Phase III trial?

A. No. The Phase II trials are early preliminary data that you try to use to design your definitive Phase III. It's preliminary data. It's data that you hope points you in the right direction, but you can't really count on those numbers and the information that you get there.

Q. Okay. We can take that slide down.

I'd like to take a look at a different document.

If we could please pull up DTX 212.

And if you need it, you probably have it either on your screen or in your binders, Dr. Yancopoulos. If you take a look at DTX 212, can you please describe what this email is that we're looking at.

A. It's an email from Neil Stahl to myself and others.

Q. Okay. And what is the date of this document?

A. It's January 2006.

Q. Who is Neil Stahl?

A. He is my long-time colleague for over 30 years and, really, my right-hand person for a lot of the work involving the VEGF Trap.

Q. The subject line of the email is "AMD expert meeting."

Do you see that?

A. Yes, I do.

Q. And what was that a reference to?

A. Well, as we already talked about, when you're involved in clinical programs, you try to engage and get the perspectives and opinions of key opinion leaders. So we were having a meeting coming up with the AMD outside experts.

Q. Dr. Stahl starts his email with a sentence that says, "These are some more explicit questions that I would like to understand better." And then if you go down a number of lines, one of them says, "They're thoughts on our Phase II trial and end point. Do they concur with our perspective that it is impossible to get meaningful VA data without doing a Phase III study?"

Do you see that?

A. Yes.

Q. What is the VA data there?

A. The visual acuity data.

Q. What is this sentence a reference to?

A. Well, it refers to the fact that, despite whatever

you do in these small Phase II studies, you really are not going to get your real answers until you do a Phase III. And we just wanted to make sure that our experts agree and were on board on that.

Of course, the most important experts that count on this issue is the FDA. And the FDA, of course, doesn't consider anything in terms of your end points and efficacy that you see in Phase II. That's why they demand not only one large Phase III but two large Phase III trials to make sure that you see it in very large numbers of patients and you repeat it and confirm it.

Q. And Dr. Stahl refers there to "our perspective."

Was that a perspective that you shared?

A. Yeah. Neil and I were sort of joined at the hip at the time.

Q. You referred to a need to have two Phase III trials sometimes by the FDA.

Why did you have two VIEW trials when you got to the Phase III program?

A. Right. Because that's what the FDA demands. They don't only need one large trial to get at what you think your effect is, but many times even one large trial could be misleading and so forth. So they require you to do two large Phase III trials to confirm what you think you're seeing.

Q. Okay. We can take that document down.

I'd like to look briefly at another document that's been marked as PTX 491, if we could pull that one up. And if we could zoom in at the top.

Dr. Yancopoulos, can you tell us what this document is?

A. This is a press release about -- from Regeneron and Bayer announcing "Encouraging 32-week follow-up results from the Phase II study of VEGF Trap-Eye in age-related macular degeneration."

Q. And there's -- the date on this is April of 2008, correct?

A. Yes.

Q. If we take a look at the second page of this document, there are some portions near the top of the second page I'd like to direct your attention to.

Do you see the line that says about that Phase III program in wet AMD?

A. Yes, I do.

Q. Okay. And in this press release did you make any predictions about what would happen in Regeneron's Phase III VIEW trials?

A. No. We're very careful about what we say in press releases. And as my quote actually says, it says these results, in this press release, resulted -- or further increase our confidence in the design of our Phase III clinical program.

So I wasn't speaking about the results that we would get, but I was confident that we had designed a very good Phase III study that would get at the truth, which is what we wanted to get at. We had designed the study that I thought could give us more information, tell us whether our drug worked, how well it worked, and whether it would work with the extended every-eight-week interval.

Q. Okay. If we take that document down, there's another document I'd like to look at briefly that we've marked -- has been marked as DTX 228. If we could pull that one up.

We touched earlier on some of the decision-making around the Phase III trials, but can you first identify for us what this email and attachment are.

A. This is an email from me to the leader of the clinical development program on VEGF Trap-Eye at Bayer, Darlene Jody.

Q. What is the date of this document?

A. April 4th, 2007.

Q. There's a line a couple down from where it says Darlene Jody called April 4th, 2007, that starts "Here at Regeneron we like a top-down approach."

Do you see that line?

A. Yes, I do.

Q. Could you please explain what you were conveying to Ms. Jody in that line.

A. Well, in the next line it talks about the fact that there was a lot of discord at the team level. So, basically, we had been arguing for weeks, if not months up to that point, about the design of the Phase III.

I knew in my mind what I wanted our Phase III design to be, and I had gotten consensus with the most important people, from my perspective, which were people like Neil Stahl, for example. And I found that this -- the way Bayer was working things, they were trying to get the teams to decide and come to some sort of unanimity at the lower levels and then sell it to senior management.

That's not how we do things at Regeneron. I was frustrated how long it was taking to get at what I thought was the clinical trial design that we thought was the right design. So I was just trying to stop the bickering and the arguing and the discord and just get down to it and get on to the study that I thought was the right study to do.

Q. Okay. There's a reference down at the bottom of this excerpt that says "VT 2.0 q8 week."

Do you see that?

A. Yes, I do.

Q. And what were you describing in that section of this document?

A. Well, it was one of the four arms. All three arms were the arms that we actually used in the two Phase III

trials, but that's the particular arm that ended up working and changing everything which was the 2q8, 2-milligram dose given eight weeks after the three initial loading doses.

Q. If we go up just to that middle sentence that's highlighted that "in this regard, after carefully reviewing the P2 data as well as all prior P1 data, which is also quite relevant," do you see that line?

A. Yes.

Q. What are those references to the P2 data and P1 data about?

A. The Phase II data, the Phase I data, but also the fact many other pieces of data, Bayer kept wanting to get what's that one piece of data that will justify exactly this design? And what I was trying to convey to them and communicate to them, that it's a gestalt. You have a million pieces of data that you try to put together, and the people who are successful in this business manage the design trials that work.

My first ten years, I didn't learn how to do that and I failed every time. But at a certain point I learned how to look at all of the data and put it together. And sometimes it's very hard to explain to other people what's that one piece of data. And I was trying to convey I looked at everything, and this, this is the design that all the data suggests that we could come up with, even though there's not one piece of data

that says we should do this.

Q. Okay. We can take this document down.

I'd like to touch briefly on the results of the VIEW 1 and VIEW 2 trials, if we could take a look at PTX 311. Just blow up the title and the authors.

Dr. Yancopoulos, what is this document that we're looking at?

A. This is a published manuscript that described the data from the two Phase III studies, VIEW 1 and VIEW 2, with VEGF Trap-Eye in wet age-related macular degeneration.

Q. Okay. And you were one of the authors on this publication?

A. Yes, I was.

Q. And who is Dr. Heier who is the first person who is listed there?

A. He's one of the principal investigators who was running our clinical trial.

Q. Did you participate in drafting this paper?

A. Yeah. I played a major role in designing the experiments and working with everybody else to carry them out and analyze the data and put together the manuscript.

Q. If we advance forward through this manuscript a little bit and go to page 8, there is a Figure 3. And then if we can look at -- we have a demonstrative that is the Exhibit B version of this page where we have added some color to make it

a little bit easier to read.

Dr. Yancopoulos, can you describe what the data shows here in this Heier paper.

A. Right. These show the results of the VIEW 1 and the VIEW 2 studies as well as what they call the integrated data. What you can see is, even in these large Phase III studies, there is noise. That's why you can't tell anything from Phase I or Phase II. Even Phase III studies are very large. I point at the data here to see the noise.

Here the yellow line is above; the green line is the worst one. In this one the green line is the top; the yellow line is the worst. But when you just average these two studies together, they're all right on top of each other, which leads -- and, honestly, the journal and everybody else agreed to the correct conclusion that all these arms are essentially on top of each other. As you can see in integrated analysis, they're indistinguishable so that basically, what had we had shown? That all three of our experimental arms, including this dream arm of 2q8, actually worked as well as Lucentis given every month.

And this is why it was a huge advance, because whenever you deviated from the monthly regimen for Lucentis, you didn't achieve Lucentis monthly-like data. And we had now done it with the every-other-month-arm regimen.

Q. Okay. And just for the sake of clarity in the

record, can you explain with reference to those dots down at the bottom of the screen what these arms are again.

A. Right. So, basically, it's the forearms that were described in the previous study. The blue line is Lucentis monthly; the yellow line is 2 milligrams of aflibercept every four weeks or every month; the green line is the 0.5 milligram dose every month; and then the red line, this last line, is the 2-milligram arm after three loads given every eight weeks or every two months. So that red one is the key arm, which you can see is right on top of all the other lines.

Q. And we can take that document down.

Dr. Yancopoulos, what was the reaction within Regeneron when the VIEW results became available internally?

A. I guess you could describe it as elation.

Q. And why is that?

A. Well, we had not been viewed as a very successful company up until that point because we had had only one small drug approved for a very rare disease. We would probably never ever make our money back from the investment we had made in that small drug. We were losing money every year. And now we had something that looked like it had an advantage over one of the most important medicines in the world. And we thought that the data suggested that this is something that a lot of doctors might consider having advantages for their patients.

So we -- our goal was to change the practice of

medicine. We had done that for an orphan disease, but now we thought that maybe we had changed the practice of medicine for a major disease.

Q. Is the VIEW 2q8 trial regimen the one that eventually was approved by the FDA?

A. Yes. It's the one that was approved, and I think this is why we're in the courtroom today, because the world adopted it as the new gold standard of care.

MS. OBERWETTER: Okay. I'm going to turn to talking about diabetic macular edema and diabetic retinopathy, and I can -- I have a bit more, just for the Court's awareness.

THE COURT: Go right ahead.

BY MS. OBERWETTER:

Q. So changing topics a little bit, Dr. Yancopoulos, let's talk now about diabetic macular edema and diabetic retinopathy.

Just briefly, what are those conditions?

A. These are very related but different disease in which it's the diabetes and the bones of diabetes that results in upregulation of VEGF in the back of the eye and a different kind of blood vessel growth and abnormality, which also results in distortion of the retina, resulting in fuzzy vision and, ultimately, potentially blindness.

Q. Okay. And did you intend that the methods of treatment that you came up with for Eylea could be used for

angiogenic eye disorders other than AMD?

A. Yes.

Q. And before we get into the development work on DME and DR, let's take a look at the original provisional patent application, which we have marked as PTX 304.

Dr. Yancopoulos, we have the title page pulled up here. If you take a look at the title, "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders," do you recognize this document?

A. Yes.

Q. And what do you recognize this document to be?

A. It's a provisional application for a patent on the use of a VEGF antagonist to treat angiogenic eye disorders.

Q. And if we take a look at the second page of this document, what is the date of this provisional filing?

A. January 13th, 2011.

Q. And there's a name there. Who is Frank Cottingham?

A. Frank Cottingham. He's an in-house attorney working on patents at Regeneron.

Q. I'd like to advance through the document a little bit to paragraph 24, which is at PTX 3040009. There's a sentence here -- there's a couple sentences here that say "Nonlimiting examples of angiogenic eye disorders that are treatable using the methods of the present invention," and then there is a list there.

Do you see that?

A. Yes.

Q. And that list, if we can highlight in particular, included diabetic retinopathies and diabetic macular edema, correct?

A. Yes.

Q. Why did you disclose that your methods could be used to treat angiogenic eye disorders?

A. Because we believe that all these disorders shared a common mechanism, that is, VEGF driving abnormal blood vessel growth and leak. And since they all had the same mechanism and we had a VEGF blocker, we thought that we could perhaps treat all of these diseases.

Q. Okay. And let's take a look back at page 1 of the provisional application, and in particular we're looking at paragraph 2, and it says PTX 3040004. Under the section called "Background," it says, "Diabetic macular edema is another eye disorder with an angiogenic component."

Do you see that?

A. Yes.

Q. And then it goes on to say, "DME is the most prevalent cause of moderate vision loss in patients with diabetes and is a common complication of diabetic retinopathy," and then it continues.

Why did you call out diabetic macular edema and

diabetic retinopathy specifically?

A. Because these were two diseases that the science said were likely driven by too much VEGF.

Q. Okay. And let's take a look at page 7 of the document, which is also paragraph 18. And there's a discussion here of secondary and/or tertiary doses of the VEGF antagonist. And in particular I'm going to direct your attention to a sentence that says, "In other embodiments, two or more (e.g., two, three, four, five, six, seven, eight, or more) secondary doses are administered to the patient."

Did you envision a method of treatment that would use four secondary doses?

A. We listed it here; so yes.

Q. And we can take that document down.

When Regeneron began its Phase II clinical trial for DME, were there any other FDA-approved anti-VEGF treatments for DME?

A. No.

Q. And what were physicians primarily using at that point in time?

A. What's known as laser, where you use laser to literally kill parts of the retina to try to save the remaining parts of the retina.

Q. Okay. Why were separate clinical trials then eventually needed for diabetic macular edema instead of just

relying on the wet AMD trials?

A. Because it's a different disease with a shared mechanism. It's sort of like treating two different types of cancers. You can get an approval for your drug that might work in lung cancer, but you might need a whole different regimen, a whole different treatment regimen to treat breast cancer.

So just like two cancers might have the same basic mechanism, can be treated by the same thing, you need different studies for both of them.

Q. Okay. I'd like to take a look at a document that's been marked as PTX 3216 -- if we can pull that up -- which has both an email and an attachment.

And, Dr. Yancopoulos, can you please tell us what these email -- what this email and what this attachment are.

A. This is an email from Peter Powchik, one of our leaders in our clinical group, to myself and our CEO, Len Schleifer.

Q. There's a PowerPoint -- first of all, the date of this document is August 15, 2007.

Do you see that?

A. Yes.

Q. And there's an attachment called "DME Expert Impressions Meeting," correct?

A. Yes.

Q. And were there sometimes slide decks sent around of

the meetings that were conducted with outside key opinion leaders and the like?

A. Yes.

Q. Let's take a look at page -- the page that is marked as 0005. The header at the top says "Impressions."

If we can pull out that middle couple of bullets on this page, both of those.

There's a reference here to "Detailed discussion of direct-to-Phase III plan not held."

Do you see that?

A. Yes.

Q. And some additional verbiage between that.

What was being conveyed about the DME program in this section of this slide?

A. Well, there was some discussion that could we use exactly the same treatment regimen for DME that we had used for AMD? And basically everybody agreed that you couldn't necessarily.

Q. Okay. And there's a reference in that second bullet to possible safety concerns in diabetic population not seen in AMD patients.

What is that a reference to?

A. Yeah. In some ways diabetic patients, they suffer higher risks of heart attacks, strokes, problems like that. And the concern was there was a possible link even at that time

between VEGF inhibitors and increasing the risks of heart attacks and strokes and so forth.

And so the concern was too much dosing or too high a dose might have a different kind of side effects, might cause more problems either systemically, in terms of heart attacks and strokes, or even maybe locally in the eye so that you couldn't predict not only the efficacy but you also couldn't predict the safety profile and whether the same regimen would behave the same way for either safety or efficacy in DME patients compared to AMD patients.

Q. I'd like to talk briefly about the Phase II study that Regeneron conducted for DME.

And if we can pull up PDX 3.004.

Dr. Yancopoulos, is this another slide that you had an opportunity to review for today's testimony?

A. Yes.

Q. And can you please walk us through, briefly, the study arms that were used in the Phase II Da Vinci trial for DME.

A. Well, in some ways they look very similar to what we tried in AMD in that we had a monthly regimen for 2 milligrams, a monthly regimen for 0.5 milligrams; then we had a three loading doses followed by eight-week regimen for 2 milligrams; and then we had three lowering doses followed by prn. And we were comparing them to the fifth arm, which was the standard

laser control.

Q. Okay. In the Phase II trial for DME, did Regeneron even test a regimen that had five loading doses?

A. No.

Q. Okay. Were you aware of any other VEGF drugs under development at the time that were using five loading doses?

A. No.

Q. Okay. We can take that document down.

Do you recall approximately when the one-year data for the Phase II Da Vinci trial became available to Regeneron?

A. No.

Q. And we'll take a look at a couple of documents that may refresh your recollection.

Let's start first with a couple of documents in your binder that are grouped together as PTX 3187 and PTX 3188.

A. Yes.

Q. And can you please identify what these documents are.

A. This is a email about an agenda and a presentation for a Bayer-Regeneron joint steering committee meeting to discuss utilization of VEGF Trap-Eye, or aflibercept, in diabetic macular edema.

Q. And what is the date of the email here?

A. October 19, 2010.

MS. MAZZOCHI: Your Honor, I'd just like to renew our objection as well that this is also to the extent they're

trying to do this to establish a prior conception type date. This was also not disclosed in their discovery responses. We'd like to brief that as well.

THE COURT: Understood. Posttrial briefing and proposed findings and conclusions will be an outstanding avenue for those arguments to be made. Understood.

Counsel, you may proceed.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, what is that? The PowerPoint is titled "JDC Presentation for JSC October 21, 2010."

Can you explain just briefly, what is the JDC and the JSC?

A. The JDC, joint development committee, is a collection of the team members at lower levels who are directly working on things. And they prepare things for these meetings, and they prepare a lot of the -- they do a lot of the work.

And the joint steering committee are the senior-level meetings that the -- senior-level individuals that JDC team members report to.

Q. Okay. And were you on one of these committees?

A. Yes. I was on the joint steering committee.

Q. I'd like to advance through the document a little bit to page 3, and there's a page called "Health Authority Feedback" on PTX 3188.0003.

There's a part near the top of that page called

"Study Design," if we could please pull that out.

And there's a reference to "Study design proposed dosing arms 2 milligrams q4, 2 milligrams q8 after three loading doses," and then "Control: Acceptable."

Do you see that?

A. Yes.

Q. As of October 2010, what number of loading doses were being contemplated for the forthcoming Phase III trial?

A. Three loading doses.

Q. There's a sentence right under that one that starts with "final one-year data."

Do you see that one?

A. Yes.

Q. Can you please explain what that sentence is in reference to.

A. That we were still awaiting some more data, and that might provide additional guidance on number of loading doses.

The reason we were so concerned is the number of loading doses is critical because you want to gain vision and then maintain it when you shift to the every-two-month dosing because you don't think you're going to be gained during the two months. So if you're off by the number of loading doses, you may never get to the same level, the equivalent level, that, for example, monthly Lucentis gets to.

On the other hand, there's also enormous pushback

from a variety of people, including commercial. They want the least number of doses. So you're playing a very tight -- you're walking a tightrope here.

Q. Okay. We can take this document down.

Did you eventually review the data that came out -- the one-year data that came out from the Da Vinci trial?

A. Yes.

Q. And let's look at two documents together. These are PTX 80 and PTX 1028C.

MS. OBERWETTER: And, Your Honor, there's a third exhibit that goes with this that we have in hard copy, if I may approach the witness.

THE COURT: You may.

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, if we go back to the email which we have up as PTX 80, there's two attachments to this document, correct?

A. Yes.

Q. Okay. And what was the date of this document?

A. December 8, 2010.

Q. All right. And you were one of the recipients of this, correct?

A. Yes.

Q. There's an email from Caroline Saxton.

What is she referring to there in her email?

A. She's referring to the data that we now have in front of us, which is the short presentation on the one-year data and then the complete data set in this bigger binder.

Q. And why don't we take -- we'll walk through some of this in order, and I assure everyone we're not going to get through every page of PTX 1170 which we've handed up to the witness.

But if we can start with PTX 1028C, what is this document that we're looking at?

A. This is a summary of the results from the one-year data from the Phase II trial in diabetic macular edema.

Q. And were these -- was this an internal presentation or an external presentation?

A. Internal presentation.

Q. And if we advance forward just to page 3 of this document briefly and pull out the upper left-hand.

This was marked, at least in part, with a confidential ledger, correct?

A. Right.

Q. Had Regeneron published the details of its one-year Phase II Da Vinci trial at this point in time?

A. No.

Q. And was it keeping that data confidential?

A. Yes.

Q. Did you have additional data above and beyond even

what was in this PowerPoint?

A. Yes.

Q. And if we just take a look for a moment at PTX 1170, what is PTX 1170 that I have handed you?

A. Well, it's the full data set from the trial that's summarized in this shorter PowerPoint.

Q. And at a high level, can you describe what kind of data is contained in PTX 1170?

A. Well, it gives detail efficacy and safety results on a group level as well as on a patient level.

Q. And did you have that data set available to you when you were deciding what to do for the DME Phase III trial?

A. Evidently, from the email, yes.

Q. Yes. Okay.

And let's take a look at the PowerPoint for a moment. If we can please take a look at page 11 of PTX 1028-C.

Can you please explain what kind of data is presented on this page.

A. Once again, this is visual acuity data, as we said. So on the vertical axis is gain or loss in vision. The white line is the current standard of care at the time because, remember, Lucentis hadn't been approved for this indication at the time; so it was laser. And you see laser; they gain a little vision, it goes up above the zero, and then by the end they've lost vision. And then the four other curves are the

four arms, the experimental arms that are trying various dosing schedules of -- dosing schedules and doses of aflibercept.

Q. Okay. And this data that we're looking at on this page, if we zoom back out, this is, again, the Phase II Da Vinci data, correct?

A. Right.

Q. Were there aspects of this data set in the visual acuity data from Da Vinci that limited its utility to you?

A. Yeah. As one can see, this is why the experts, as we talked about before, in the other slides that we went through, agreed that you can't really count on Phase II data because the data sets are so small and why the FDA doesn't accept this sort of data.

If you just look up there, these top three curves, see the dark green one, the light blue one, and this purplish one. Okay. At least through 12 weeks, these groups are all treated the same. So in a perfect world or if you had, for example, hundreds or thousands of patients per arm, those three groups would have been right on top of each other. They literally should be identical.

And it just shows that you can't count on the results. These things are bouncy. They're bouncing around. They don't look like the Phase III data, and arms that should be identical can look -- as you can see the green from the other ones -- very different.

So even before you get the different treatments for these three curves started at the 12-week time point, but you can see by then they're already different.

So these are important directionally. We do these studies -- first of all what you can see is every single one of these arms definitely looks like it's better than laser. So it made us feel that, frankly, many of these regimens would be better than laser. But the question is which regimen might actually be better -- or which regimen might actually work with a lower treatment burden compared, for example, to monthly Lucentis and so forth.

These are things that are, frankly, almost impossible to tell from these small studies. So you incorporate -- as I was saying before, those of us who have managed to figure out how to get successful in the business, you incorporate millions of points of data, including things like this, including data that you're seeing there, and many other pieces of data to try to make your best judgments as to which regimens are you going to bet on in these Phase III trials.

Q. Okay. And was this data on this page of PTX 1028-C sufficient to decide on a five loading dose regimen?

A. No. It would be very hard for anybody to definitively come up with any definitive regimen based on this data based on the noise that you're just seeing right here.

Q. And how is it that you decided ultimately on a five

loading dose regimen for DME?

A. Well, like I said, it's a matter of integrating a million pieces of data. I mean, these are questions that sometimes are unanswerable. I mean, how did I come up with the idea to invent the VEGF Trap in the first place? It sort of just came to me, but I incorporated a million pieces of information that I had -- I had integrated over the years.

And the same thing here. I realized that we had to maximize the -- so the whole notion -- the basic notion, the basic thing that we described is you want intense dosing, and then you back off to go to the every-other-month dosing.

And how long you do the intense dosing, we reasoned, or I reasoned, should be different for diabetic macular edema based on, like I said, many points of data. There were many others who thought that VEGF signal was higher in DME than it might be in AMD. We had reason to think that in dosing, division continued to improve as you dosed with monthly treatment.

So there was a lot of things that went into it. It's impossible to point to one thing. But this is why some people are successful in this business, because they guess right more often than not.

Q. Okay. Thank you.

We can take that document down.

I want to turn to talking briefly about the results

of the Phase III VIVID and VISTA trials.

THE COURT: Counsel, before we transition topics, is that a good point to take a brief break or --

MS. OBERWETTER: We could, Your Honor. I have a little bit more; so yes.

THE COURT: Okay. Why don't we do that.

Doctor, we're going to take an afternoon break at this point. We're going to take 15, given the crowd numbers we have and our limited restroom facilities here in the building.

During this break, because you're midstream on your testimony, no one can talk with you. I don't want you to think anyone here is being rude or discourteous, but it's part of the rules that govern this proceeding. So you're a little bit of a man without a country, for lack of a better term, during the next 15 minutes. So if you see folks turn and scatter from you, that's why. It doesn't have anything to do with the PowerPoints we talked about earlier.

But you can go ahead and step down if you'd like, and you can leave all those materials there. We'll deal with those. Thank you very much, sir.

Otherwise we'll take 15 and resume at that point. Thank you all very much.

(A recess was taken from 3:04 p.m. to 3:19 p.m.)

THE COURT: Are you ready, Doctor?

Counsel?

BY MS. OBERWETTER:

Q. All right. Dr. Yancopoulos, we were turning to the Phase III results for Regeneron's VIVID and VISTA trials. If we take a look at PTX 932. And can you please identify this document for us.

A. Yes. This is the published manuscript that describes the two Phase III trials for aflibercept in diabetic macular edema.

Q. And you are listed on this paper?

A. Yes, I am.

Q. Okay. If we take a look again -- if we go to the data page of this document, which is at page -- advancing forward to Figure 1A, which we've marked for convenience as PDX 932-C, could you please describe the results that Regeneron obtained from its Phase III VIVID and VISTA trials with reference to this figure.

A. So once again, the vertical axis, the Y axis, is vision gained or lost in letters. The red line is the standard of care at the time, which was laser, which is keeping the patients stable.

And what you can see here is that both of the aflibercept treatment arms do almost identically in terms of gaining and maintaining the vision. And once again, the key thing about this is that the 2q8 arm -- that is after five

loads, then going on to every-other-month dosing -- maintains the vision as well as monthly.

Once again, that was the big take-home message and the big advance here that allowed Eylea to become such an important drug for this disease.

Q. Okay. Going into these trials, the VIVID and VISTA trials, did you have an expectation as to the five loading dose eight-week arm would perform?

A. Did I have a what?

Q. An expectation.

A. I had hope, for sure. I mean, I was hoping that it would work. But that's, of course, why we had the two arms because we were, once again, taking the higher likelihood thing which would be monthly, and then we were hoping beyond hope that the every-other-month would behave as well as it did.

Q. Okay. After the completion of the VIVID and VISTA trials, did Regeneron ask the FDA to approve this regimen for patients?

A. Yes.

Q. And why?

A. Because, clearly, it was an advance over the standard of care at the time which was laser, but the results resulted in impressive safety and efficacy, and the regimen that the FDA approved was the every-other-month regimen.

Q. We can take that document down.

Was Regeneron also ultimately able to get an indication for diabetic retinopathy?

A. Yes, we were.

Q. And at a high level, how did that indication come about?

A. Well, we had some evidence from this trial, but the FDA felt that we hadn't prospectively identified all of our end points and so forth, and so it wanted us to confirm it; so we had to do a separate single Phase III trial.

Q. Okay. And that was the PANORAMA trial?

A. Yes.

Q. Have there been other significant -- I'm going to change topics a little bit.

Have there been other significant treatments for wet AMD that have come onto the market since Eylea?

A. Well, for those of us in the field, it almost seemed like back to back to back. I mean, there was the big advance of the Macugen, the first drug. Then that was rapidly displaced by Lucentis. And then Eylea came along and became the new gold standard of care. And it seemed like it was really easy.

In the following ten years, the field was littered with many, many failures, including our own. We had several studies, several attempts to improve on Eylea.

So as I said, Lucentis had set a high bar, which we

were able to meet and exceed. But after that, the Eylea set such a high bar that none of us, including for ten years our own efforts, were able to exceed it. Only in the last year there was an approval of another anti-VEGF agent, but it did not seem to really distinguish itself or exceed in any way Eylea. It was only as good more than ten years later.

And it just shows how hard this field is, how hard it is to get everything right from the drug to the formulation to the regimen and so forth, to get success, let alone success that exceeds what the bar is in the field right now.

And so the whole field failed for more than ten years, many, many, many failures, and the one recent success just matched Eylea, did not in any way surpass it.

Q. And in your view, what has accounted for Eylea being as successful as it has been for as long as it has been?

A. Well, the impressive safety and efficacy profile. It's very hard. Some of the drugs that I talked about failed because of safety problems. Some of them failed because of efficacy problems. So having the safety and efficacy and what is now acknowledged as the longer duration of action really made such a difference, and it became adopted as the standard of care.

MS. OBERWETTER: Thank you. No further questions.

And I pass the witness.

THE COURT: Thank you.

Counsel.

MS. MAZZOCHI: Thank you, Your Honor. We have some binders for the Court and for the witness.

THE COURT: Everyone may approach.

Counsel, go right ahead.

CROSS-EXAMINATION

BY MS. MAZZOCHI:

Q. Do you have your binders, Dr. Yancopoulos?

A. One binder.

Q. Yeah, one binder.

Dr. Yancopoulos, you talked quite a bit about some of your patents in your direct examination.

Do you recall why you decided to file for these patents?

A. Why I decided to file for these two patents?

Q. Right.

A. Because they were demonstrating a new approach to treating angiogenic eye disorders that we thought could have value that we wanted to protect.

Q. I'd like you to take a look in your binder at an exhibit that is numbered DTX 3196. And these are going to be exhibit pages 7 and 8. And I'm going to pull some information from them up on the screen, specifically your deposition transcript pages 25, line 24, through deposition transcript page 26, line 2.

If we could just pull that up on the screen, please.

A. Could you repeat the numbers again, please.

Q. Yes. DTX 3196. I'll put these specific lines up on the page. They're on exhibit pages 7 and 8. If you see in the lower right-hand corner 001, 002. And actually we're going to take a look at line -- transcript page 25, line 24 and 25, over to page 26, line 1.

Do you recall giving a deposition in this case?

A. Yes.

Q. All right. Can you confirm that at that deposition I asked you the question, "Do you recall why you decided to file for these patents?" and you gave the answer, "I don't recall"?

A. I may have said that. I don't recall.

Q. Do you know how many of your patents over the years have been held invalid?

A. No, I do not.

Q. Do you know how many have been held unenforceable for inequitable conduct?

A. No, I do not.

Q. Are you aware -- do you know that at least one of your patents has been held invalid for inequitable conduct?

A. I guess 1 out of 150? I can understand that.

Q. You can understand that?

A. I can understand that. Sometimes something happens that something invalidates a patent. I don't know much about

the patent business. Sorry.

Q. Well, are you aware that one of the reasons why your patent was held unenforceable for inequitable conduct is because the court found that you made material misrepresentations regarding unexpected results to the PTO that were false?

A. I thought it was because we failed to cite what was considered one citation that was prior art. So we missed one citation. That was my understanding.

Q. Tell you what. Let me pull up for you.

MS. MAZZOCHI: Tom, this is in --

THE WITNESS: Are you trying to imply that I tried to misrepresent something in one of my patents?

THE COURT: Doctor, your role here is simply to answer questions.

Counsel, next question, please.

BY MS. MAZZOCHI:

Q. If it would be helpful to you, I can refresh your recollection on some of the details. If we can turn to page --

MS. OBERWETTER: Objection, Your Honor. I don't understand the relevance of this as it relates to any of the patents at issue in this case, and there has been a prehearing ruling on their motion to amend to add inequitable conduct.

THE COURT: Correct. But I assume this is aimed at the witness's credibility. Is that correct?

MS. MAZZOCHI: Correct.

THE COURT: Understood, but the exhibit that's displayed currently on the Court's screen is a case. I can barely read it. But we need to ask the witness about things he has personal knowledge about, including -- and that includes impeachment or credibility.

Objection overruled at this point.

BY MS. MAZZOCHI:

Q. And if we can -- we're going to page 1349.

A. Which document are we in?

Q. This is a court decision entitled "Regeneron Pharmaceuticals Inc."

A. What number? What am I looking for?

Q. We're going to put it up on the screen because I have to actually see if this is going to help refresh your recollection. Then if it does, we can talk more about it.

A. Okay. Couldn't I just turn to it? Could you just tell me which document it is?

THE COURT: It's not in the binder, Doctor.

THE WITNESS: It's not in the binder.

THE COURT: Use the screen there. Thank you.

Go ahead, Counsel.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, you indicated that you thought that all that was at issue was that you didn't cite a reference.

According to the court decision, one of the things it said Regeneron did was that "Regeneron sent -- also sent a presentation to the PTO with the reply. In that presentation, Regeneron asserted that it had developed a commercial embodiment of the claimed mouse with surprising results. It is undisputed that that assertion was false. Regeneron had not developed any such mouse at the time."

Does that help to refresh your recollection as to one of the reasons why one of your patents was held unenforceable for inequitable conduct?

A. You know, I am not involved in these sorts of patent disputes and I was not present. I didn't testify in that case. I know very little about it. And I somehow had thought that it had to do with citations. I don't know exactly what this is referring to.

Q. Okay. Well, Dr. Yancopoulos, given the fact that Regeneron had been -- had one of their patents, one that you were on, held invalid for inequitable conduct based on -- based on a false statement to the PTO, did you after that point make sure that your scientific representations and specifications were reviewed for scientific truth and accuracy?

MS. OBERWETTER: Objection, Your Honor. The question is lacking foundation in multiple respects at this point, both with respect to what the ultimate conclusion of the court was, the reasons for it, and this witness's lack of knowledge.

THE COURT: The witness indicated he's not familiar with this background, Counsel. I think if you want to ask about any changes in business practices, that's appropriate, but he's not expressed any personal knowledge about this at this point.

MS. MAZZOCHI: Right. And that was exactly what I believe I just asked, is that given --

THE COURT: I disagree. Objection sustained. Rephrase.

MS. MAZZOCHI: Okay.

BY MS. MAZZOCHI:

Q. Did you implement any business practices to ensure that the accuracy of all of the scientific representations that your patent applications were making were truthful and accurate?

A. I don't really know how to answer that question. I think that we always endeavor to do everything truthfully and correctly. And I'm sure on occasion some things get missed, no matter how good our due diligence.

So I don't know the details about this. I don't know how -- clearly, we did develop a commercial embodiment of the claimed mouse that was very successful. I don't know whether the timing is what was at issue. I don't know whether that was done deliberately or was somehow a mistake. But I'm sure that we have practices that try to ensure that things happen

correctly and truthfully all the time. Not to say that sometimes mistakes don't happen.

Q. Let's put up on the screen DTX 2745, exhibit page 1. A copy of this should be in your binder.

THE COURT: What number was that, Counsel?

MS. MAZZOCHI: 2745.

THE COURT: Understood. Thank you.

BY MS. MAZZOCHI:

Q. Can you confirm this is a publication by Jocelyn Holash, you, and others, titled "VEGF Trap: A VEGF Blocker with Potent Antitumor Effects," which I believe was published in the proceedings of the National Academy of Sciences in 2002?

A. Yes.

MS. MAZZOCHI: Your Honor, we'll move DTX 2745 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 2745 was admitted.)

MS. MAZZOCHI: Thank you, Your Honor.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, in DTX 2745, pages 1 to 2, I'd like to direct your attention to the "Materials and Methods" section that appears under the subheading "Engineering VEGF Traps." Let me pull that up on the screen for you.

Do you see those on the screen?

A. Yes.

Q. If we look at the last sentence, which appears on the top of exhibit page 2, you reported in your papers that all of your VEGF Trap variants were produced and purified from Chinese hamster ovary cells. True?

A. I know that we produced them using Chinese hamster ovary cells. I assume that this statement is true.

Q. And using CHO cells will cause your VEGF Trap proteins to be glycosylated, right?

A. It depends on which Chinese hamster ovary cells you use. There's some that cause glycosylation, some that don't.

Q. And let's go to the second page of DTX 2745, right-hand column, where you are discussing your injections into mice. It's the text that starts "obtained from American-type culture collection."

Do you have that there on the screen?

A. Yes.

Q. And roughly in the middle of the text we have up on the screen, there's a reference to a vehicle that states PBS plus 0.5 percent glycerol.

PBS stands for phosphate-buffered saline, right?

A. Yes.

Q. And it's an isotonic solution?

A. I'm not sure, actually.

Q. Dr. Yancopoulos, let me call up DTX 8180, exhibit page 1, which is an article titled "The one-year results of the CLEAR-IT 2, a Phase II study of vascular endothelial growth factor Trap-Eye dosed as-needed after 12-week fixed-dosing," from the journal *Ophthalmology*, June 2011, Volume 18, pages 1098 to 1106.

You were a coauthor on this publication, yes?

A. Yes.

MS. MAZZOCHI: Your Honor, we move DTX 8180 into evidence.

THE COURT: Any objection.

MS. OBERWETTER: No objection.

THE COURT: Without objection, so admitted.

(DTX 8180 was admitted.)

MS. MAZZOCHI: Thank you, Your Honor.

BY MS. MAZZOCHI:

Q. Let's go to the second page of DTX 8180, the second full paragraph that starts off "vascular endothelial growth factor Trap-Eye."

Do you have that on the screen?

A. Yes.

Q. I'd like to direct your attention to the second sentence in that paragraph that's talking about VEGF Trap-Eye that says, "It was developed specifically as an ultrapurified iso-osmotic solution for ophthalmologic use."

Do you see that?

A. Yes.

Q. And as support for that statement, do you have a notation there, a citation number 25?

A. Yes.

Q. If we can turn to the DTX 8180, exhibit page 8, can you confirm that citation number 25 in the right-hand column is to Holash, et al., VEGF Trap, a VEGF blocker with potent antitumor effect, proceedings of the National Academy of Sciences USA, 2002, Volume 99, 11393-8, which we were just looking at before as DTX 2745?

A. Can we go back to the previous paragraph that we were looking at?

Q. I'm not sure. Let's start first. Can you just confirm this is the citation, that I read it correctly?

A. It's just that, clearly, a mistake was made in the position of the reference. It should have been after the first sentence of that paragraph as opposed to the second sentence because there was nothing about that point in that reference. So it was -- that reference refers to the wrong sentence.

Q. Let me be clear. It's your testimony here today that the citation support in a journal with your name on it in peer-reviewed literature is wrong?

A. No. I'm saying it was inappropriately moved one sentence. It should have been one sentence earlier.

These things happen. It could have been done in -- at the editorial stage or somebody could have missed it. But clearly the paper is not referring to anything about ophthalmic use, but the previous sentence is the one that describes what the VEGF Trap is.

Q. Again, I just want to be clear. It's your testimony today that you believe that there is a mistake in your journal -- in this journal publication?

A. There was a mistake in the position of -- how many footnotes are in here? Yeah. It was a mistake in the position of one in 50 or so footnotes. I'm sorry. By one position.

Q. Dr. Yancopoulos, I believe we've heard a lot from you earlier today that you believe it was the properties of aflibercept itself that allowed for your eight-week dosing regimen to work where you believe it had failed with other molecules, right?

A. For sure, part of the reason for the success was the molecule. Without a molecule, you have nothing. On the other hand, if it hadn't been delivered to that concentration and purity and so forth, it quite possibly would not have worked either. So it's a combination of many factors that allowed it to actually work. Obviously, if we had given a tiny amount of it, it would never have worked, so -- no matter how good the molecule was.

Q. But ultimately, you believe your eight-week dosing

regimen worked because you had a molecule you thought was a better molecule, which was aflibercept?

A. And for many other reasons as well, including the fact that we were able to concentrate and deliver enough of it so we could last longer. If we gave one molecule of the greatest blocker in the world, it obviously would not have worked for two months.

Q. All right. Now, even though you had found this extremely potent VEGF inhibitor, I believe, in late 1990s, you said you were having some difficulty finding big pharma partners to fund you?

A. Yes.

Q. And the lack of target validation in the clinic, together with that lack of recognition of commercial opportunities, also contributed to that difficult partnering environment for Regeneron, fair?

A. Could you just repeat that.

Q. Sure. The lack of target validation in the clinic, together with a lack of recognition of commercial opportunities, initially led to a difficult partnering environment for Regeneron, right?

A. Yes. Yes.

Q. Now, when it came to finding partners, one of the first game changers, when it came to using VEGF inhibitors for cancer indication, were the Avastin cancer results, right?

A. Yes.
Q. And those came out around 2003?
A. Yes.
Q. And then the next game changer for Regeneron was the clinical trial data that came out for Lucentis. That's what allowed you to partner with Bayer, right?
A. That contributed to the partnership.
Q. That was a game changer, right, the Phase III Lucentis data?
A. It contributed to the interest in the field, yes.
Q. Do you recall whether you called it a game -- the Phase III Lucentis data a game changer that led to the global collaboration with Bayer HealthCare for VEGF Trap-Eye?
A. It would not surprise me if I called the Lucentis results a game changer. I think I referred to them that way today. I don't know if I necessarily publicly linked them to our deal. I couldn't remember whether I did that or not.
Q. Whether you said that publicly, internally you understand that, right? That was what was -- that's what incentivized or enticed Bayer to want to partner with you, true?
A. Well, it was a major reason that the fact that, as you said, it was now clinical validation in the field contributed to somebody wanting to partner with us.
Q. Right. And it was the Phase III Lucentis data that

was the driver on that for Bayer, right, in terms of wanting to come to you?

A. Like I said, it was one of several things that contributed. You have to ask Bayer if it was the major driver.

Q. By 2010 Lucentis was a 2 to $3 billion market, correct?

A. I don't remember the timing of when it became an important drug in the revenues, but if you say so.

Q. If it would help you out, let's pull up DTX 2053. And do you see that this is titled "RBC Capital Markets, Moderator Phil Rosenfeld, October 1st, 9:00 a.m. Central Time"?

A. Yes.

Q. Do you recall receiving a copy of this transcript?

A. I don't recall. I may have.

Q. If it will help you out, I can give you the document showing that this was attached to your email. Let's go ahead and pull up what I'll designate as DTX 2053A.

Can you confirm that this is an email dated Tuesday, October 19, 2020, from Murray Goldberg to Len Schleifer as well as you and others? It says, "Attachments, transcript.doc."

A. That's what it says.

Q. It says, "Attached is the transcript of the conference call that RBC hosted with Phil Rosenfeld and Quan Nguyen re: Lucentis, Avastin, and VEGF Trap-Eye. Lots of interesting observation."

Do you see that?

A. Just trying to find the document in my book here.

What was the question?

Q. Sure. Just do you see what I just read out from the highlighting?

A. I see it. I see the highlighting here.

Q. So does this help to refresh your recollection that you probably did, in fact, receive a copy of the RBC transcript?

A. This implies that I received it. Whether I read it or not, this doesn't help me.

Q. But, nevertheless, you received a copy of it as part of your ordinary customary business activities at Regeneron, right? Through your email?

A. Yeah, looks like I received an email of this.

MS. MAZZOCHI: Your Honor, we move DTX 2053 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: Depends on the purpose for which it is offered, Your Honor.

THE COURT: Fair enough.

Purpose?

MS. MAZZOCHI: Sure. The relevance is that there's some information in there that they thought was interesting about Lucentis and Avastin. It relates to some of the issues

in the case that we're going to get into in terms of what people were thinking at the time in 2010, which is shortly before the patents were filed in this case.

THE COURT: What specific issues?

MS. MAZZOCHI: I don't know if you want me to say it in front of the witness, Your Honor, but there are certain things in there relating to, as stated here in the covering email, hospital academic centers, Avastin, and private practice, physician reimbursement, as well as -- I was actually going to use it initially just to point out that they acknowledge that the Lucentis market was over $3 billion.

THE COURT: Any objection?

MS. OBERWETTER: Your Honor, it's a long document. So I will reserve on further hearsay objections, but subject to that, no, Your Honor.

THE COURT: So admitted.

(DTX 2053 was admitted.)

MS. MAZZOCHI: Thank you.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, let's go back now to DTX 2053, and let's look at the exhibits page 2, sixth paragraph down. And can you confirm that in this transcript that was attached to your email, it says, "Lucentis dominates the branded-approved market with about 3 billion in sales"?

A. I see that.

Q. Was that consistent with your recollection in that time frame of 2010 that Lucentis had a market that was billions in sales?

A. I probably knew that Lucentis had lots of sales. I probably did not know the exact number.

Q. And did you also have an understanding that Avastin, even though -- let me take a step back.

You understood that physicians in this 2010 time frame were using Avastin off-label to treat wet AMD, right?

A. Yes.

Q. And the formulation that was being injected into patients' eyes was a formulation that had been developed for intravenous cancer use, right?

A. Yes.

Q. And physicians were, to your knowledge, still being reimbursed by CMS, the federal government, in connection with those uses, right?

A. Yes.

Q. All right. Now, one of the other things that this conference call mentions is that in 2010 Lucentis was charging about $2,000 per injection.

Do you recall whether that price point also guided your decision on how to price Eylea?

A. Yes, it did.

Q. Let's move on to DTX 913, exhibit page 1.

Can you confirm that DTX 913 is an email thread that was forwarded to you, your CEO Leonard Schleifer, and others on Monday, February 5th, 2007, from Avner Ingerman about Lucentis labeling that had been approved in Europe?

A. Yes.

Q. And one of the things Mr. Ingerman was forwarding to you by this February 2007 date was the Lucentis labeling that was approved in Europe?

A. Yes.

Q. And one of the things that the European regulatory authorities did do is they approved Lucentis for both monthly dosing in AMD as well as for use with a loading dose of one injection per month for three consecutive months, followed by a maintenance phase or monitoring that was described as being given on a prn basis.

A. This was a highly controversial decision because it was based on absolutely no data. And what we know in Europe, they tend to do things because of cost as opposed to patient benefit. And as has now been largely validated by subsequent studies, that was a really inferior regimen that resulted in lots of vision loss.

So it was a controversial decision for them to approve a regimen that was never tested or studied in Phase III trials and which resulted in worse vision outcome for patients.

Q. Dr. Yancopoulos, let's start first with you don't

dispute that one of the things that the dosing instructions for Lucentis included in the European Lucentis label was a loading phase of one injection per month for three consecutive months?

A. Followed by prn dosing, which I just want to point out was a very controversial decision at the time. It was subsequently realized to be very inferior regimen that led to poor visual outcomes for patients.

Q. I just want -- Dr. Yancopoulos, I just want a clear yes or no. I understand you're going to say you don't like prn dosing regimens. I just want to be clear that your understanding, as of February 2007, is that the European regulatory authorities approved a dosing regimen that had three monthly loading doses followed by a maintenance phase that would allow for an extended dosing interval beyond one month.

A. It was followed by prn dosing, which was a highly controversial decision at that point in time, which resulted in worse visual outcomes.

Q. Prn dosing allows for a regimen or a dosing interval to go beyond one month, right?

A. Prn dosing is dosing as needed. That's what it stands for.

Q. Right. And if the patient does not need the dose at the next month, they can extend until the next office visit, right?

A. The problem is, is how do you determine "as needed"?

And the problem with prn dosing is it depends. "As needed" means the patient starts to fail and that you treat them when the patient fails. And what that has resulted in is in systematic underdosing of patients and poor visual outcomes, which is why it is no longer used.

Q. Well, with the DME data that you saw that was coming out of Phase II when the doctors were allowed to dose the patients as needed in a prn regimen, they actually got better letter gains relative to what happened for the three loading doses followed by the fixed eight-week dosing interval, right?

A. Well, as you said, in Phase II studies, prn at times appeared like an attractive dosing regimen. When prn was studied in large Phase III trials, such as CATT and HARBOR, it resulted in the realization that the prn dosing regimen was a very inferior regimen that resulted in worse visual outcomes, which is why sophisticated drug developers don't focus and count all their data just on Phase II. That's why you need large Phase III trials, which have invalidated prn, which is why prn is no longer utilized.

Q. That's your opinion, right? You haven't done any surveys or anything in that regard that you've presented in court today?

A. Well, I can tell you that prn is no longer utilized by the community.

MS. MAZZOCHI: Your Honor, I'd just like a very, what

I think, is a yes-or-no answer. Did he know that the European labeling would allow for three loading doses followed by a maintenance phase that would permit an extended dosing interval? It either did or it didn't.

A. I think I've answered that question.

THE COURT: Try one more time, Doctor. Were you aware that's what the label says?

THE WITNESS: Well, I think a yes-or-no answer can be used in a misleading way, and I don't want to mislead anybody. I think that there was -- as I described it, the full answer is that this was a controversial decision, which has subsequently been realized to have resulted in poor vision outcomes and is a regimen that's no longer utilized.

BY MS. MAZZOCHI:

Q. But it's a regimen that you utilized in your own clinical studies, right?

A. It was one of the many regimens that we included in our various clinical trials.

Q. You were also, in the 2006 to 2007 time period, tracking what was happening with Lucentis for the DME indication, true?

A. State that again.

Q. You, in the 2006 to 2007 time period, were tracking what was happening with Lucentis for the DME indication, true?

A. Yes.

Q. Let's take a look at DTX 4070, a publication titled "Vascular Endothelial Growth Factor is a Critical Stimulus for Diabetic Macular Edema" by Quan Dong Nguyen, et al., from 2006.

You've seen this paper before, haven't you?

A. Folder just completely fell apart.

THE COURT: It's 4070.

MS. MAZZOCHI: The title is up on the screen for you as well, Dr. Yancopoulos.

THE COURT: Just one second, Counsel. We're reassembling the exhibit notebook.

THE WITNESS: Yes.

MS. MAZZOCHI: Your Honor, we move DTX 4070 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 4070 was admitted.)

BY MS. MAZZOCHI:

Q. Now, Dr. Yancopoulos, back in 2006 when you first reviewed this paper directed to the use of Lucentis for diabetic macular edema, you believed that this study had a lot of important implications, right?

A. Yes, I did.

Q. And one of the reasons why you believed the study had very important implications is because it showed patients had

substantial visual gain, right?

A. Can you keep going?

Q. I'm just saying, do you recall stating --

A. I actually showed Figure 4 from this paper in the Bayer presentation. That was what we spent time on in the previous discussion, and that figure summarized why I thought this paper important because in Figure 4 it clearly shows that Lucentis did not appear to last for two months. It only lasts for one month. That's why I thought this paper was important, as we summarized in the Bayer presentation that I showed, if you want to go to Figure 4.

Q. I'm asking a different question, sir, and I'd appreciate it if you just try focusing on what I'm asking you.

You characterized the results of this paper as showing that these patients have substantial visual gain, right?

A. I don't know if I characterized, but I would characterize that they had substantial vision gain, yes.

Q. Let's pull up DTX 8127, exhibit page number 1.

Can you confirm that this is an email from you to Peter Powchik and Neil Stahl and others dated Thursday, December 7, 2006, subject line, "Lucentis pH 1 in DME and implications, attachments, read Lucentis pH 1 DME."

Is that your email?

A. Yes.

Q. And if you take a look at the second point that you put in your email, did you indicate that these patients have substantial visual gain?

A. Yes.

Q. Okay. Did you say yes?

A. Yes.

Q. Thank you.

All right. Attached to this particular exhibit -- so let's just stay in this one since you had the paper -- a version of the article attached.

A. What was the DTX for that email?

Q. 8127.

A. Could you put that back up for a second?

Q. We've got your -- oh, you want the email back up?

A. Yeah.

Q. Sure.

A. Because like I said, the most important point is Point 1, which says that "Lucentis clearly does not last past four weeks, according to this study."

So as I said, that was the major point to me of this paper, Point 1, as I summarized in this email, and as was detailed in the Bayer presentation that we showed before. That was the major take-home message from this paper.

Q. Let's go to DTX 8127, the actual paper itself, and let's go to the "Methods" section that appears on the second

page of the exhibit.

Can we agree that ten patients with chronic DME received, as of this publication date, intraocular injections of 0.5 milligrams of ranibizumab at baseline, and at one, two, four, and six months.

A. That's what it says.

Q. And if they -- the patients received a dose at baseline and at one, two months, those would be three loading doses spaced a month apart, right?

A. Yes.

Q. And then the next dosing interval was eight weeks later at month four?

A. Where does it say that here?

Q. Where it says at baseline and at one, two, four, and six months, right?

A. Yes.

Q. All right. So the fourth dose in the regimen would have been eight weeks after the third dose in the regimen, right?

A. This is exactly the data that we went over, which actually showed that Lucentis at eight weeks didn't last, the one with the red arrows and the bracket that said Lucentis doesn't last eight weeks.

MS. MAZZOCHI: Your Honor, I'm really trying to move things along here. It's not going to go very well if the

witness argues with me at every single opportunity.

THE COURT: Repeat your question, Counsel.

MS. MAZZOCHI: Sure.

BY MS. MAZZOCHI:

Q. My question, Dr. Yancopoulos, is was there an eight-week, or two-month, separation between the third dose in the regimen and the fourth dose in the regimen? Yes or no.

A. There was an eight-week separation that resulted in lack of vision gain.

Q. I'm just -- I'm not asking for additional commentary. I just want to know --

A. I'm providing useful context. I don't want to say something out of context.

THE COURT: Everybody, questions are asked, Doctor. You may answer them and provide context within reason.

Next question.

BY MS. MAZZOCHI:

Q. Can you confirm that the next -- that the -- there were then also -- there was a second eight-week dosing interval between four and six months?

A. Yes. There was another eight-week interval that also failed to result in visual gain.

Q. Dr. Yancopoulos, nevertheless, in your covering email, you did note that, overall, at the end of this regimen, patients did, in fact, experience gains in visual acuity and

improvements -- I'm sorry -- gains in visual acuity.

A. Well, we had a context, because the most important point was Point 1 which says, "Lucentis, which clearly does not last past four weeks, according to the study." That's the take-home message. That was why I made that whole figure for the Bayer presentation, not what you're trying to seemingly imply, that eight-week dosing worked. The whole point of my email says Lucentis clearly does not last past four weeks. Clearly, eight-week intervals did not work.

Q. I am asking at the conclusion of the study, did the patients experience an improvement in visual acuity?

A. From their baseline levels.

Q. Yes. And --

A. That's not what Point 2 says, though, in the email.

Q. And compared to their baseline levels, by the end of the dosing regimen, patients did, in fact, experience an improvement in macular volume?

A. I'm really confused here because, if what you're trying to imply is that Lucentis every two months would have worked, clearly, that's not the case.

So is that what you're trying to imply?

Q. All I'm asking, Dr. Yancopoulos, is did patients overall at the end of the regimen experience an improvement in their vision compared to baseline?

A. As they did in the PIER regimen, which is

every-three-month dosing.

Q. And they also experienced an improvement in macular volume at the end of the dosing regimen compared to baseline, right?

A. The question is were they achieved as good --

THE COURT: Doctor, Doctor, you need to answer the question that's asked.

Will you repeat that question, Counsel.

BY MS. MAZZOCHI:

Q. Yes. Dr. Yancopoulos, can you confirm that the patients in this study at the end of the regimen did, in fact, experience an improvement in macular volume?

A. For context, they achieved improvements. Nowhere in this study does it show that they improved -- achieved improvements that would be equivalent to that to monthly ranibizumab.

Q. I wasn't asking you that question, sir.

A. That is the relevant question.

THE COURT: Doctor, with all due respect, that's my decision as to what questions are relevant or not.

The question was answered. Move on, Counsel.

BY MS. MAZZOCHI:

Q. Let's take a look at Example 5 of your '572 patent, which is in PTX 3. I believe it's around page 22 of the exhibit in Column 14.

A. Is this in your book or in my prior book?

Q. It's in your prior book, PTX 3. Lawyers kill a lot of trees, but we do try to not repeat exhibits if we don't have to.

THE COURT: What page in that exhibit, Counsel?

MS. MAZZOCHI: It is exhibit page 20, Column 14, starting at lines -- around 30 to 50. We've got it up here on the screen for you as well.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, can you confirm that the dosing regimen set forth in Example 5 of your '572 patent is described -- one of the arms is described as giving three initial doses of 2 milligrams VEGFT once every four weeks, i.e., at baseline and weeks 4 to 8, followed through week 52 by either once every eight weeks dosing or as-needed dosing with a very strict repeat dosing criteria, prn.

A. Yes.

Q. And the dosing regimen that was described as three initial doses, i.e., at baseline and weeks four and eight, every four weeks, followed by every eight weeks dosing, at least for the first six months, tracked the Lucentis DME study we were just looking at in terms of the steps of the regimen being the same?

A. The steps of the regimen but not the visual acuity outcomes, which track very differently.

Q. Dr. Yancopoulos, the name that Regeneron gave to the clinical trial that corresponds to your patent's Example 5 was the Da Vinci trial, right?

A. Yes.

Q. Do you recall who made the decision to use three monthly loading doses?

A. The ultimate decision would have probably been on me, after consultation with our team, though I can't specifically remember that at this point in time, 10 to 15 years later.

Q. Well, you do remember it or you don't remember it. Do you not remember?

A. I don't specifically remember it, but I assume that that was probably the case.

Q. Let's go with what you actually do or don't remember.

Now, even though -- well, you were not listed as a coauthor for the publication about this clinical trial, right?

A. If you can point me to the paper.

Q. Sure. Let's pull up PTX 686, first page. This is the Diana Do, reporting on the outcomes of the Da Vinci study.

Can you confirm that you are not even listed as a coauthor on the article reporting on this study?

A. I can see that I'm not listed on the list.

Q. Now, you talked a bit about this decision to move from three to five loading doses for the Phase III clinical trials. Is there data that you put into your '572 and '601

patent specifications for any rationale, such as about reaching a plateau in the context of DME therapy, that would justify increasing the number of loading doses before switching to the eight-week dosing?

A. I can't say right now without reading the patent whether there's anything in there; but as I said before, that decision was based on a million points of data, as we saw before in this book and in the presentations and so forth. How much of it might be in the patent, I couldn't tell you without reading the whole patent right now.

Q. All right. Again, do you remember that I asked you this question at your deposition?

A. Do I remember that you asked me this specific question at the deposition?

Q. Right.

A. No.

Q. All right. Well, let's put up DTX 3196, exhibit page 11, which is your deposition transcript.

THE COURT: I'm sorry, Counsel. What exhibit number is that again?

MS. MAZZOCHI: 3196.

THE COURT: Thank you.

MS. MAZZOCHI: Exhibit page 11, transcript lines 40:24 through 41:14.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, did I ask you, "Well, is there any data that you put in your '601 patent or any rationale about reaching this plateau in the context of DME's therapy that would justify increasing the number of loading doses before switching to the eight-week dosing?"

And did you give the answer, "In my attempt to read the whole patent very quickly earlier, I'm not aware of seeing that data shown, though it could well be in some of the many references that are included."

Was that the question you were asked and the answer you gave?

A. If that's what the transcript says, I guess that's what I said.

Q. Okay. Let me take you back to your -- well, actually, let's try to move along.

Let's actually switch gears for a minute and talk a little bit more about some of these formulation issues.

If you could take a look -- we'll go back to PTX 3 again, and now we're going to go to exhibit page 16, which corresponds to Column 5. And I'd like to direct your attention to lines 64 to 67 in your '572 patent.

Do you have those lines on the screen?

A. This is Column 6?

Q. Column 5, lines 64 to 67 in your '572 patent.

A. Yes.

Q. Did you state there, "A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists, Remington's Pharmaceutical Sciences," and then gives the citation.

A. Yes.

Q. Was this a true statement you made in your patent there?

I'm just asking if it's a true statement, Dr. Yancopoulos, that you put in your patent.

A. Right. It's caveated right below, "Provided that the VEGF antagonist is not inactivated by the formulation, the formulation is physiologically compatible and tolerable with the route of administration." Yes.

Q. Dr. Yancopoulos, I'd like to now direct your attention to one of your other VEGF patents, which is DTX 2730, and we'll start with exhibit page 1. U.S. Patent Number 7,303,747, which issued on December 4th, 2007.

Do you see that?

A. Yes.

Q. And you're a named inventor on this patent?

A. Yes.

Q. Do you remember if this patent actually covers your aflibercept molecule?

A. I'd have to look at this patent. Was it in my --

your book?

Q. Oh, yeah. You've got a copy of it in the binder that we gave you.

A. Under --

THE COURT: 2730.

MS. MAZZOCHI: 2730.

Your Honor, while Dr. Yancopoulos is looking for that, we'd like to move DTX 2730 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection, Your Honor.

THE COURT: Without objection, so admitted.

(DTX 2730 was admitted.)

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, to try to move things along, I'd like to direct your attention to exhibit page 13 of DTX 2730, specifically Column 1, the brief summary of the invention of your '747 patent at lines 46 to 55.

Do you see that on the screen?

A. Yes.

Q. One of the things your invention in this patent was about involved ameliorating an eye disorder, right?

A. Yes.

Q. And if we take a look here -- or starting around line 50, one of the eye disorders you listed included age-related macular degeneration? It's right there on the

screen, sir.

A. Yes.

Q. And another embodiment you listed there was the eye disorder to treat diabetic retinopathy?

A. Yes.

Q. Now let's go to the 15th page of this exhibit, which is your '747 patent at Column 5, lines 3 to 26. And we've got that up on the screen there for you.

Do you see that?

A. Yes.

Q. And do you see the text that is highlighted that starts at line 25, over to line 26, that reads, sequence -- "SEQ ID" -- meaning sequence ID -- "and then VEGFR1R2-Fc delta C1(a)."

Do you see that?

A. Yes.

Q. That's the sequence ID for aflibercept, right?

A. That, I'm not sure of.

Q. You're not sure?

A. I don't know.

Q. All right. Well, let's pull up PTX 3, which uses your '572 patent we were looking at earlier. Let's go to -- I think it's around exhibit page 11. Let's try 14. There we go. Column 2, lines 51 to 56.

Isn't it true that you stated here that

VEGFR1R2-Fc delta C1(a) was aflibercept?

A. It says here that that name refers to aflibercept, yes.

Q. Okay. And --

A. I don't know that sequence corresponds to aflibercept, but yes, the name here says it's otherwise known as aflibercept.

Q. Okay. And that was a true statement you made in your '572 patent asserted here, right?

A. I believe so.

Q. All right. Let's go back then to DTX 2730, which is your '747 patent, exhibit page 16.

A. Which patent is this?

Q. This is your '747 patent, which is DTX 2730. And we'll go to exhibit page 16, and I'd like to direct your attention to Column 7, lines 5 through 28.

Do you see there there's a heading that's titled "Methods of Administration and Compositions"?

A. Yes.

Q. And does it also say, starting at line 13, that compositions -- strike that.

I'm sorry. I wanted to direct your attention to the last part of this. It says -- starting at line 26, it says, "Aqueous compositions of the invention have ophthalmically compatible pH and osmolality." Do you see that?

A. I see that.

Q. Can we agree that your '747 patent taught to put VEGF inhibitor compounds, like aflibercept, into pharmaceutical formulations that had ophthalmically compatible pH and osmolality?

A. I don't know -- you're using certain legal terms, and I'm not the guy who writes the patents. I don't know what you mean by "taught." So I can't -- I can't comment on that. It sounds like that means something that I don't understand.

Q. Okay. We'll phrase it this way for you.

Can we agree that on exhibit page 16 of DTX 2730, your 2007, '747 patent at Column 7, lines 26 to 28, you wrote that "Aqueous compositions of the invention have ophthalmically compatible pH and osmolality"?

A. Yeah. And let me also clarify. I didn't write this patent, but -- we have patent attorneys who write these patents. But it says in here, "Aqueous compositions of the invention have ophthalmically compatible pH and osmolality." Yes, that's what it says.

Q. Do you have an understanding that an aqueous composition with an ophthalmically compatible pH and osmolality, as you use that phrase in your '747 patent, will be isotonic?

A. Ophthalmologically compatible could or could not include isotonic.

Q. But if it's ophthalmically compatible osmolality, because that's the particular metric, right? pH plus osmolality will determine whether it's isotonic?

A. Compatible means compatible. It doesn't mean the same. Isotonic means, by definition, the same. Compatible means something that would be compatible, which does not have to be the same.

Q. Let me ask you this: When you used the term "isotonic" in your '572 patent, did you intend for it to just mean the same as what we get in the eye?

A. Well, isotonic, by definition, means the same tonicity. So, yes, I intended it to mean the same tonicity.

Q. Do you know whether there's any range that is permitted for that tonicity within the eye?

A. For compatibility? For what purpose? For compatibility?

Q. Any purpose.

A. Well, yes, there can be -- compatibility has to be tested, and presumably a range of tonicities have been used and can be used that would be compatible with research in the eye. It doesn't mean they have the same tonicity. That's a chemical term, "same tonicity." "Iso" means same tonicity.

Q. And if it is iso-osmolar, will it also be isotonic based on your understanding of how you use the term isotonic and osmolality in your patents?

A. Now we're going back to chemistry 101. I believe that iso-osmolar would be the same as isotonic, but this is not something that I'm an expert on.

Q. If we can compare what you said in your '747 patent about some of these formulations with what you have in your '572 patent, do you believe that your '747 patent's description of pharmaceutical formulations in the context of isotonic added anything different beyond what we saw in your '747 patent about requirements for the isotonic solution?

A. I think you said '747 twice; so I'm a little confused.

Q. I'm sorry '747 patent versus '572 patent. Let me start over because I don't want you to be confused.

Did you add anything conceptually that you considered to be new in terms of describing an aqueous composition of the invention that has an ophthalmically compatible pH and osmolality that we saw in the '747 patent as compared to what you talked about for pharmaceutical formulations that were isotonic in your '572 patent when we were looking at Column 6, starting around lines 18 to 34?

A. Ophthalmically compatible pH and osmolality would include, as we said, a range that could, for example, be hypertonic, hypotonic, or isotonic. We specifically highlighted the isotonic solution in the '572 patent.

Q. Now, the description of isotonic solution that you

provide here in your '572 patent, that's not something that you actually came up with, right?

A. No, I did not.

Q. And you did not actually come up with this idea of a formulation that has the isotonic solution containing glucose that may be used in combination with an appropriate solublizing agent, such as an alcohol, right?

A. As I said before, I relied on our formulation experts to develop and recommend and show me data as to which was the best formulation that they had recommended.

Q. And just to be clear, when we're looking at this isotonic solution in your '572 patent, you did not actually come up with the idea of a formulation that was isotonic and also had a solublizing agent, right?

A. I did not come up with the formulation. As I said, I relied on my experts and chose between the choices that they gave me and the recommendations at the time.

Q. Sure. I'm talking more specifically about what you actually wrote here in -- or what is written here in your patent.

Do you believe you came up with an idea of an isotonic solution that may be used in combination with an appropriate solublizing agent?

A. No, I did not come up with that idea.

Q. All right. Did you come up with the idea of an

isotonic solution that might also be combined with a nonionic surfactant?

A. No, I did not come up with that idea.

Q. Let's go ahead and jump ahead to exhibit -- let's go ahead and pull up DTX 5073.0001. So, Dr. Yancopoulos, let's go through a little bit with the Court about what the Eylea formulation was that was used in your clinical trials.

Dr. Yancopoulos, do you dispute that the ingredients of the 2-milligram Eylea formulation that the FDA approved in November 2011 were also the same ingredient list for the 2-milligram formulation that was actually given to the doctors performing the VIEW 1-VIEW 2 clinical trials with aflibercept?

A. Do I dispute?

Q. Right.

A. Can you ask that again?

Q. Sure. Maybe I'll -- since you don't like the word "dispute," I'll rephrase it this way.

Do you agree that the Eylea formulation that the FDA -- the ingredient list for the Eylea formulation that the FDA approved in November of 2011 was the same formulation ingredient list for the 2-milligram formulation that was actually given to the doctors performing the VIEW 1 and VIEW 2 clinical studies?

A. I believe it was.

Q. Okay. And if we can take a look at the first page of

DTX 5073, can you see that this is titled 2.7.1, "Summary of Biopharmaceutic Studies and Associated Analytical Methods"?

A. Yes.

Q. And do you have an understanding that these are the types of things that are submitted by Regeneron in connection with its BLA with the FDA?

A. Yes.

Q. Is this work that you, as president and chief scientific officer, ultimately were responsible for overseeing?

A. These functionalities reported up to me. I did not directly oversee them.

Q. That's fine.

MS. MAZZOCHI: Your Honor, we move DTX 5073 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection.

THE COURT: Without objection, so admitted.

(DTX 5073 was admitted.)

BY MS. MAZZOCHI:

Q. And let's go ahead and move along to -- let's have you take a look at DTX 5082, and we'll start again with exhibit page number 1. This is a part of the Regeneron BLA that is titled "2.3.P Drug Product."

Do you see that?

A. Yes.

Q. And is this also work that you, as president and chief scientific officer, were ultimately responsible for overseeing?

A. When you said formulation development, that did report up to me. If we're talking about some of the aspects that are under here -- you know, the manufacturing, the drug process, and so forth -- that reports up to our head of manufacturing.

Q. And does your head of manufacturing report to you, or do they just report to your CEO?

A. They report to our CEO.

Q. Let's go ahead, and we'll move along.

Now, ultimately, though, Dr. Yancopoulos, you would agree that pharmaceutical formulations is not an area of expertise for you, right?

A. Yes, I would agree.

Q. Dr. Yancopoulos, we did look earlier -- I think it was PTX 311. Let's go ahead and call that up.

This was your 2012 article titled "Intravitreal Aflibercept VEGF Trap-Eye in Wet Age-Related Macular Degeneration."

Do you have that?

A. Yes.

Q. Let's take a look as well at the exhibit that you had pulled up. I believe it was PDX 3-0311-B. See if we can pull

that up on the screen. I think it was the one that had what you called the integrated data on it.

MS. MAZZOCHI: Pardon me, Your Honor, with a lot of these exhibits going on.

BY MS. MAZZOCHI:

Q. All right. There we go. Dr. Yancopoulos, is this the slide -- can you confirm that up on the screen you have PDX 3-0311-B?

A. Yes.

Q. And this is one of the slides you testified about in your direct examination?

A. Yes.

Q. Can you confirm that, if we take a look at the integrative data, the dose that performed the best in terms of letter ranking was the 2q4 regimen in yellow, yellow-orange?

A. Numerically, it had a higher number at the end; statistically, these were all no different from each other.

Q. Right. And my questions are just going to be at the end of the dosing regimen. So can we agree, then, that the 9.3 2q4 aflibercept monthly dosing regimen was the best numerically in terms of number of letters gained?

A. Well, in VIEW 1 it was numerically better; in VIEW 2 it was actually numerically worse. They were reversed to the point that I made before, and then they were within less than a letter difference at the end of the trial.

Q. That's why I asked you about the integrated data. So can you confirm that at Week 52 the integrated data curve from the VIEW 1-VIEW 2 study put the monthly aflibercept dosing regimen numerically at the top with 9.3 letters gained?

A. There was not statistically significant difference of 0.9 letters, in which the 2q4 was 0.9 letters numerically different from the 2q8, but not statistically different.

THE COURT: Yes or no, Doctor.

BY MS. MAZZOCHI:

Q. Do you need me to repeat the question?

A. Yes.

Q. Can you confirm that in the integrated data set for the VIEW 1-VIEW 2 clinical studies, the aflibercept 2q4 dosing regimen numerically performed the best with 9.3 letters?

A. It was numerically higher.

Q. Right. And then the next numerically higher number, at 8.7 letters, was ranibizumab dosed monthly, right, with 8.7 letters gained?

A. I think this was a misrepresentation of the data. I can't -- I can't in good conscience say yes to things that are misrepresentations. You're making -- trying to make a point about .3-letter differences that are statistically insignificant, that didn't repeat in the two studies.

Q. All I'm asking you, Dr. Yancopoulos -- this is your slide --

A. Right.

Q. -- can you confirm that the integrated data set you presented here had ranibizumab monthly, R q4, at 8.7 letters?

A. It had it at 8.7.

Q. All right. And, likewise, right below that, at 8.4 letters, was your aflibercept 2q8 regimen, which was three monthly loading doses followed by every-eight-week dosing?

A. At 8.4 for 2q8.

Q. And your -- that at 8.3 letters was your 0.5-milligram dose given monthly, right?

A. Those are the numbers.

Q. And if we look at your VIEW 1-VIEW 2ETDRS letters in A and B, even -- can we agree that the letter range variation for the monthly Eylea dosing was from 7.6 to 10.9?

A. Yes.

Q. And can we agree that for the ranibizumab, the ultimate letter range in VIEW 1 and VIEW 2 ranged from 8.1 to 9.4?

A. Yes.

Q. And can we agree that for the 2q8 dosing -- so the three loading doses followed by eight-week dosing with aflibercept -- that dosing range was from 7.9 to, I believe, 8.9?

A. Yes.

Q. And for the 0.5 dose of aflibercept given monthly,

your letter variation range was from 6.9 to 9.7 across those trials?

A. Yes.

Q. Now, when it comes to this Heier -- oh, I'm sorry. When it comes to the Heier publication that you're a coauthor on, PTX 311.001, you did at some point submit a version of this publication to the *New England Journal of Medicine*, right?

A. Yes.

Q. And the *New England Journal of Medicine* rejected your manuscript?

A. Yes.

Q. All right. Let me put before you DTX 915. It's also in your binder, and I'd like to go to the first page of the exhibit.

Can you confirm that DTX 915, the first page includes an email from you to Bala Dass and others dated Thursday, January 19, 2012?

A. Yes.

Q. And did you write the commentary in this email? "I would agree with Peter and Dave and do whatever is necessary to get the first paper out in NEJN," meaning *New England Journal of Medicine*.

A. Whatever is necessary refers to the line below that says "withdraw a related paper from consideration in another journal."

Q. By the way, that was -- you did write commentary in this email, right?

A. Right.

MS. MAZZOCHI: Your Honor, we move DTX 915 into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection.

THE COURT: Without objection, so admitted.

(DTX 915 was admitted.)

MS. MAZZOCHI: Thank you, Your Honor.

BY MS. MAZZOCHI:

Q. If we go to the second page of this exhibit within the email string, did you receive various reviewer comments about your manuscript from the *New England Journal of Medicine*?

A. Yes.

Q. All right. Let's take a look at a few of them.

If we can go to exhibit page 6 in DTX 915.

I'd like to go through a couple of the comments from Reviewer Number 1, particularly Item 18, which was commenting on your manuscript page number 11. Let's pull that up for you on the screen.

Do you have it?

A. Yes.

Q. And did they -- if we go to the -- three, four, five, six -- seventh line down in terms of talking about the CATT

study, did the reviewers tell you that the -- I'm sorry -- in talking about your study, that the average number of injections in your VTE, meaning VEGF Trap-Eye, 2q8 group was 7.6 and the average number of injections -- average number for the ranibizumab prn group equivalent in efficacy to ranibizumab monthly was 6.9.

Is that what the reviewer wrote to you?

A. I see that. I'm not sure it's correct, though.

Oh, this is the ranibizumab prn group. I'm sorry. This is not in our study. This is comparing cross-study comparisons. Sorry. I didn't understand comparing our study from the study from CATT, yes.

Q. Yup. And then the reviewer took that data and said, "While the argument of decreased burden for the patient by eliminating five monthly monitoring visits in the first year is solid, the argument for increased patient safety is overstated, particularly relative to ranibizumab prn."

Is that one of the comments you received?

A. Yeah. This is comparing our regimen to a regimen that is now obsolete because it's considered not as effective, yes.

Q. Sir, I just wanted confirmation that these are the comments you received. Because you're not an expert, I'm actually trying to not invite commentary. I'm just trying to confirm the commentary you received.

A. I'm just putting it into context.

Q. Let's take a look at exhibit pages 6 and 7, the text that goes from the bottom of page 6 in DTX 915 and over to the top of page 7, which are some of the comments from Reviewer Number 2.

If we look at the top paragraph of the text on DTX 915, exhibit page 7, Reviewer 2 gave you the feedback that "The primary finding that may differentiate VEGF Trap as compared to the many prior reports is an apparently noninferior semimonthly dosing schedule as opposed to monthly dosing. Although clearly of burden -- benefit to patients and physicians, this is not a major conceptual advance."

That was the feedback you got from Reviewer Number 2, right?

A. That was.

Q. Okay. Now let's go a little bit more than halfway down, exhibit page 7 in DTX 915. We now have comments for the author from Reviewer Number 3 that I'd like to pull up on the screen.

And let's take a look at Reviewer Number 3's first full paragraph of text and the second-to-last sentence.

Reviewer Number 3 said of your manuscript, "The paper also lacks balance and is much too heavy-handed in its treatment of every-two-month dosing, so much so that it comes off as the beginning of a marketing campaign."

Was that feedback that you received from Reviewer Number 3?

A. That is what he wrote.

Q. Let's go to exhibit page 11 in DTX 915 and look at some more feedback you received from Reviewer Number 3. And this time I'll ask that the top paragraph be put up on the screen. So we're in exhibit page 11. Let's pull up the top paragraph. It's pretty lengthy. We'll scroll on through it.

Let's begin around the fifth line down on DTX 915, page 11. It says -- actually, to be fair, let me do the whole sentence.

So do you see starting in the third line down there's a reference to the CATT and HARBOR clinical trials?

A. Yes.

Q. And in the CATT clinical study, ranibizumab, Lucentis, was tested head to head against Avastin, bevacizumab, in connection with wet AMD, right?

A. Yes.

Q. And they found that there was really no clinical difference in that class -- in that CATT study between the two drugs, right?

A. No. That's incorrect.

So as I said, at this time, prn was very much in favor. And particularly with the early results from CATT and HARBOR, some people were failing to see the problems with prn.

Once the field evolved, probably a year or two after this, especially when they had the subsequent year's data, it became very clear that these prn regimens were just not delivering the visual acuity outcomes. And the evidence for this is they rapidly dropped out of favor and were no longer being utilized to this day. So these experts are among the experts at the time that had it wrong in terms of favoring at that time based on early data prn regimens.

So I don't want to be -- I had publicly at that time pointed out the difficulties with prn dosing which have since been validated, though, as I said, people at the time were still stuck in that regimen. But history has proven these ineffectual and obsolete now.

MS. MAZZOCHI: Your Honor, I'd like to move to strike because my question --

THE COURT: Denied. That motion is denied. We're reviewing random comments from reviewers for a medical journal. I'm about to ask the question what is the relevance of this line of questioning anyway, Counsel?

MS. MAZZOCHI: Your Honor, the relevance of this line of questioning is that many of the arguments that we're going to hear from Regeneron's witnesses in connection with unexpected results are making exactly the type of arguments that were made in that Heier paper that the -- that Regeneron's going to rely on.

And they're trying to treat those comments that are in the Heier paper as if they are gospel and uncontested. And our point is that no, in fact, there were people who disagreed with some of the premises that you put into that paper; therefore, it shouldn't be accepted as truth in this case.

THE COURT: This is getting to one of the many reasons the Court denied all the motions for summary judgment. I think there's a genuine dispute that the doctor just articulated on that. So the motion to strike is denied. You may ask your next question.

BY MS. MAZZOCHI:

Q. The question with regard to CATT is did they discover any differences between the number of letters gained between bevacizumab versus -- versus ranibizumab for comparable dosing regimens?

A. I think it's hard for me to remember all the details now, but the ultimate conclusion after looking at the follow-up data of CATT was that prn regimens were not as effective. And that largely explains why they are no longer being followed. Also, that Avastin was not as effective and, even under prn regimens, had to be dosed more frequently than Lucentis.

Q. In a way that was statistically significant, to your recollection?

A. I don't remember all the details, but clearly the field had -- has come to the conclusion that prn dosing is

suboptimal and that Avastin is suboptimal to Lucentis when given the same way.

Q. If we carry on with the reviewer comments, one of the reviewer comments back to your manuscript was that you state that CATT and HARBOR still required mandatory monthly visits. In the next line you refer to the CATT prn treatments as difficult treatment decisions. "I would not characterize these as difficult since they are what clinicians do every day in their practice."

Was that also feedback that you received?

MS. OBERWETTER: Your Honor, I am going to object at this point to the continuation of this line as to the series of unidentified reviewers as to the relevance and probative value.

THE COURT: Overruled for the reasons counsel previously articulated.

BY MS. MAZZOCHI:

A. So we can talk about subjective judgments. I don't think anybody would disagree that bringing an elderly patient in once a month or once every two months is not more difficult and much more burdensome on the patient, no matter what characterizations your treatment is on. I think everybody would agree, if you've ever had an elderly parent, bring him to the doctor once a month or once every two months is twice as burdensome.

Q. But in your clinical trials, the VIEW 1-VIEW 2

clinical trials, even in the every-eight-week dosing regimen you still required the patients to show up every month, right?

A. The FDA deemed that that was what was conducted in the trial, but the data clearly showed that there was no need to be bringing them in. So the label did not require any of those monitoring issues. So the FDA, which is the ultimate arbiter, said that there is no need for these burdensome monitoring visits.

They were required for the protocol to make sure that there would be no need. And the studies showed to the FDA's satisfaction that there was no need for monthly monitoring visiting, thus cutting the number of burdensome visits by half and also taking all need to do these various testings, whether you think they're difficult or not -- I mean, physicians may like to do them because they are compensated for doing these assessments, but what the FDA agreed was there was no need for the patients to come in, and there was no need for the doctors to do these assessments if you used their approved regimen.

Q. Didn't the FDA require you in the Eylea label to include language that said patients should be assessed regularly?

A. And regularly would be consistent with coming in every two months for their dose.

Q. Let's go to the last eight lines on exhibit page 11 in DTX 915, first paragraph. I'd like to direct your attention

to some additional text that says, "Lastly, you say that aflibercept will decrease treatment burden."

Did *New England Journal of Medicine* Reviewer Number 3 give you feedback that said, "Lastly, you say that aflibercept will decrease treatment burden. So does prn dosing, which is the primary way Lucentis and Avastin are used, and maybe to a greater degree in the first year and maybe with an equivalent result"?

Do you see that?

A. Once again, the field at the time, which we've already acknowledged, believed that prn dosing was the way to dose. It has been almost completely abandoned now because it was realized that it was not a way to get the best visual outcomes. So they're comparing us.

So the whole point of prn was to decrease treatment burden. Everybody says treatment burden was so important. Prn was devised to try to decrease treatment burden. It's now been abandoned because it did not lead to equivalent visual outcomes. We delivered a way to avoid all that, to decrease the treatment burden by half and deliver the same visual outcomes as the FDA agreed.

So you're trying to say that yes, of course, I could not treat the patients at all and there would be no treatment burden, but of course they would lose their vision. So you're comparing us to a regimen that's no longer being utilized. I'm

sorry, but the reviewers at the time were trapped in their old paradigm. No matter how expert they were, no matter how utilized they were by the *New England Journal of Medicine*, they've now been proven wrong by history.

Q. In what year do you believe history decided to prove the prn regimens wrong in your understanding?

A. From that period of time, which was --

Q. This was in 2011.

A. -- 2011, over the ensuing five years, prn gradually completely fell out of favor.

Q. Dr. Yancopoulos, let's go back, then, to PTX 3, your '572 patent. And I'd like to start at exhibit pages 21 to 22, which has your Example 7. And we'll pull that up for you on the screen.

Dr. Yancopoulos, let's take a look at the first regimen you put in your Example 7 titled "Dosing Regimen."

It says, "Specific nonlimiting examples of dosing regimens within the scope of the present invention are as follows." And then it says, "VEGF T 2 milligrams, 0.05 milliliters, administered by intravitreal injection once every four weeks, monthly."

Do you consider your '572 patent -- strike that. Let me start over.

Do you believe that you invented a monthly dosing regimen for aflibercept?

A. I don't know what the legal definition of invention is. We were the first to actually utilize this regimen and demonstrate its efficacy in clinical trials.

Q. Now, you've spent a lot of time today saying how much you hate the prn dosing regimen, that you thought it was just the dumbest thing that you could be doing. Well, let's move over in your patent to exhibit page 22 and take a look at the part of your Example 7 dosing regimens that appears in Column 17 of your '572 patent at lines 33 to 37.

Now, this dosing regimen is basically a first injection followed by nothing but a prn dosing regimen, right?

A. Could you direct me again to where we're talking.

Q. It's right here on the screen, but it's at Column 17, lines 33 to 37, exhibit page 2.

A. Yes. It's one of the examples of regimens that could be used.

Q. Okay. So you claimed as your invention a dosing regimen that you called earlier today the dumbest dosing regimen ever?

A. I think the point is that they're within the scope of the present invention. Nowhere am I saying that this is the preferred. This would work and provide some benefit to patients, just not a -- it would not provide the best visual outcomes, as we now know.

Q. Dr. Yancopoulos, you put a whole series of prn dosing

regimens in Example 7 as supposedly within the scope of your present invention, right?

A. Well, once again, I did not write the patent; but yes, these are listed as regimens that are within the scope of the invention, not necessarily highlighting which would be the regimen that resulted in the best visual outcomes for patients. That was what would be determined by our clinical programs and our FDA-validated Phase III clinical program.

Q. Would it be fair to say, then, that in Example 7 you were trying encompass all the ways in which aflibercept was utilized and shown to have some efficacy?

A. Not being an expert in these patents, but I think all these list dosing regimens that would be within the scope of the present invention. And I don't think that we would be saying which would be the best one that would produce the best visual outcomes.

Q. Let's stay in PTX 3, exhibit page 22, and look at the text that's at the end of Example 7, which I believe is near the bottom of Column 17, starting at lines 45 to 53, which then goes over onto the next column, 18, through line 3.

Do you have that on the screen?

A. Yes.

Q. All right. Now, if we look at this list of diseases there which are described -- now, one of them is described as wet AMD, right?

A. Yes.
Q. You have FDA approval for that with aflibercept?
A. Yes.
Q. Do you have FDA approval for an indication that is specifically called exudative AMD?
A. That's another way of saying the same thing.
Q. Now, you do have -- do you have an FDA approval for --
I'm sorry. Can you keep that up, please.
Do you have FDA approval for choroidal neovascularization?
A. Choroidal neovascularization is something that marks a variety of different diseases, including AMD. So if we look at the list, we have an approval, age-related macular degeneration, wet AMD. That's the first one. Retinal vein occlusion, RVO, yes.
(Reporter clarification.)
THE WITNESS: I'm reading the list in order.
So the first one is AMD and particularly wet AMD. Yes, obviously, we have the approval.
Retinal vein occlusions, yes, we have the approval.
Central ventral vein occlusion, yes, which is example macular edema following -- yes.
Branch retinal vein occlusion, BRVO, yes.
Diabetic macular edema, DME, yes.

Choroidal neovascularization, that marks a variety of different diseases, including AMD and DME; so it's not a specific disease.

Iris -- so we did not do Phase III trials in iris neovascularization. So we've knocked off the first whatever it is on the list. We haven't necessarily done all of those things subsequently on the list. It is pretty remarkable that, of the first five or six things that we've tried, there's extraordinary clinical benefit and they're all approved.

BY MS. MAZZOCHI:

Q. Can we agree that one of the things that is not here on the list is diabetic retinopathy?

A. Well, vascular retinopathy, I see is on the list. It's the last thing actually on the list.

Q. I'm talking about specifically diabetic retinopathy.

A. Like I said, vascular retinopathy is the same category. It's just that it occurs in diabetes.

Q. Does this language contain any statement of preference to use a particular dosing regimen from Example 7 for diabetic macular edema?

A. Not in this paragraph.

Q. All right. Let's stay in PTX 3 but go to exhibit page 15, which --

THE COURT: Counsel, before we do that, can I ask you how much longer you anticipate cross taking?

MS. MAZZOCHI: I apologize, Your Honor. I've probably got, I would guess, another maybe 30 minutes. I'll try to move it along. I'd hoped we'd be able to go faster.

BY MS. MAZZOCHI:

Q. Let's stay in PTX 3 but go to exhibit page 15, which is Column 4 of your '572 patent, lines 22 to 31. And this is the paragraph that starts off "The methods of the invention may comprise administering to the patient any number of secondary and/or tertiary doses of a VEGF antagonist."

Are you there on the screen?

A. Yes.

Q. All right. And now let's highlight the next sentence that reads, "For example, in certain embodiments only a single secondary dose is administered to the patient. In other embodiments, two or more -- e.g., two, three, four, five, six, seven, eight, or more -- secondary doses are administered to the patient."

Do you see that?

A. Yes.

Q. You did not put any upper limit on "or more" for the secondary doses, right?

A. That is correct.

Q. And likewise if we take a look at the tertiary dosing description administered to the patient, you did not put any upper limit on the number of tertiary doses, right?

A. Correct. These are intended to be treatments for life for these elderly patients.

Q. Can we agree that, of the options you've listed here, we're going to have at least ten or more options for secondary doses and certainly more than ten different options for tertiary doses in terms of the number given?

A. There is a number of embodiments.

Q. Right. But in terms of the actual number of options that are contemplated here, can we agree there's going to be at least ten or more for the secondary doses and at least ten or more options for the tertiary doses?

A. Yes.

Q. And if we -- and if a patient is going to be taking tertiary doses for a lifetime, that could be as many as 100 or 200 doses, right?

A. It's possible. These are elderly patients, however.

Q. If these doses can be given either on a fixed-dose regimen, a prn-dosing regimen, or a treat-and-extend basis, that's three additional options to impose on the dosing intervals, right?

A. Now I'm totally confused. What do you mean by that?

Q. Sure. Well, you don't specify here that the secondary dose is going to -- I'm sorry. Let me strike that and take a step back.

You don't specify that the tertiary doses are going

to be administered either on a fixed monthly basis, a prn basis, or a treat-and-extend basis, right?

A. I'd have to go over this, but I thought that the secondary doses would be given monthly. Okay? So let me just read what it says here.

"In one exemplary embodiment of the present invention, a single initial dose is administered to a patient on the first day followed by two secondary doses, each administered four weeks after the immediately preceding dose, i.e., at week four and eight, followed by at least tertiary doses each administered eight weeks after the immediately preceding dose, i.e., weeks 16, 24, 32, 40, and 48. The tertiary doses may continue at intervals of eight weeks indefinitely during the course of the treatment regimen. This exemplary administration is depicted graphically in Figure 1."

So I think the embodiments, yes, they cover a variety of ways to do it. But we specifically give exemplary examples that the secondary doses, for example, are intended to be given monthly. So the whole notion -- the whole idea was a short period of intense dosing monthly and then switching to an every-eight-week regimen, which is obviously eventually what we studied in the clinic. But that's, for example, what is in Figure 1, a single exemplary embodiment. But I agree, the embodiments, you could try to do some math and say that there's a lot of them.

Q. Okay. Well, let's stay on this exhibit page and look at your '572 patent at the text that appears at Column 3, starting at line 66, and which then runs over to Column 4, line 1. Now, I understand you said that you gave an example of monthly dosing, but your specification says here that the secondary dose can be administered on an interval of two, two and a half, three, three and a half, or four weeks, right?

A. Right. Once again, my expertise is not in writing these patents. My understanding is that they give embodiments that will cover a lot of possibilities. But in the key exemplary embodiments, we highlight what ends up being relevant to the particular examples and -- including the ones that ultimately were the ones that we tested in Phase III and got approved by the FDA.

Q. Sir, did you give the possibilities of two, two and a half, three, three and a half, or four weeks for your secondary dose interval?

A. Right. There are a listing of many numbers that you just listed, yes.

Q. Right. And, likewise, for the dosing range on the tertiary dose, did you also give an interval option of 8, 8 and a half, 9, 9 and a half, 10, 10 and a half, 11, 11 and a half, 12, 12 and a half, 13, 13 and a half, 14, 14 and a half, or more weeks after the immediately preceding dose?

A. Yeah, that's what's written in the patent.

Q. All right. And that's an additional -- that's at least 13 different tertiary interval options, right?

A. Yes. I mean, if you multiply these, you can get all sorts of possibilities. But like I highlighted, the ones that we put into a figure and ended up utilizing are just specific ones. You couldn't possibly test all of these.

Q. Now let's jump over to page 15 of Exhibit PTX 3 to Column 7 of your '572 patent, top of the column, from lines 1 down to 28.

Do you have that on your screen?

A. Yes.

Q. This is where you're listing all the possible doses to include in your dosing regimens, right?

A. Yes.

Q. And because the hour is late and our court reporter is heroic, I'm just going to ask if you'll accept my representation that there are at least 60 different dosing possibilities listed there.

A. Yes.

Q. Thank you.

And, likewise, you do not require -- or your regimens did not require using the same dose for the secondary and tertiary doses; you contemplated also having one dose for the secondary doses and a different dose for the tertiary doses, right?

A. Yes.

Q. All right. Now, let's go to -- let's pull up, if we can, PTX 3333. I believe on one of these pages you said that there was some data that you relied on. Let's see if I can get the exact exhibit page number.

A. Are you looking for Slide 47, the one that we were talking about during the prior --

Q. Well, unfortunately, the versions that we got from plaintiff's counsel didn't have an exhibit number on them. It's the one that ends in page 3752. So it looks like it's about ten pages from the end of the exhibit.

Let's go four more pages forward, please. 372 are the last four Bates numbers -- I'm sorry -- the last three Bates numbers. There we go.

The data, particularly this idea of the three month, three month, three month, and the arrows that you put on here that you said represented your great insight as to what needed to happen with these dosing regimens, did you put any of that data in your '572 or '601 patent?

A. Did we put the data from the PIER study into the patent?

Q. Right.

A. I would have to read the patent to know, but you can tell me, I'm sure.

Q. I didn't see it. Did you put your insight that you

needed to make sure that you weren't getting any vision loss before you did your next dose interval anywhere in your patent?

A. Say that again.

Q. Whatever you called your great insight as to why Lucentis failed, did you put that guidance anywhere in your patent specifications?

A. The thought processes about when Lucentis would fail, okay, I think, as we summarized in this slide and the very next slide, was the basis of deciding for us what design to do in our Phase III program. I do not think that we put in when Lucentis failed in our patent.

Q. And you didn't put in your reasoning as to why you believed Lucentis, as you put it, failed in your patent, right?

A. Yeah. I didn't say that this was any great insight, by the way. I think it's obvious that, after the first three injections, you lose vision. I just pointed it out. I didn't say it was a great insight. But it's right there. It was in the Genentech FDA label. We probably cited the Genentech label as a reference in our patent. We should look at that.

Q. You also talk --

A. Can you check to see -- I mean -- so before I say we didn't, we probably had the Lucentis label as a reference in our patent. So this data was in there then.

Q. Did you provide your reasoning or explanation? That was the point, sir. Your reasoning, your explanation, your

insight.

A. I'd have to read the patent in detail, but I don't know.

Q. It's not there.

All right. You also talked about how you needed to have some meaningful Phase III data. Can we agree that, in your '572 and '601 patents, there is no Phase III data for DME?

A. That is probably the case. We did not have Phase III data at that time.

Q. And, likewise, there was no clinical diabetic retinopathy data from any phase, Phase I, II, or III, in your '601 or '572 patent, right?

A. It's hard to remember all the timelines, but I think in general we create these patents and you try to cover the embodiments that you will try in the future as in your Phase III trials.

Q. Dr. Yancopoulos, you're not a board-certified ophthalmologist, right?

A. No, I'm not.

Q. And at some point do you recall the situation where patients were being denied Eylea monthly treatments when they needed them and prescribers were being denied payments for monthly administration of Eylea?

A. Yes.

Q. And in response, Regeneron prepared a labeling

submission to the FDA to allow for a change in the label, right?

A. Yes.

MS. MAZZOCHI: Your Honor, we'd like to call up DTX 902.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, can you confirm this is an email on which you were copied on this issue?

A. Yes.

Q. And one of the reasons Regeneron was willing to make these changes for the label for AMD and make a similar change for DME was to allow for patients who were being denied their physician-recommended treatment to actually get insurance coverage for the monthly dosing treatments they were being denied, right?

A. Yes.

Q. Dr. Yancopoulos, you would agree that, while clinical trial results may show results for the overall population or an average patient, we all know that individual results for almost any drug for any disease are going to vary for each individual, right?

A. That is quite possible, yes.

Q. And, Dr. Yancopoulos, you also know that the FDA and current practice allows physicians the individual freedom to treat individuals differently for various reasons, right?

A. Yes.

Q. And while a doctor may have to defend their decision if they prescribe off-label, you know that they do have the freedom to prescribe Eylea, or aflibercept, off-label, right?

A. Yes.

Q. And while you talked about your current Eylea product here today, Regeneron is planning on launching a new version of its aflibercept intravitreal product, right?

A. Yes.

Q. You're trying to get FDA approval for an extended dosing interval that is as long as 16 weeks, right?

A. Right, with a different, more concentrated formulation of aflibercept.

Q. Because from your perspective, there remains a need to alleviate treatment burdens with intravitreal VEGF inhibitors, right?

A. Yes. We would agree that, even treating patients every eight weeks, and as you said some people might require more frequent treatment, alleviating treatment burden further would have more advantages, yes.

Q. Let's pull up DTX 228.0002 that counsel asked you about.

A. Which book am I in?

Q. This is in the ones that your attorneys used with you. And let's look particularly at the -- what was described

as Lucentis control VT 0.5 q4w, VT 0.2 4qw, and then VT 2.0 q8w, dose somewhat still undecided.

Do you see that?

A. Yes.

Q. You testified that this reference to VT 2.0 q8w actually referred to not just an eight-week dosing regimen but one with three loading doses.

Do you have any documents that you're aware of that corroborate that statement.

A. It's hard to remember any documents from 15 years ago.

Q. Okay. But somehow you're remembering that that actually meant three loading doses even though three loading doses aren't written there?

A. Yes. I distinctly remember that because that was exactly what we were planning on designing.

Q. Let's take a look at PTX 3216. This is the key opinion leader discussion.

You said that some unnamed key opinion leader told you that there were safety concerns with DME dosing. Who was that key opinion leader?

I believe it was in the slide presentation.

A. Can you say again? What is it that you're referring to that an expert said?

Q. Yeah. If we take a look at -- it's the page of the

exhibit that ends in 5555; so second-to-last page of the exhibit.

You said that there were key opinion leaders who told you that there were possible safety concerns with the diabetic population.

Who do you contend told you that?

A. Well, I think there were already in the label, the original label for Lucentis, there was a possible association with what they called ATPC events or events related to heart attacks and strokes and so forth. And I think the concern was that the diabetic population might be more prone to the same safety concerns that were seen with AMD because, as we all know, if you have diabetes, it increases your risk of heart attacks and strokes.

So there was already the concern with the class, and that was in the Lucentis label, that it might be associated with an increased risk of heart attacks and strokes for AMD, and the possible safety concern in the diabetic population was that perhaps anti-VEGFs would have even more of a risk, which caused us to be concerned about going to even higher doses.

Q. Doctor, I'm not asking you what the basis was. I'm asking you who offered that opinion at your key opinion leader meeting.

A. I would not remember an individual, but I think that a lot of individuals were concerned about that, both internally

and externally.

Q. Can you give me the name of any one of your key opinion leaders who attended that meeting who you believe expressed that concern?

A. I'm sorry, but at this point I can't give you the name of any key opinion leader who even attended the meeting.

Q. Okay. This brick of an exhibit, PTX 1170 -- it's about 4 inches thick -- did any of this data, to your knowledge, make its way into your '572 or '601 patent?

A. I have no recollection.

Q. Do you recall whether you even put any DME monthly visual -- I'm sorry.

Do you recall whether you put any monthly visual acuity data results for DME anywhere in your patent specification?

A. We could review the patent. I don't remember off --

Q. Well, the only place where you have any actual DME data is in Example 5. So let's go ahead and pull that one back up, PTX 3. I believe it's exhibit page 22.

I'm sorry. Let's go to Example 5. It's one or two pages earlier. And let's go down to Table 2.

Did you provide any monthly data showing mean change in visual acuity?

A. Apparently, yes.

Q. Sorry. Did you say yes?

A. Apparently, yes, in this table.

Q. On a month-by-month basis?

A. It says here "VEGF Trap .5 milligram monthly, .2-milligram monthly."

Q. Then my question was too confusing. I apologize. I don't mean did you have a monthly dosing? I mean did you provide the letter results each and every month?

So you had that graph that you were pointing us to earlier where you showed the drop-off for the Phase II DME data.

A. Right. You're saying the -- is this the Da Vinci study that we're talking about?

Q. Yes. It's Example 5.

A. So you're saying that we previously saw the graphs over time, and here we have the table of the results at Week 24.

Q. Right.

A. So we did not show the data between months zero and 24, yes.

Q. But it was the data that you saw in those -- at each of those intervening months that caused you to realize you wanted to have more loading doses, right?

A. Well, I think, as I said before, there was a lot of data, from here to the data that you're referring to to much other data that I used to come up with that decision to use

five loading doses, yes. So there's a lot more data that was utilized than is in this patent.

Q. Just so the record is clear, let's pull up PTX 1028-C.0011.

A. Which book is that in?

Q. That's your plaintiff's counsel's book, I believe.

A. PTX --

Q. 1028-C.0011, the Da Vinci mean change in visual acuity data that was set forth on the month -- I'm sorry -- the every-four-week basis.

Can you confirm you did not put that data into your patent?

A. Yes. As we just reviewed, this graph does not appear in the patent.

Q. But can you also confirm that, if we take a look at the 16-week mark, that is where the three loading doses followed by every-eight-week dosing dropped off, right?

A. Yeah. I don't think -- as I said before, we consider a lot of these changes in these very small number of patients noise. So if -- let me just use my laser pointer.

If you're trying to make the point that this line here meant anything different than this line here or this line here, it did not. So, no, I don't think you can make any conclusions because I think we all agree the change here looks just like the change here looks just like the change here. So

you could draw no conclusions from these small numbers of patients and the extreme variability seen in these small numbers.

Q. Let's take a look at PTX 1028-C.0016, the mean change in retinal thickness. Can we agree that, numerically, according to this graph, your 2q8 dosing regimen, which was three loading doses followed by every-eight-week dosing, numerically had performed the worst by Week 16 for mean change in retinal thickness?

A. Yes.

Q. And that was the fifth dose day, right? The fifth dose given within the context of that regimen?

A. I'm not sure that's correct.

Q. Well, there was a dose given at baseline at week zero, right?

A. Yeah. It was not the fifth dose.

Q. For the 2q8 regimen, was the first dose given at time equals zero?

A. Yes.

Q. The second dose was given at time equals 4?

A. Yes.

Q. And the next one was given at time equals 8?

A. Yes.

Q. Then skip the dose on week -- on Week 12?

A. Yes.

Q. All right. And then a dose was given at Week 16?
A. Yes. That would be the fourth dose.
Q. Now, for the prn dose at Week 16, those patients performed better numerically, right?
A. Yeah. The prn, I think at that point, was monthly dosing at that point.
Q. All right. Your understanding is that the prn was still doing monthly dosing in the Da Vinci study at the 16-week mark?
A. Let's go to it.
Q. That's fine. I'll withdraw it. Let's move along.
A. Yes.
THE COURT: How much longer do we have, Counsel?
MS. MAZZOCHI: Sorry?
THE COURT: How much longer do we have?
MS. MAZZOCHI: Your Honor, let me just wrap this up here, and I'll warn my colleagues that, if there's anything further they think I need to do, then they can start gesticulating frantically.
THE COURT: They're your sticky notes.
Go ahead, Counsel.
BY MS. MAZZOCHI:
Q. Dr. Yancopoulos, is it true that your net worth has been pegged at over $1 billion because of the value of Regeneron's stock that you own?

A. I honestly have no idea what my net worth is. I don't follow those sorts of things.

Q. We can at least agree, Dr. Yancopoulos, that your current stake in Regeneron is worth over $100 million, right?

A. Probably for sure, yes.

Q. All right. And, finally, you have not actually been treating patients for the many conditions that we've discussed today any time in the last 10 to 15 years; is that fair?

A. No, I have not been a practicing physician.

MS. MAZZOCHI: Thank you, Your Honor. We'll pass the witness.

THE COURT: We're going to take up recross tomorrow, assuming it's longer than five minutes.

MS. OBERWETTER: This will be very short, Your Honor.

Would you like a break? Your Honor, as long as we're coming back to finish this, then I'm happy to have a break.

THE COURT: I was going to come back tomorrow morning to finish it. What's your definition of very short, Counsel? Let me ask that.

MS. OBERWETTER: Five minutes, plus moving in the exhibits that I identified earlier.

THE COURT: I've fallen for that trick before.

MS. OBERWETTER: I'm pretty sure it's not a trick, Your Honor.

THE COURT: I didn't mean -- that was nothing

personal.

REDIRECT EXAMINATION

BY MS. OBERWETTER:

Q. Dr. Yancopoulos, just a few more questions for you today.

First of all, Ms. Mazzochi had some questions for you about DTX 4070, which was an article by Dr. Nguyen, if we could pull that up briefly.

And, Dr. Yancopoulos, do you recall the questions about this exhibit generally?

A. Yes.

Q. Okay. If we could actually take a look at the last page of text of this document, which appears at the top of DTX 40700009, and if we could actually hone in on just the top five lines there.

Dr. Yancopoulos, this is an article that you included in that Bayer 2007 PowerPoint that we looked at earlier today, correct?

A. Correct.

Q. How did Dr. Nguyen conclude his article?

A. In terms of you want me to read this or --

Q. Yes. Yes. What were the questions that he was posing after the data he presented?

A. Whether the different patterns of response to the Lucentis in different patients was because of different levels

of VEGF production in these patients and what was the optimal timing for injections.

Q. Okay. And that is where he ended in terms of identifying regimens, correct?

A. Yes.

Q. We can take that document down.

If we could put back up PDX 3-0311-B, which was that colorized excerpt from the Heier 2012 reference.

And you recall Ms. Mazzochi had some questions for you about the numeric differences in Table C on this page, the integrated data. Do you recall that?

A. Yes.

Q. Could you please explain, briefly, the difference between the numeric data and looking at things from the standpoint of statistic significance?

A. Right, which is how the FDA looks at it.

When you're doing any study, even if two things are identical, you use the same exact regimen twice, there's always going to be numeric differences that can be very misleading and meaningless. So the FDA is focused on whether statistically significant differences, which they were not between these, as the FDA concluded.

So these were meaningless differences that one could not make any points about, which is why trying to say there's a difference between 8.7 and 8.4 is just scientifically invalid

and misleading.

Q. And, Dr. Yancopoulos, if we go back to the first page of this document, which is PTX 311, the Heier 2012 reference, what journal was this published in?

A. *American Association of Ophthalmology*, known in the field as *Ophthalmology*.

Q. Is that a peer-reviewed journal?

A. It's a peer-reviewed journal.

Q. Ms. Mazzochi asked you some questions about individual reviewer opinions from the *New England Journal of Medicine*.

Are all important innovations published in the *New England Journal of Medicine*?

A. No, they are not.

Q. And apart from the reaction of the *New England Journal of Medicine* reviewers that Ms. Mazzochi asked you about, what was the reaction of clinicians at large when Eylea came onto the market with the approved regimen?

MS. MAZZOCHI: Objection, Your Honor. He's not competent to testify to physicians at large. He can talk about his own experience.

MS. OBERWETTER: Your Honor, it's my last question, and she marched us through eight anonymous reviewers. So I think he's allowed to --

THE COURT: Overruled. Ask the question again. I'm

sorry.

BY MS. OBERWETTER:

Q. Yes. Dr. Yancopoulos, apart from the reaction of those *New England Journal of Medicine* reviewers, what was the reaction of clinicians at large when Eylea came onto the market with the approved regimen?

A. I think the physicians spoke with their actions, just like almost immediately when Lucentis came out, physicians almost completely started switching over to Lucentis from Macugen in the same way, very rapidly with Eylea, Eylea became the preferred drug of choice for the majority of ophthalmologists.

MS. OBERWETTER: Thank you.

At this point I would like to move into evidence the exhibits that we have used with Dr. Yancopoulos, which I am prepared to list if that's the easiest way to do this. I can also reconcile it with your clerk after we go off the record.

THE COURT: In Madam Court Reporter's survival interests, we're going to reconcile those afterwards. But were there any that there's any objections to?

MS. MAZZOCHI: Your Honor, as long as -- let me put it this way: We accept that a lot of these are business records and that sort of thing. I will say, though, again, I just want to ensure that it's not with any prejudice to us to continue to raise this issue that some of these documents

probably shouldn't even be admissible or, at the very least, relied on because they were not part of -- to the extent I think I know where counsel's going to use them for, they were not disclosed, timely disclosed either in the expert report or the discovery responses; so...

THE COURT: That's an issue we'll take up in the posttrial briefing and the rest. Thanks.

It's a bench trial. This Court will receive evidence for the parties' opportunity to create a relatively appropriate record, and then we'll place the appropriate weight, if any, upon the evidence as it comes in and its findings of fact and conclusions of law.

But the transcript will be clear as to what exhibits were referenced. If there are specific objections, we can take those up at another time.

Is there any recross at this point, Counsel?

MS. MAZZOCHI: Two things, Your Honor.

RECROSS-EXAMINATION

BY MS. MAZZOCHI:

Q. First, Dr. Yancopoulos, I'd like to go back to DTX 4070, exhibit page 009. Since your counsel only showed you a portion of the results about optimal timing for injections, let's put the whole thing up.

Did the whole thing -- did the whole set of sentences say, "What is the optimal timing for injections? There

appeared to be a plateau in the amount of reduction of foveal thickening during the first three months of the study when monthly injections of ranibizumab were given" -- then let's add this in -- "with additional benefit achieved by switching to injections every other month."

Is that what the article said?

A. That's what it said.

Q. Let's call up DTX 916.

Can you confirm that this is an email that you were cc'd on dated January -- Saturday, June 9, 2012? And after you got rejected, did you then use your connections to get your manuscript published in *Ophthalmology*?

A. I did not use any connections since I didn't have them with *Ophthalmology*.

Q. But you'd agree that this is at least an email that you were cc'd on in around Saturday, June 9, 2012?

A. Well, it says here, "In full agreement with you, I want to write back and suggest we" --

THE COURT: Slow down, please, Doctor.

THE WITNESS: Well, I'm reading it. I haven't seen this --

THE COURT: Doctor, here's the issue with your reading. Madam Court Reporter can't listen --

THE WITNESS: Sorry.

THE COURT: Doctor, one second, please. Thank you.

Madam Court Reporter can't read it while you're speed-reading it as well. So if you're going to read, that's perfectly fine. I understand it's your answer to the question. I just need you to slow down while you do that to ensure we have an accurate record. Thank you.

BY MS. MAZZOCHI:

Q. Dr. Yancopoulos, I just want to confirm that this is an email you were cc'd on.

A. Right. I'm just saying I'm reading this email, and it says, "I am in full agreement with you. I saw this email this morning and wanted to write back and suggest that we submit to *Ophthalmology*. It is a very fine journal."

MS. MAZZOCHI: Your Honor, we request that DTX 916 be moved into evidence.

THE COURT: Any objection?

MS. OBERWETTER: No objection, Your Honor.

MS. MAZZOCHI: We're done. We're done, Your Honor. Thank you.

THE COURT: Without objection.

Reredirect.

MS. OBERWETTER: None, Your Honor.

THE COURT: Doctor, you may descend the stand, sir. Thank you very much.

I'll leave it to counsel to tidy up the exhibits there.

Is the doctor subject to recall, or is he free to go?

MS. MAZZOCHI: As far as we're concerned, he's done.

THE COURT: All right. We'll proceed then at 9:30 in the morning, subject to counsel squaring up the list of exhibits that were used during the witness's testimony, and we'll see everyone then. Thank you very much.

You can leave whatever you'd like in the courtroom. Nobody will be in here in the interim. But to give everybody advance warning, we do have another criminal matter we need to take up at noon tomorrow or whenever we take a lunch break, just as a planning FYI.

Have a pleasant evening. We'll see you tomorrow.

(Proceedings concluded at 5:46 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 12, 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 12th 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 2

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 13, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

- - -

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

Tuesday Morning Session,

June 13, 2023, 9:30 a.m.

- - -

THE COURT: Convene for day two of trial. Plaintiff may call its next witness.

MS. OBERWETTER: Your Honor, if I may, Ellen Oberwetter for Regeneron. A brief housekeeping matter from yesterday relating to the admission of exhibits used in Dr. Yancopoulos's direct and redirect testimony.

I'm happy to handle this however you would prefer. I can either read the list into the record. We've had an opportunity to make sure our list conforms to what Ms. Kinsey had yesterday so that those are moved into the record as evidence.

THE COURT: Let's go ahead. If you'll read that slowly for Madam Court Reporter's benefit. Go right ahead.

MS. OBERWETTER: I'm happy to do that, Your Honor. PTX 0001, PTX 0003, PTX 3333, DTX 212, PTX 0419.

THE COURT: Is that 19 or 91?

MS. OBERWETTER: My list says 19.

THE COURT: Okay.

MS. OBERWETTER: Your list is correct, Your Honor.

THE COURT: As is Mr. Ruby's.

MS. OBERWETTER: PTX 491, DTX 228, PTX 0311, PTX 0304, PTX 3216, PTX 3187, PTX 3188, PTX 0080, PTX 1028-C,

PTX 1170, PTX 0932.

THE COURT: I've got two others a little further down my list.

MS. OBERWETTER: Yes.

THE COURT: DTX 4070.

MS. OBERWETTER: That was the Nguyen 2006 reference. That's correct, Your Honor.

THE COURT: And PTX 0311?

MS. OBERWETTER: Yes.

THE COURT: That's the Heier article on wet age-related macular degeneration.

MS. OBERWETTER: Yes, Your Honor. That one was further up in my list. That's correct.

THE COURT: Any objection to any of those, Counsel?

MS. MAZZOCHI: No. But, again, as long we -- I know you instructed we are going to be doing the issue of whether they are allowed to use their conception surveys --

THE COURT: Try it again.

MS. MAZZOCHI: Yesterday the Court indicated -- my understanding is that the Court indicated that, to the extent we had an objection as to whether Regeneron can use any of these exhibits in connection with, for example, its conception or reduction practice theories or other theories not disclosed in their interrogatory responses, we will have the opportunity to raise that in posttrial briefing. Thank you.

THE COURT: Subject thereto, all of those are hereby deemed admitted.

(PTX 0001, 0003, 3333, 0419, 491, 0311, 0304, 3216, 3187, 3188, 0080, 1028-C, 1170, 0932, and DTX 212 were admitted.)

(DTX 228 was admitted.)

MS. OBERWETTER: Thank you, Your Honor.

THE COURT: Anything else we need to do before we hear from our next witness from plaintiff's perspective?

MS. OBERWETTER: No, Your Honor.

THE COURT: Defense perspective?

MS. MAZZOCHI: No.

THE COURT: Plaintiff may call its next witness, then.

MS. KAYALI: Your Honor, plaintiffs call Dr. Karl Csaky.

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

MS. KAYALI: With Your Honor's permission, I'll approach to bring a binder to the witness.

THE COURT: Yes, please.

MS. KAYALI: My colleagues have already provided the Court with them.

THE COURT: Understood. Thank you.

MS. KAYALI: I should correct myself. We also have demonstrative slides, which you do not have in front of you.

THE COURT: I do not appear to.

MS. KAYALI: So I will, if I may, provide these to the witness and to Your Honor.

THE COURT: Thank you.

MS. KAYALI: These contain our slides and a handful of exhibit excerpts that you're going to be seeing a lot of.

THE COURT: Understood. Thank you.

Counsel, go right ahead.

MS. KAYALI: Thank you. Good morning, Your Honor. I'm Kathryn Kayali for Regeneron.

THE COURT: Good morning.

MS. KAYALI: It's my privilege to present the direct testimony of Dr. Karl Csaky. We will offer him as an expert in vitreal retinal diseases and their treatment. We're here to talk today about infringement. He will be back same time, same place next week to talk about validity.

THE COURT: Outstanding.

MS. KAYALI: So today is infringement day. So with no further ado.

DIRECT EXAMINATION

BY MS. KAYALI:

Q. Good morning, Dr. Csaky.

A. Good morning.

Q. Before we go any further, let me ask, have you ever testified in court as an expert witness before?

A. I have not. This is my -- as they say in Texas, my first rodeo.

Q. Well, then let's get back to what you do as your day job. What do you do for a living?

A. So I'm a vitreal retinal surgeon.

Q. What is that?

A. I am somebody that takes care of, studies diseases of the retina.

Q. What's your day-to-day? What do you do as a retinal specialist?

A. As a retinal specialist, we are involved in evaluating patients, offering treatments. There's a host of other activities, but in the clinic our primary responsibilities are seeing, diagnosing, and treating patients with various vitreal macular diseases.

Q. Let's talk about those diseases. Are there any diseases you treat that are particularly relevant to this case?

A. Right. In reviewing this case, the diseases that I take care of are things like age-related macular degeneration, diabetic macular edema, and diabetic retinopathy.

Q. And I have a feeling that you and I are going to lapse into acronyms here shortly; so maybe we can clear some of those up.

Wet age-related macular degeneration, do we often call that wet AMD?

A. Correct.
Q. And diabetic retinopathy is often DR?
A. Correct.
Q. And then, finally, diabetic macular edema, is that DME?
A. Correct. We can call it DME.
Q. Is there an umbrella term for those diseases?
A. So it's not uncommon to term these angiogenic eye diseases.
Q. As a retina specialist, do you use Eylea?
A. Yes.
Q. Where do you currently work?
A. So my present position is at the Retina Foundation of the Southwest in Dallas.
Q. What kind of practice is that?
A. So this is a not-for-profit academic research institution. We see patients. I see difficult-to-treat patients. I get referrals that are more difficult. I interact with the community on challenging cases. We do research, trying to push our understanding of what are the limitations of our present treatments, how we can improve care of these patients.
Q. What's your current title at Retina Foundation of the Southwest?
A. So my current title is a mouthful, unfortunately.

It's -- I'm the chief executive officer, chief medical officer. I am the T. Boone Pickens director of the molecular laboratory, as well as the director of the Center for Innovation for Age-Related Macular Degeneration.

Q. And where is your practice located?

A. In Dallas, Texas.

Q. How long have you been there? How long have you been at Retina Foundation of the Southwest?

A. I've been there part-time since 2009, and then sometime in 2018 I transitioned to full-time.

Q. I want to come back to your professional experience in a moment, but let's go back in time and start with your education.

Where did you receive your undergraduate degree?

A. I went to Vanderbilt University.

Q. Where did you head next?

A. I went to the University of Louisville for my medical school and graduate school.

Q. What brought you to Kentucky?

A. Well, I'm from Lexington originally, grew up in Kentucky. And, of course, being in state, it's much cheaper to go to an in-state school; and so I continued my training in Louisville.

Q. After you got your medical degree -- let me ask this: What degree did you get at the University of Louisville?

A. Right. I got a combined what's called an MD-PhD. So I did both a medical degree, and I did some graduate work as well.

Q. Well, then after you received those degrees, your MD-PhD, did you continue your medical education?

A. Correct. I went to Duke University and did an internship in medicine. I then was fortunate to get a Fulbright scholarship and spent a year in Europe in an eye clinic in Germany.

And then I came back, continued some training in retina, and then did my ophthalmology residency at Washington University in St. Louis.

Q. Where in that process did you first start treating patients?

A. So probably -- even as residents, we treat. But probably when I did my fellowship at Hopkins. I went to Johns Hopkins, and I specialized in medical retina. And I started treating patients there more intensely.

Q. Medical retina, is that a distinction you're making between that and other retinal specialties?

A. Right. So in retina, I know somewhat surprising, but, actually, we take retina and we treat it medically, so in the clinic; and we also have surgical approaches for our retinal diseases. So you can get training in both or you can get training primarily in medical retina.

Q. Which one is it of those that you do?
A. I do mostly medical retina.
Q. That's in the clinic?
A. That's in the clinic.
Q. And at some point you found yourself in Washington, DC, right?
A. Correct.
Q. And where were you then?
A. Right. So when I finished my fellowship, I went to the National Institutes of Health and I did some work there. I was also at Georgetown University seeing patients. I also then went from there to the National Eye Institute where I was involved in the clinic, I was involved in clinical research, and also ran a laboratory as well.
Q. Where did you head after DC?
A. I went back to Duke. I was on faculty at Duke University in starting probably sometime around 2005.
Q. At Duke were you treating patients in Durham?
A. I was treating patients in Durham. I was treating patients at the VA hospital in Durham, but I also went to a satellite clinic in Wilson, North Carolina, as well.
Q. What is that? What's a satellite clinic?
A. So satellite clinics are kind of part of a lot of retina practices, and the idea behind satellites are that we go into rural communities; that way the patients don't have to

travel as far. Wilson, for example, is about 80 miles outside of Durham. So we could go to Wilson, and in that way the patients didn't have to travel as far. And so that was a typical clinic that I would go to, let's say, once a week.

Q. So after treating patients in Durham and in Wilson, did you eventually leave Duke?

A. I left Duke in 2009. I then went to Dallas and became a partner at Texas Retina Associates.

Q. What kind of practice is Texas Retina Associates?

A. So Texas Retina Associates is a large private practice retina practice, still one of the largest retina practices in the country. It is a private practice. And we do basically what retina people do. It was very intense clinical kind of work in the clinic.

Q. What were your colleagues like there?

A. So I had a spectrum of colleagues. I had about 16 partners. It's a large practice. And you had a whole variety of individuals. You had people who were a little bit more -- went to meetings; you had other people who just stayed in the clinic and took care of patients, went to the OR. So it's a pretty wide spectrum of individuals that I was exposed to.

Q. And at Texas Retina, again, were you treating patients in Dallas?

A. So I had a clinic -- again, I had a clinic in Dallas, but I also went to a clinic, again, in Paris, Texas. There is

a Paris, Texas, and it's about 120 miles northeast of Dallas. And, again, I went every other week. It's about 120 miles.

And so, again, the idea is a similar idea. Texas is big. And so this was -- we were able to, then, have a big catch basin from patients who lived in that area, and they could drive a shorter period of time to our clinic in Paris rather than having to come all the way to Dallas.

Q. So when you were treating patients at Texas Retina in Dallas, in Paris, about how many patients did you see a day?

A. Right. So during that period of time I was very busy. I mean, clinics in retina practices can vary anywhere from 30, 40, 50 patients a day. In Paris, for example, there could be more because, obviously, we were there only once a week, and so our catch basin was pretty large. So we could be seeing up to 60 or 70 patients in a day at times.

Q. Of those patients you were seeing, up to 60 a day, about how many of them would you say were suffering from diseases like those at issue in this case, AMD, DME, DR?

A. So those are, obviously, the more common diseases we take care of, right? Those are the diseases that people notice vision change, come to our clinics for complaints. And so probably easily over a half to two-thirds of our patients have one of those forms of DM problems.

Q. At some point did you step back from Texas Retina and transition full time to Retina Foundation of the Southwest?

A. Yeah. In 2018 I made the decision that I really wanted to kind of, again, focus on trying to improve some of the aspects of our care that we were providing patients. And so I cut back from the busy clinics and saw patients at the retina foundation in smaller numbers but in a different kind of capacity.

Q. So if you look back on your career, Dr. Csaky, about how long would you say you've been focused on the care of patients with retinal disease?

A. 30 years, 31 years.

Q. Do you attend conferences or give talks relating to AMD, DME, and DR?

A. Yeah. So I've been very fortunate in that I'm part of most of the major what we call societies in retina. There's the Macula Society, the Retina Society, the American Society of Retina Specialists. There's also a more kind of prestigious Society called the American Ophthalmologic Society. So I attend many, many of those meetings.

I'm also involved in lots of committees. So we have very specialized meetings with a small group of individuals that we tend to be -- it's considered the thought leaders. And so we sit around, and we'll have discussions about what our present treatments are for things like diabetic retinopathy, diabetic macular edema. I'm on what's called the classification of AMD committee.

So there's lots of these committees that I end up partaking. And so it's kind of the -- an involvement in the community, and I hear a lot from my fellow colleagues about their thoughts and ideas.

Q. So do you teach other doctors how to treat retinal diseases?

A. Right. I've taught fellows, in fact, two of the fellows still. The Texas Retina Associates are essentially down the hall from me; so we interact a lot. I continue to interact closely with them, and these are fellows that I've trained there. I also train residents.

I also, like I said, go -- I get invited into communities. I was in El Paso three weeks ago or Waco. And I go, and I have discussions with the local docs there, and we -- they get my input or insight, and we talk about how to manage different kinds of cases.

Q. Have you published any papers on retinal diseases?

A. Yes.

Q. Do any of those papers relate to AMD, DME, and DR?

A. Yeah. I would say I published probably over 140. I would say at least a half to more than a half in some capacity related to those diseases.

Q. And then have you participated in the design or evaluation of any clinical trials related to angiogenic eye disorders, retinal diseases?

A. Yes. I've been very fortunate. When I was at the NIH as a government employee, I was able to work closely with the Food and Drug Administration and worked with them on designs and aspects of clinical trials, end points, how to get drugs approved.

I've been involved with lots of clinical trials. I have run clinical trials. I've helped organize clinical trials. And, obviously, right now I'm very much active in clinical trials as well.

Q. Okay. On that note, Dr. Csaky, I'm going to put up what has been marked as DTX 7053.

Dr. Csaky, do you recognize this document?

A. Yes.

Q. What is it?

A. It's my curriculum vitae.

Q. Does your CV provide more detail about your education, your experience, your publications, and your qualifications?

A. Yes.

MS. KAYALI: Your Honor, at this point we offer Dr. Csaky as an expert in ophthalmology with a specialty in angiogenic retinal diseases and their treatment.

THE COURT: Any voir dire or objection to the motion?

MS. LESKO: No objection.

THE COURT: Without objection then, motion granted.

The doctor is so deemed qualified.

MS. KAYALI: Thank you, Your Honor.

BY MS. KAYALI:

Q. Dr. Csaky, we've just taken some time to explain your experience treating AMD, DME, and DR. I want to switch gears and talk about the diseases themselves for a little bit.

Have you assisted in the preparation of a set of demonstratives or slides so that you can illustrate your testimony?

A. Yes, I have.

Q. Let's bring those up.

And do you recognize the slide deck? Is this your slide deck?

A. Yes, I do. Yes.

Q. That's good. So let's take a look at what you're showing here on PDX 4-2.

MS. KAYALI: I recognize this is in two dimensions. So with Your Honor's permission, I'd like to bring up a model of the eye to Dr. Csaky, which, of course, counsel has seen. And this is marked as PDX 4064.

THE COURT: You may. I was wondering what that was.

MS. KAYALI: It does catch the eye. No pun.

THE COURT: I'll note for the record, I know it's only day two, but all this talk about the eyes causing contact lens irritants on the bench. When I start wearing my glasses

later this week and next, you'll know why.

MS. KAYALI: Now I know why. Go right ahead, counsel.

THE WITNESS: Without making too many people nervous, we'll then talk about this is a -- basically a cross-sectional diagram of the eye. Again, the light comes in through the pupil here and then gets focused onto the back of the eye.

The critical structures that I think we need to talk about, of course, obviously, is the retina, and we'll see that better in this kind of three-dimensional model, but it goes all the way to -- almost to the front of the eye here.

And then the critical feature -- it's very interesting in retina that 90 percent of our vision is focused on the macula. So macula is a very dense group of cells, and it translates the light into electricity. But that macula is what gives us the ability to read, drive, see TV, to be able to see people. And so then this electrical signal then gets transmitted to the brain through the optic nerve.

And I'll just -- if I may, Your Honor, just so that you can see, the retina really extends -- so all the way to the front like this.

And the inside of this is the jelly, the vitreous. So this is -- it's a substance, and then, of course, there's this inner limiting membrane that goes all the way and separates the vitreous from the retina.

BY MS. KAYALI:

Q. Well, Dr. Csaky, is this a healthy eye or a diseased eye?

A. So this is a cross section of a healthy eye.

Q. Well, then, let's turn to the next slide, DDX 4-3.

What happens in an eye that has angiogenic eye disorders?

A. So one of the typical aspects of angiogenic eye disorders is -- we heard it yesterday briefly -- there's this protein called vascular endothelial growth factor, called the VEGF for short; and for reasons that we still don't fully understand, these tissues that are affected by these various diseases start to express VEGF in abundance, and so the VEGF levels in the eye go up.

The consequences of VEGF really come down to two major consequences of note. One is the abnormal growth of blood vessels, normal blood vessels in the eye. VEGF actually causes these blood vessels to try to grow abnormally. These are abnormal blood vessels. They can grow on the retina, and we call that diabetic retinopathy in various stages. They can also grow in some cases under the macula as well, so abnormal blood vessel growth.

And then the third kind of aspect of VEGF is the idea that it can cause swelling of the tissue, especially if that swelling occurs in the macula.

So that's -- those are the three aspects that VEGF can cause.

Q. I just want to pause for one second on what I think is an important point today. Is a lot of VEGF in the retina a good thing or a bad thing?

A. That's a bad thing. So there's, as you heard yesterday, very small normal amounts; but as those levels start to go up, then these bad things start to happen inside the eye.

THE COURT: Counsel, if I could interrupt.

We talked a lot about VEGF. What is VEGF made of? Or is that just the condition?

THE WITNESS: No. VEGF is a protein.

THE COURT: It's a protein.

THE WITNESS: It's a protein, and it's made by various cells in the retina. Okay? And what happens is, when the tissue is affected, let's say in diabetes, it's because it's not getting its abnormal glucose; or in macular degeneration -- we don't know why -- there's some inflammatory, and that causes the tissue to respond and start making too much VEGF. So it's a protein that's made by these cells.

THE COURT: So it's a naturally occurring substance inside the eye, but these various conditions, whether it's folks suffering from diabetes, as you mentioned, whatever causes the age-related condition, it's an overproduction of that protein?

THE WITNESS: Absolutely.

THE COURT: Thank you very much. Understood.

Sorry, Counsel. Go ahead.

MS. KAYALI: No. Please.

BY MS. KAYALI:

Q. So you mentioned, I think you just explained, some of the causes of these disorders, the overproduction of VEGF, and then the kinds of harms that can cause to the eye.

Are the results of too much VEGF in the eye the same or different for all the diseases we're going to talk about?

A. So they're different. And so each disease, they will talk about the consequence of that elevated VEGF level is different in terms of what we see in patients' eyes. So they are disease-specific.

Q. Then let's walk through those and start with wet AMD.

What happens to people's eyes in wet AMD specifically?

A. Right. So just as the term is, wet age-related macular degeneration, all of the activity is in the macula, right? And the macula, again, is this critical part of the eye that allows us to see.

And in this macular degeneration, the VEGF levels cause abnormal blood vessels to grow under the retina, and that also then causes bleeding, swelling, in the overlying tissue.

Q. How does wet AMD -- and we're looking now at

PDX 4.005. How does wet AMD affect patients' vision?

A. Again, when that macula is affected, then it can't work as well. When it can't work as well, then one of the symptoms is you just can't focus. So unlike here where you see a nice focused image, someone who has macular degeneration wet, this now becomes a blurry.

Q. Does it get blurry in the center of the peripheral vision?

A. Mostly in the center. Again, this is involving that center -- what we call center vision.

Q. Dr. Csaky, turning to PDX 4006, are there other facts of AMD on vision?

A. Yes. So especially with wet AMD, as these blood vessels grow under the retina, the retina becomes distorted, right? And so the patient then perceives the vision as distortion. So unlike here where there's -- these are nice and straight pillars, here you can see they're wavy. And that's one of the symptoms of macular degeneration -- wet macular degeneration.

Q. Finally, looking at PDX 4.7, is there a third AMD symptom?

A. Yes. And so what happens is, if those blood vessels are allowed to continue to develop, they will start to cause the tissue itself to stop working. When they stop working, then you're left with areas where the cells don't work and you

start to see dark spot in your vision.

Q. How does that affect patients' ability to get around in the world?

A. Yeah. So this is the problem. If you have these dark spot right in the center where you need to drive, see vision, read, see TV, in older people, seeing your grandkids, all of a sudden now you see a big black spot. And so essentially that can be very debilitating.

Q. How common is wet AMD?

A. So it's estimated to be somewhere around a million people. There's other forms of macular degeneration, but this form is close to a million. Of course, as we're living longer, and as you see, it's age-related; so the prevalence is going up.

Q. What happens if this doesn't get treated?

A. So if it doesn't get treated, this dark spot gets darker and in some cases a little bit bigger. And so now you've got a permanent dark spot right in the center. And so that results in legal blindness, which means the only letter you can see on the chart is the big E. The peripheral vision is unaffected; so they can still ambulate. But it's a devastating disease because you're retired, you're ready to go play golf, and you can't see right in the center. So it's a truly debilitating disease.

Q. Well, on that happy note, then, let's turn to the

second of the three diseases we're going to discuss, diabetic retinopathy. Could you explain what happens in the eye with diabetic retinopathy.

A. Correct. So here -- again, we're talking about a different disease. It occurs in a different age population for the most part. These are younger patients who have diabetes.

And what happens here is, again, for reasons unknown, they produce, again, VEGF. And the response is the retina, the normal retinal tissue, the normal retinal blood vessels, become affected. They start forming these little outpouching or microaneurysms. They can bleed. And then eventually, the most devastating, is these little blood vessels again will start to grow on the surface.

They don't do anything, but they're in response to this injury and driven by VEGF. So you now have these blood vessels on the surface of the retina. You can imagine now -- I'll use this model one more time to see it. These will be growing right on the surface all along the surface of the retina like this.

Okay?

Q. So what effect does that have on patients' vision?

A. Well, initially what happens is that these little abnormal blood vessels can bleed. And as they bleed, they bleed into the jelly. Jelly is a jelly. And so these little blood vessels will float around. People will notice kind of

dark spots in their vision initially as one of the early signs that there's already blood vessels that are starting to bleed.

Q. Can patients also get blurry vision with DR?

A. Correct. So in some cases, they can. But for the most part, the devastating thing about diabetic retinopathy is, in some cases, the central vision is not affected. And so people can be walking around thinking everything's fine. Then they'll notice a couple little dark spots and little floating spots in their vision. And they don't make a big deal about it. So it's a little bit of a tricky issue trying to make sure we get good screening on patients, because their center visions may still be okay.

Q. What happens if this doesn't get treated, if DR goes untreated?

A. So this is by far the most devastating disease we have from a blindness perspective because these abnormal blood vessels, they grow on the surface. They start to form scar tissue. That scar tissue contracts. And eventually that retina becomes detached off the back of the eye. And as that retina becomes detached, there essentially is no function of the retina. And in many cases these are patients who will go totally blind, like, they can't see light. Unlike macular degeneration patients, these are by far the most devastating untreated complications we see in the clinic.

Q. How common is that, Dr. Csaky?

A. So, again, diabetic retinopathy is still roughly around, if you look, about a million people. Again, with the growing prevalence of diabetes, we know that it's a growing epidemic, and so the likelihood, especially in areas that have poor treatment and poor service, these prevalences are going to go up.

Q. Well, then, let's turn to the third and final disease we'll be talking about today. That's diabetic macular edema. Could you explain to the Court what happens to a patient's eye when they have DME.

A. Sure. So here, for whatever reason, again, these are kind of unique features of these diseases. In this case, the VEGF causes the tissue in the back of the eye, the macula, to start swelling. So as you start swelling, the tissue gets thickened. And so in this case the normal little capillaries that are there start to become abnormal, as I said, leak fluid, in some cases, leak a little bit of blood as well.

Q. How does DME affect patient vision?

I should say for the record we're on PDX 411.

A. Right. So it's very similar to macular degeneration albeit a little bit slower. So it doesn't progress quite as quickly as macular degeneration. But, again, the same thing happens. Your macula is the -- I always tell -- it's the Malibu real estate of your retina. You got to keep that intact. And in this case of diabetic macular edema, if that's

affected, vision gets blurry. And, again, untreated, those cells become dysfunctional.

Q. How common is DME?

A. Again, we think it's somewhere in the order of one to two million people will have some form of diabetic macular edema in this country.

Q. Dr. Csaky, can AMD, DR, and DME all be treated using Eylea?

A. Yes.

Q. How does Eylea work?

A. So Eylea is -- as you heard partially yesterday, the way it works is essentially it's designed to kind of seek out and bind to this VEGF molecule and wrap around it. So it's designed specifically to seek out this protein of VEGF and bind to it.

Q. And when Eylea binds to VEGF, can VEGF still make bad things happen in the eye?

A. Yeah, no. So once you have this bound Eylea VEGF complex, it inactivates that VEGF already.

Q. How is Eylea administered?

A. So we give, you know, Eylea through an intravitreal injection. So there's an area right here in the front part of the eye where you can place a needle. You don't violate the retina. And you can place a needle through this area right into the jelly portion of the eye.

MS. KAYALI: Your Honor, I'm sorry for what's coming next.

THE COURT: I've been bracing. Go ahead.

MS. KAYALI: Let's pull up PTX 963. We're going to look at page 1. It's not going to be too bad yet, but -- you know. Can we blow up the title and author so it's a little easier to see.

BY MS. KAYALI:

Q. What is PTX 0963, Dr. Csaky?

A. Right. So this is a review article that describes an approach for doing these types of injections inside the vitreous.

Q. And now let's blow up the upper right corner of the document and take a look at the images of intravitreal injections.

Apologies to the squeamish among us.

Dr. Csaky, using these images, can you walk us through the process of performing an intravitreal injection.

A. Right. So there are several steps that we routinely do when we're doing an intravitreal injection. The first is we want to clean the eye; so we have some kind of Betadine that we put on the lids.

The second step is we want to remove the eyelids away from the injection site; so we try to keep the injection site as clean as possible.

Then you'll see here in this we place either a pledget -- there's different ways to do the numbing portion, which, of course, is critical for the patient and to try to numb up this area as much as possible.

And then once that area is numbed, in this case, a little caliper is measured. As I said, there's a little area. It's about 3.5 to 4 millimeters from what we call the limbus or this portion of the eye. You make a little mark. And you know that that's a safe area to put your needle through. And then you push your needle through this numbed area into the eye, quickly inject, and remove.

Q. Dr. Csaky, looking at these images I do feel compelled to ask how do patients feel about the prospect of you sticking a needle in their eye?

THE COURT: That's an outstanding question.

THE WITNESS: I can tell you that, of the thousands of injections I've given, I don't think I've had anybody come in saying please, please, please, I want another injection. It's just not a -- this is not something that is on a number one list of things you want to do in your life. So it's not something that is a pleasant experience. No matter -- as much as I try to ensure that they have no discomfort, it is -- you can well imagine it's a problem.

BY MS. KAYALI:

Q. Do you ever have to help patients prepare to receive

these injections?

A. Oh, yeah. I mean, there are people that I've had to give Valium to beforehand. There are a handful of patients who will demand Valium before they come in for their injections. Even though this is their 20th injection, they -- I can't come in unless I have my Valium. So it's -- I can well imagine that it's not -- I don't think anybody would want to go looking forward to this, for sure.

Q. Well, then, let me ask a different question.

Why all these steps to the process?

A. Well, you have to remember that the eye is -- was not meant to be violated. The idea of putting a needle in somebody's eye is not something that the eye really wants us to do. And of course the inside of the eye is sterile, right? So as you're putting a needle into the eye, you want to be really careful that you don't inadvertently introduce bacteria inside the eye. So that's why it's so critical that we try to clean and prevent that from happening.

Q. And I want to turn back to your slide deck now. I'm looking at PDX 4.13. Actually, let's move ahead to 4.14. Excuse me.

Can you use this slide to explain some of the risks or burdens of intravitreal injections.

A. Right. So we can kind of divide it into two kind of buckets, right? The one bucket is the actual risk for the eye,

right? So of course this is what I just talked about, the risk of introducing a bacteria inside the eye. We call that endophthalmitis --

Q. And --

A. Sorry.

Q. I was just going to ask, Dr. Csaky. What happens if patients have infected eyes?

A. So this is infections inside the eye. That's probably the most devastating complication, bacteria inside the eye. In some cases, we can treat it. But in some cases, if it's a really virulent bacteria, you can end up losing the eye itself.

Q. Okay. What about -- what are some other risks?

A. So, again, the eye doesn't like having a needle stuck in it. And so it sometimes will respond with some inflammation. Sometimes just like in the process of binding the tissue, depending on how you inject, so the eye will cause -- have some nonbacterial inflammatory cells that will come into the eye as well.

THE COURT: I'm with the eye on this. I don't think I care for it either, but go ahead.

MS. KAYALI: You and me both, Your Honor.

BY MS. KAYALI:

Q. I see a third risk there, risk of retinal detachment. That also does not sound good. What is that?

A. So as you go in, you're pulling on the jelly. The jelly -- it's a liquid, but -- it's like a Jell-O. And so when you push in, you kind of tug on it. You can sometimes pull on the retina and cause a retinal detachment.

Q. Yikes. Okay. Well, then, let's turn to the second half of the slide here. Patient anxiety, I think the courtroom well understands. What about patient discomfort?

A. We talked about this, right. This is something that none of us want to do in terms of the patient. And so the patients, as you saw, have a lot of anxiety. And, really, it's a point of concern for them. Obviously, every time they come into the clinic and you have to tell them that they're -- you're going to do an injection, it's something that, no matter how many times I've done this, patients are still anxious about it.

Q. Does it hurt?

A. Again, you know, you try to numb it up as best as we can, but you -- you can just well imagine. It's just not something that you can go oh, yeah, it's no big deal. It's a big deal, right? And there's different approaches to kind of numb it up. You try to do it quickly. But there's still -- there's pressure. And just the thought itself, it's something that's not the most pleasant.

Q. Understood.

I see the last item on your slide is burden of travel

and office visit on patient and caregiver. Could you explain that.

A. Right. So this is something that I think we underestimate at some point, but I think it's one of the most critical features, right? And that is that many of these patients who are coming to see us -- again, they're coming to see us because they don't have good vision. They can't drive, right? Or if they're getting the injection, they can't drive home; so they're constantly needing someone to come with them, right, a caregiver, a family member. And imagine you're doing these on a frequent basis.

And so it really becomes an enormous burden on the patients, on the families. It's something that -- it's really in many ways underappreciated, because there are very few things in medicine that require us to constantly see patients. And in many cases it's for an indefinite period of time. I mean, there are patients I've been seeing for ten years.

And so it's a real problem when we talk about, you know, that burden, the patient, and on their caregivers on getting back. And, obviously, this is not something we can do in the home. We can't do it in the pharmacy. They have to come -- and that's one of the reasons that these satellites are so important.

As you can well imagine, if I live in a small town and I can only -- need to go 20 miles, that's easier. If I

have to come all the way to Clarksburg or Wheeling, it's going to be a much more challenging process for me.

Q. And you say you have to give them for an indefinite period of time. By that do you mean these diseases are long in duration?

A. Right. So it depends. There are some cases where we just -- we can control the disease, but we have to continue to give these injections on a continuous basis.

Q. Let's turn to the next slide. And that's 4.015.

What happens when Eylea is injected into the eye? I'll play the animation for you.

A. Right. So what happens is it's really in some ways quite elegant, right, because we know that this VEGF is the bad actor, right? We want to get its levels to come down, right? So we do this injection. And the VEGF is sitting there looking for VEGF molecules. And they bind them, right? So right away there's some degree of inactivity that occurs following an injection.

Q. And then do the Eylea and the bound VEGF depart the eye?

A. Right. So a portion -- during these initial phases, we can start to slowly reduce the VEGFs. And so they get bound. And then the VEGF and bound Eylea then get transported out of the eye. And so there again we've gotten rid of some of it. We've inactivated some of it. Some of the Eylea stays

around a little bit longer. So we're trying to figure out how to control that VEGF level.

THE COURT: Where do the bound VEGF and Eylea go?

THE WITNESS: We had a big argument about this. So it's interesting. They go --

THE COURT: Sounds like a good time, Doctor.

THE WITNESS: We had some good beers on that too. But, you know, the interesting thing is they go out both through the normal retina and also through what's called -- the normal flow -- the eye makes fluid, and it goes out through the trabecular meshwork. And so it kind of gets out through the iris and out around the pupil and then out of the eye. So there's a normal flow. The jelly, I kind of said, it has a static structure. And it is, but there's liquid that's made that's constantly circulating out of the eye. And that's where that complex goes out.

BY MS. KAYALI:

Q. So when the VEGF gets bound and when it exits the eye -- I'm going to ask this as simply as I can -- does the bad stuff go away?

A. Well, it begins to go away, right? So, again, as we're trying to control the disease, we're trying to control the VEGF levels, right? And so this relationship with reducing the VEGF levels and then getting the tissue to start to kind of quasinormalize is what we're attempting to do with our

treatments.

Q. And so the macular edema, the leaking blood and fluid, the abnormal blood vessel growth, when the bound VEGF departs, some of that resolves. Is that what you're saying?

A. Right. So it will take some time and it depends on the disease. It's not an immediate effect in some cases. As you start to lower the VEGF levels, the tissue will start to try to repair itself to some degree.

Q. Well, then, Doctor, let's talk about the dosing regimen for Eylea. And I'm looking at PDX 4.17. I think we may have covered this, but does one injection of Eylea solve the whole problem here?

A. No. So, again, we're dealing with VEGF in different locations inside the retina. In some cases, in the jelly, we've got a certain amount. And so it's not a one and done kind of process. We know extreme -- lots of experience that you have to again start to think about injecting the Eylea and then repeating it and repeating it, again, first slowly bring those levels of VEGF down, and allow the tissue to repair itself.

Q. Are you familiar, Doctor, with the concept of loading doses?

A. Yes. Yes.

Q. What is a loading dose? And you may want to use the slide to explain.

A. So in the clinic, we think -- a new patient comes into the clinic, right? New patient comes in. I make the diagnosis of whatever these angiogenic disorders. I then think, okay, so I'm going to have to give an initial injection. So that's what we see. And the loading means that we're trying to load up the eye with some Eylea and try to start to change the concentrations of VEGF.

So the idea is that I'm beginning to do the injections. That's my kind of initial loading dose. And then it will have some effect. And that'll be a process of, again, going from what's typically high levels of VEGF. These are patients coming in off the street. They've been walking around for weeks or months, and so I'm trying to now slowly reduce their VEGF levels.

Q. So how frequently do ophthalmologists administer Eylea during the loading dose phase?

A. So it's disease-dependent, right? Each disease has its own level of VEGF and its own ability to repair its tissue. So the amount of loading doses that you would give is disease-specific.

Q. So it sounds like you're saying the number of loading doses is disease-specific. How often do you give loading doses?

A. So we all -- I mean, it's very standard that we give loading doses every four weeks.

Q. And is that what's being shown on PDX 4.19?

A. Correct. So we see at the bottom here that this was -- you know, the first time I saw a patient, I see them, make the diagnosis. I inject, let's say, in this case, Eylea, with a loading dose. And then I tell the patient, okay, let's see what happens. I'm going to have you come back in four weeks.

And at four weeks I'm going to administer another loading dose because I know from experience and from clinical trials that, again, depending on the disease, we're going to need multiple loading doses to bring those levels down and let the tissue start to repair itself.

Q. So is there an initial loading dose and then some secondary loading doses after that?

A. Correct. So the initial is always the first. And then you've got these secondary loading doses that occur afterwards.

Q. And then let's talk about the number of loading doses now. I think you mentioned this.

For age-related macular degeneration, how many loading doses of Eylea do ophthalmologists administer?

A. So we typically give -- we have usually the initial and two secondaries. So we have three loading doses. And part of that is because, as I said, in macular degeneration it's only the macula that's involved. And so the levels of VEGF

tend to be a little bit lower. So we can typically get away with using a fewer number of loading doses to kind of bring down that VEGF level and try the tissue to start to repair itself.

Q. And what about for DME?

A. For DME, it's different. So DME, we know from multiple studies that the levels of VEGF are higher. So you can imagine, if it's higher, I've got to give more to first reduce it, keep it reduced, and let that tissue repair itself.

Q. And that description, that's a 2023 perspective, right?

A. Correct.

Q. So are you familiar -- well, let me ask a better question.

What happens after secondary -- let me try that again.

What happens after the loading dose phase is complete?

A. So the -- after these loading doses, we know from research and also just from observation that these are in general -- and, again, we have to always remember that every patient is different, right? So these are all -- no patient is the same. But, in general, you know, you would say in the average macular degeneration patient, I give three of these doses. I can be pretty comfortable that I'm going to get as

good a response that I can to the tissue repairing itself, right?

However, the Eylea -- and this is critical -- doesn't cure the disease; it's just curing what we would call a symptom, which is VEGF levels. So the patient still has macular degeneration. I tell patients I ain't curing anything; I'm just trying to control the disease. And so the patient is continuing to make VEGF, albeit now at a slower rate because I've controlled it at the beginning.

And so now I can wait eight weeks in some cases and say, okay, let's make sure that that repair that I -- I've achieved kind of can be maintained so that I can keep -- not only get your vision a little bit better in some cases but keep you at that stable level.

Q. And I think I heard you say you're going to maintain their vision. Do you call these maintenance doses?

A. Correct. You try to maintain the anatomy and the vision.

Q. And we're going to talk about this in some more detail in a moment, but how frequently does Eylea's label recommend that doctors administer maintenance doses?

A. Right. So the label recommends in both conditions that maintenance doses be given every eight weeks.

Q. Let me ask a different question, then. Why do you switch? Why do you transition from four weeks to eight weeks

instead of just going on administering every month?

A. Well, there's two reasons. Initially, when we were -- at the very beginning of anti-VEGF therapies, right, the thinking was that maybe we just give it every week -- I mean, every month forever, right? And, in fact, that was the original trials and those were the original recommendations of ranibizumab was to give every-four-week injections almost indefinitely.

And, of course, that is unattainable. Patients just can't come into the clinic. And so the thinking was that is there an alternative to try to reduce the number of injections and still be able to keep the tissue as healthy as possible, not let the VEGF levels get to a critical point where we have to start over from square zero? So that's really the key here is to find that interval. And it turned out that eight-week interval was kind of a sweet spot where we could keep the vision stable, the tissue relatively under good control, in these eight-week blocks.

Q. Let's take a look at Eylea's label.

Can we pull up PTX 917.

And, Dr. Csaky, do you recognize this document?

A. Yes.

Q. Is this the -- what is it?

A. This is the prescribing information and label for Eylea.

Q. And do you see in the bottom right-hand corner, what's the date on this label?

A. The date is August 2022.

Q. So in the August 2022 version -- let me withdraw that.

Let's take a look at what Eylea's label recommends for the treatment of AMD, DME, and DR, please. And I'm going to pull up -- this is still on page 1 of Exhibit 917.

Let's take AMD first, just to do one at a time. How does Eylea's label recommend that doctors administer Eylea for the treatment of AMD?

A. Right. So under "Dosage and Administration" it states that for neovascular AMD, the recommended dose for Eylea is 2 milligrams to be administered by these intravitreal injections every four weeks, or approximately 28 days, for the first three months; so three loading doses. And then we can switch to 2 milligrams with this intravitreal injection once every eight weeks. So that's for neovascular wet AMD.

Q. And then what about for DME and DR? How does Eylea's label recommend that doctors administer Eylea?

A. Right. So the label here is a little different. Again, we're still administering 2 milligrams or administering those 2 milligrams every four weeks, but in this case we're doing five injections, not three; and then it's recommended that you can then switch to an every-eight-week dosing

interval.

Q. So what's the difference between how Eylea's label recommends doctors administer Eylea for AMD versus for DME and DR?

A. Right. So the big difference, as we showed in the little cartoons up there, is the idea that you need more loading doses to reduce that VEGF level in diabetic retinopathy and diabetic macular edema. So you need to give five monthly injections at the beginning, again, to get that tissue resolved, try to get some repair. And that's the big difference -- three with macular degeneration; five with DR and diabetic macular edema.

Q. We're going to talk about this in a little more detail in very short order, but let me just ask at a high level. Do some doctors follow the instructions in Eylea's label for the treatment of AMD, DME, and DR?

A. Yes.

Q. How do you know?

A. Well, I mean, for one, I've done this, and this is not -- this is evidence-based approach and it's a recommended approach so we know that it works. I've also, again, in talking with my colleagues and discussing various approaches, this is an approach that clearly people use in some patients, in some conditions, both in diabetic macular edema, diabetic retinopathy, and for wet AMD.

Q. Let me ask a different question.

Do some doctors ever change the frequency of the maintenance doses in a way other than the label suggests?

A. Absolutely.

Q. And in what way?

A. So, again, over time we have still -- we're still kind of struggling with figuring out this idea of when you're getting to these maintenance phases, right, how best to control the tissue, control the VEGF, and trying to prevent or trying to keep -- having to keep doing injections.

And so there's been various approaches that people have used and especially in the maintenance phases to try to alter those intervals and see what is the best interval, meaning how far can you go or what can you change to keep the tissue as healthy as possible before it kind of regresses and yet, as you saw, not having to have the patients come back as frequently.

Q. We heard yesterday about prn, or pro re nata, dosing. Is that one option for maintenance phase?

A. Correct, that's one option.

Q. What does that mean?

A. So prn was really one of the first approaches that my good friend Phil Rosenfeld worked on, and the thinking was that we had a machine called OCT, optimal coherence tomography, and you could see if the tissue was swelling.

So this was especially true for wet AMD initially. And the idea was that, as these blood vessels would start to become active, you could start to see swelling of the tissue. And so you could use this OCT in the vision to say this patient needs an injection. Right?

So prn would mean having patients come back, you look at them, and then decide do I need to do an injection? I don't see any of these signs of activities. No. Come back.

So we would have patients come back, not every time you would inject, but you would see them frequently because you would have to see them frequently because that was the time when you would make the determination if they needed treatment or not.

Q. Let me make sure I understand. For prn a patient comes into the office, but you don't know yet whether you're going to inject them?

A. Correct.

Q. And then you make an assessment, and you, on the basis of that assessment, decide whether to inject them?

A. Correct. That's the typical beginning stages of a prn approach.

Q. Do people use that approach anymore?

A. You know, that fell out of favor for several reasons. One, is it really -- well, in some cases cut down the number of injections. People still had to come into the clinic. So

while the injections are terrible, no doubt, coming into the clinic is also equally as challenging. And so it became challenging to figure out do I want to let Ms. Smith have to come in every four weeks or every five weeks? And so that was a problem.

The other problem was it was -- the treatment paradigm was driven by reactivation of the disease. So unlike a normal maintenance that we just talked about where we try to keep everything at bay, here we're allowing the tissue to kind of -- the disease to kind of come back, then we inject, and then we go forward.

So it kind of fell out of favor. You know, there's some people who do use it in some circumstances, but for the most part, at least in wet AMD, the majority of my colleagues don't use this type of approach.

Q. And so notwithstanding the fact that some doctors use prn, and it sound likes some doctors extend the maintenance dose phasing beyond eight weeks, why do some doctors use Eylea on the fixed-dosing regimen the label prescribes?

A. Well, I think -- there are certain advantages to having a fixed dosing. Again, it's -- it depends. It's very -- one of the things that I think is important to understand is that all of our approaches are very disease-specific, patient-specific, location-specific. You know, it's a negotiation in many cases between the patient,

their families, and the disease, right?

A good example is you have to remember that wet AMD typically will affect both eyes, right? So if a patient comes in, the first eye is affected and -- but the second eye still sees well, my approach for the first eye may be one that I want to give that patient a little bit more kind of regularity. I don't want them to come back and forth and come back and forth. So I might tell that patient, Look, let's just plan out, here's the strategy for this eye. We're going to give you this fixed-dosing schedule; we're going to give you these three -- in the case of wet AMD three loading doses; and then I'm going to see you every two months going forward.

So it's really kind of -- there's scenarios in which that kind of fixed-dosing approach has some benefits, again, very location-specific, patient-specific, disease-specific, eye-specific.

So there is -- and, of course, the other option, the other idea is that there's some of my colleagues who really want to be evidence-driven, and clearly they are -- the evidence around can you get the best vision for patients using this type of approach? There is evidence to suggest that's the case.

Q. When you say there's evidence to suggest that this type of approach gives the best vision, are you talking about the fixed-dosing regimen of the label?

A. Correct.

Q. Are there other drugs, drugs other than Eylea that can be used to treat AMD, DME, and DR?

A. Absolutely.

Q. Then why do doctors choose to use Eylea?

A. Well, I mean, again, these are all patient-specific, disease-specific, situation-specific. By far the most common drug we use now is Avastin. And the real reason we use Avastin is cost, right? Avastin is roughly about $150; injection fees, depending on the carrier, $75. So it's clearly a very cheap alternative for treating patients. And in most cases it's effective.

Now, the reason, for example, personally I choose in some cases Eylea is because there has been evidence, for example, diabetes, where in certain types of patients the outcomes with Eylea are better. A little bit better vision, a little bit better response. And there is a sense within the community -- and I've sat on many committees where, when we think about it from a community perspective, we all kind of believe that Eylea still is the best anti-VEGF agent out there.

Q. Dr. Csaky, let's shift gears slightly. What is Yesafili?

A. So my understanding is Yesafili is a biosimilar for Eylea.

Q. Do you know whether Yesafili has been approved yet by

the FDA?

A. I've been informed that it has not been approved.

Q. So thinking back to the time you wrote your opening report in this case, what company was seeking approval for Yesafili?

A. That was Mylan.

Q. Are you aware that Mylan has now sold its biosimilar business to an India company called Biocon and that they have now joined the case?

A. Yes. I was informed that you-all -- you-all informed me that Mylan has sold and now Biocon will be marketing Yesafili.

Q. So do you understand that, if anyone sells Yesafili, it will be Mylan's successor in interest, Biocon?

A. Yes, that's what I've been told.

Q. In the course of forming your opinions regarding infringement in this case, did you review proposed labeling for Yesafili?

A. I did.

Q. Let's put up PTX 3097.

Dr. Csaky, is this the version of label you relied on in forming your opinions as set forth in your reports?

A. It is.

Q. How can you tell?

A. Well, the date, the date, again, is August 2022.

Q. And if we flip to the last page of the label -- that's page 26 -- is this a Mylan label or a Biocon one?

A. Clearly it says Mylan.

Q. In the last few days have you had an opportunity to review a new label from Biocon?

A. I have.

Q. Let's put that up. That's PTX 3338.

Is this the Biocon label you reviewed?

A. Yes. This appears to be, based off the word Biocon and the date, that this is the Biocon label.

Q. And so if we turn to the last page, can you see for sure whose label this is?

A. Yes. It says Biocon Biologics.

Q. Let's put the label you analyzed in your report on the left side of the screen. That's PTX 3097. And let's put the label that we just looked at, PTX 3338, Biocon label on the right side. And now can we pull out the dosing instructions for AMD, DME, and DR.

Dr. Csaky, based on your review, is there any difference between how the Mylan label you relied on in your report recommends that doctors use AMD, DME -- excuse me. Is there any difference between the dosing recommendations in the Mylan label you relied on as to how doctors should use Yesafili to treat AMD, DME, and DR versus how the new Biocon label recommends that doctors should use Yesafili to treat AMD, DME,

and DR?

A. No, I didn't see any difference.

Q. Okay. Because you used the Mylan label when you formed your opinions for purposes of the report, we're going to proceed with that copy during your testimony, but I just want to be clear. Is there any difference between the Mylan label in your report and the new Biocon label that's at all relevant to your infringement analysis?

A. Not that I could find.

Q. Let's bring back up the demonstratives and take a look at PDX 425. Sorry. If we could go -- I apologize. Let's go back two slides to PDX 23.

Dr. Csaky, do you understand that Regeneron is asserting Claims 6 and 25 of the '572 patent and Claims 11 and 19 of the '601 patent at this trial?

A. Yes, that's what I've been told.

Q. Okay. And will you understand if I call those the asserted treatment claims?

A. Yes.

Q. In the course of performing your analysis in this case, were you asked to determine whether Mylan, or now Biocon, will induce infringement of each of the asserted treatment claims if Mylan or Biocon markets Yesafili?

A. Yes.

Q. We're about to walk through the bases for your

opinions in some rather painstaking detail, but let's start with the bottom line first.

In your opinion, if Mylan or its successor Biocon markets Yesafili, will Mylan or Biocon induce infringement of the asserted treatment claims?

A. Yes. My opinion was yes.

Q. Let's dig in. We're about to spend a lot of time talking about the proposed labeling for Yesafili. We've already looked at the Eylea label in some detail. I'd like to bring up Mylan's label for Yesafili and compare it to Eylea's label from Regeneron.

Can we bring up PTX 917 on the left and PTX 3097 on the right.

Dr. Csaky, on the left you've got the Eylea label, and on the right you've got the Mylan/Biocon label.

Do you understand that?

A. Yes.

Q. Is there any difference between how Regeneron recommends that doctors use Eylea to treat AMD, DME, and DR as compared with how the proposed labeling for Yesafili recommends that doctors use Yesafili to treat AMD, DME, and DR?

A. I did not see any difference.

Q. So we're going to come back to various portions of this slide once or twice throughout this examination, but I wanted to set the stage first.

So let's just dig in. Let's jump to Claim 6 of the '572 patent. If we could put PTX 3 up on the screen.

Dr. Csaky, do you recognize this document?

A. Yes.

Q. What is it?

A. It is a U.S. patent, for abbreviation, '572.

Q. And have you reviewed the '572 patent in total, in full, over the course of your work on this case?

A. I have.

Q. You've read the whole thing?

A. Yes.

Q. I want to focus on just one part of it for today. Let's turn to Claim 6. And this is on page 25 of the -- of Exhibit PTX 3.

What does Claim 6 require?

A. So Claim 6 basically, my understanding, requires two things. It requires that aflibercept be formulated as an isotonic solution and that it is -- it's, what I was taught, is a dependent claim, and it depends on Claim Number 3.

Q. And so because it's a dependent claim, do you understand that that means it incorporates all the limitations of some claims that come before it?

A. Yes.

Q. Let's pull those claims up on the screen. That's the first two claims of the '572 patent.

We're still looking at page 25 of PTX 3, and you see on the screen Claims 1, 2, 3, and 6. And I understand you said Claim 6, shown in purple at the bottom, references Claim 3.

Do you see that Claim 3 itself references Claim 2 which references Claim 1?

A. Yes.

Q. And do you understand that to mean that Claim 6, in fact, incorporates all the limitations of Claims 1, 2, 3, and 6?

A. Yes.

Q. Let's add your slide deck back up to the screen, and I think we're looking at PDX 424.

On PDX 424 have you tried to compile all the limitations of those claims into one list?

A. Right. I tried to redo it so it's rewritten in an independent form.

Q. Is it okay if I refer to language on PDX 24 as Claim 6 or Claim 6 independent form? Will you understand that this is what I'm talking about?

A. Yes.

Q. Let's take down the patent and just look at the claim for a second. And then I want to take a moment to explain to the Court the questions you're going to try and answer today in your testimony with respect to infringement. So if we progress to Slide 25. Let's turn to the first question.

What's the first question your testimony will answer today?

A. So in my process I was asked to -- I asked myself the first question, which is does Mylan, in this case Biocon's label encourage, recommend, or promote doctors to perform methods that infringe?

Q. And we're going to talk about that question now in the context of Claim 6 of the '572 patent.

So let's turn to PDX 426.

Is this the same language you had on the colorful slide before but now just in a checklist?

A. Yes.

Q. Before we get going, I noticed that one of the items in the checklist is crossed out. Could you explain why that is?

A. Well, I was informed that the Court had decided that that claim was nonlimiting and so could not be included in my analysis.

Q. So are you going to present any testimony about infringement of that particular limitation today?

A. No.

Q. Well, then, let's go back to the top. What is the first limitation you analyzed in order to attempt to determine whether Mylan or Biocon's label encourages, recommends, or promotes infringement?

A. The first limitation was the method of treating angiogenic eye disorder in a patient in need thereof.

Q. Let's add the Mylan Biocon label to the screen. That's PTX 3097. We're looking at the first page.

Dr. Csaky, does Mylan or Biocon's label recommend that doctors use Yesafili to perform a method of treating an angiogenic eye disorder in a patient in need thereof?

A. Yes.

Q. Where does it do that?

A. So it says specifically that Yesafili, the VEGF inhibitor, is indicated for the treatment of patients with these diseases. I'm not going to name them all, but all of these diseases are angiogenic eye disorders.

Q. And you say "all of these diseases." Are you referring to neovascular wet AMD, macular edema following retinal vein occlusion, diabetic macular edema, and diabetic retinopathy? Are each of those angiogenic eye disorders?

A. Yes.

Q. And does Yesafili's proposed labeling recommend doctors use Yesafili to treat each of those diseases?

A. Yes.

Q. Which of those four diseases are you going to be focusing your testimony on today?

A. So three of these is where I'll be really focusing: neovascular wet AMD, macular edema -- I mean, diabetic