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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DR. REDDY'S LABORATORIES S.A. and
DR. REDDY'S LABORATORIES, INC.,
Petitioner,

v.

EYE THERAPIES, LLC,
Patent Owner

IPR2024-00467 (Patent 11,833,245 B2)
IPR2024-00563 (Patent 11,596,600 B2)

Record of Oral Hearing
Held: May 13, 2025

Before JOHN G. NEW, ZHENYU YANG, and RYAN H. FLAX,
Administrative Patent Judges.

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The above-entitled matter came on for hearing on May 13, 2025, commencing at 2:00 p.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia.

P R O C E E D I N G S

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JUDGE YANG: Good afternoon. This is a consolidated hearing for IPR2024-00467 and -563. I am Judge Yang. Joining me here are Judge Flax and Judge New.

Now, Counsel, please introduce yourselves. Let's start with Petitioner, please.

MR. FREDERICKSON: Good afternoon, Your Honors. Robert Frederickson on behalf of Petitioners, the Dr. Reddy's Laboratories entities.

MS. CIPRIANO: Linnea Cipriano, on behalf of Petitioners.

JUDGE YANG: Thank you, welcome.

MR. DINER: Good afternoon, Your Honor. Bryan Diner on behalf of Patent Owner, Eye Therapies. And I'll introduce Christina Yang as counsel, as well, and David Weingarten.

JUDGE YANG: Thank you, and welcome, everyone. As we said in the trial order, each party has 60 minutes to present your argument, starting with Petitioner, and Patent Owner will respond. And both parties may, if you wish, to reserve time for rebuttal, no more than 20 minutes.

This hearing is open to the public. Can I just see if there is anyone from the public here? No. So it's all parties.

I just wanted to remind the parties that we see there are motions to seal, so if you see somebody you don't recognize, don't say anything you don't want others to hear.

The court reporter will provide a transcript of the hearing as the official record. Just so that the transcript is useful later, please identify the

record, so when we read it, we know what you are talking about.

Because this is a consolidated hearing, if there is any issue that's specific to only one case, please identify it for us.

A reminder, no new evidence or arguments. And if you think the other side is presenting one and you want to object, hold until it's your time. In other words, don't interrupt. If it's truly new, we will not consider it later when we write the decisions.

Any questions?

MR. DINER: No, Your Honor.

JUDGE YANG: All right, Petitioner, would you like to reserve any time for rebuttal?

MR. FREDERICKSON: Yes, Your Honor, 20 minutes.

JUDGE YANG: Twenty minutes? All right, whenever you're ready.

MR. FREDERICKSON: And the demonstratives, are they able to be published?

JUDGE FLAX: We also have them in front of us.

MR. FREDERICKSON: All right, terrific. Well, I'll get started, because my introduction doesn't require any illustrations. My name is Robert Frederickson, on behalf of the Petitioners. We are here today, as Your Honor indicated, on a consolidated hearing regarding two patents that we refer to as the '245 and the '600 Patents. The two patents share specification and there's near complete overlap between the claims. The instituted grounds in both IPRs are identical and rely on the same prior art.

Now, the two patents at issue in this proceeding are follow-on patents to the '742 Patent, which the Board has previously issued a final

written decision following a full IPR proceeding that is currently pending on appeal. Now, coincidentally, the argument on that appeal was last week. We have not received a decision from the Federal Circuit yet, and so although we put some slides in that talk about the issue of collateral estoppel, I do not intend to get into the legal issues of collateral estoppel today, because we don't have that final decision.

But, nevertheless, that prior decision does loom large in this proceeding, because the arguments in that IPR, the prior art that was considered, the arguments by both sides, were identical, and the Board issued several factual findings that we think are material to the issues that are at issue in this proceeding.

JUDGE YANG: Yes, the prior art references are identical, but the claims are -- there are quite some differences, right?

MR. FREDERICKSON: There are some differences between the claims, and we do intend to talk about those. There was some narrowing that was done as part of the prosecution of the '245 and '600 Patent claims, and that's actually quite significant, Your Honor, because of the timing and the context around when those amendments were made. Both the '245 and the '600 Patent were filed as patent applications nearly 13 years after that '742 Patent application was filed, and all of these share the same specification. And what we'll submit is that the amendments that were made to the patent claims, those narrowing amendments, they were done with the benefit of hindsight, knowing both the prior art and the arguments that were being advanced in the '742 Patent.

Now, there's nothing wrong with that, in and of itself. But what we hope to go over, over the course of today and in our papers, which we've

already gone over, is a lot of the arguments that Patent Owner has advanced are divorced from the underlying knowledge of a person of ordinary skill in the art, what the specification actually teaches about what this invention actually is. And so we think that context is actually quite important.

Now, I'll go to Slide 3, which is a bit of a road map of what we view to be the key disputed issues. Like I said, we'll skip over the issue of collateral estoppel as a legal matter, and my colleague, Ms. Cipriano, will start with one of the claim construction differences that applies only to the '245 Patent, and specifically Claim 1 of the '245 Patent. After that discussion, I'll return and talk about the key obviousness arguments, which we think the fundamental question in these IPRs is whether a person of ordinary skill in the art would have been motivated to use brimonidine alone in low concentrations for the purposes of reducing eye redness, and whether there was a reasonable expectation of success to do so.

Now, even though the prior art on which Petitioner relies expressly discloses the use of brimonidine in low concentrations for purposes of achieving vasoconstriction, the mechanism of action of redness reduction, or just outright redness reduction. Patent Owner has relied very heavily on three labels from three different Alphagan products, and we see that as being one of their central arguments, which we'll address later on today. We'll also talk about this concept of dosing versus concentration, which makes a little bit, gets a little bit of air time in Patent Owner's sur-reply.

And then, finally, the other issues, number four and five, talk about two other limitations that were not at issue at the '742: the use of a particular common preservative, benzalkonium chloride, and the concept of this efficacy limitation that was added to the '245 claim. So we'll address both of

those. Those are two differences, Your Honor, that we do intend to address.

And then, finally, we'll talk a little bit about secondary considerations and the objective indicia of non-obviousness, which, again, we think overlaps quite substantially with what was at issue in the '742.

So, with that, I'll turn it over to my colleague, Ms. Cipriano, to talk about the claim construction issue for Claim 1 in the '245 Patent.

MS. CIPRIANO: Good afternoon. Linnea Cipriano for Petitioners. As Mr. Frederickson mentioned, I will be addressing Patent Owner's claim construction arguments. And to set the stage here, the claim construction argument at issue today, as Mr. Frederickson indicated, relates only to one of the challenged patents, and that's the '245 Patent.

JUDGE NEW: Ms. Cipriano, excuse me for interrupting. Could you please identify for the record the demonstrative you're referring to, by slide number, just for the record?

MS. CIPRIANO: Absolutely.

JUDGE NEW: Thank you.

MS. CIPRIANO: I turned to Slide 8, and I will get to that in just a moment, the specifics. So, the claim construction argument only relates to the '245, and within the '245, only Claim 1 and its dependents.

So, on this slide, I summarized the key disputes between the parties, as we see them. And Patent Owner has argued that Claim 1 of the '245 is limited to administration of only a single drop of a brimonidine composition, where that administration is the only step in the method.

Patent Owner's construction, however, is just another example of litigation driven positions, that to bolster the challenged claims, rather than any indication of the invention that the patents actually describe and claim.

As a result, Patent Owner's proposed construction suffers from several flaws. It's not in line with the plain meaning of the claim, it's unsupported by the specification and the prosecution history, and it leads to inconsistent application of the claims toward the alleged commercial embodiment, versus the prior art. And I'll go through each of these in turn.

So let's start where all claim construction analysis should begin, and that's the language of the claims. I put the language of Claim 1 of the '245 Patent on Slide 9 of the demonstratives. Claim 1 of the '245 Patent, for issues relevant to this dispute, Claim 1 reads, a method for reducing eye redness in a human subject having ocular hyperemia, consisting of topically administering to an eye of said human in need of said reduction of eye redness a composition in the form of an ocular drop. And then it continues, consisting of 0.025 percent weight by volume brimonidine.

The parties agree that the claim is limited to a single step of topically administering brimonidine. The parties also agree that the composition can only include brimonidine at the claimed concentration, and no other active ingredients. The dispute here is whether the phrase 'a composition in the form of an ocular drop' limits the claimed method to administering a single drop, or whether it can include more than one drop.

Now, the claimed meaning of the term 'a composition in the form of an ocular drop' is that the composition is formulated as an eye drop, as opposed to other dosage forms that are identified in the specification. And that is that the brimonidine composition is provided to the patient as a bottle of eye drops.

Now, this is common parlance. If you wanted to describe how you present a composition to a patient in plain English, you'd say that it's in the

form of a tablet, in the form of a syrup. Taking this particular claim language --

JUDGE FLAX: So, let's say it was in the form of a tablet, as opposed to an ocular drop.

MS. CIPRIANO: Yes.

JUDGE FLAX: And the claim said administer a tablet. It is sort of saying administer an ocular drop here. Why would that not be one tablet?

MS. CIPRIANO: Under the ordinary meaning of 'a' in a patent claim, as I'm sure you're aware, is one or more. There are distinct situations where claim language of an 'a' is limited to a specific one, and I'll go through some of the case law here. Let's say all of the prosecution history was the same, was just talking about a tablet, where they narrowed --

JUDGE FLAX: For those cases where 'a' might mean more than one thing, are those consisting of claims, or are they comprising claims?

MS. CIPRIANO: Where it was limited to one?

JUDGE FLAX: Right.

MS. CIPRIANO: They were consisting of claims.

JUDGE FLAX: So in a consisting of transitional phrase type claim, if it says a thing, it means one thing, but if it says comprising a thing, then it might be more than one of the 'a' things?

MS. CIPRIANO: I think --

JUDGE FLAX: Is that confusing, the way I'm saying that?

MS. CIPRIANO: No, I think I understand you. I would agree that if the claim said that the method was consisting of administering 'a' tablet, and all of the specification and prosecution history supported that construction, then it would definitely be one tablet. Here, that's not what this

claim says. This claim says consisting of administering to a human in need a composition in the form of an ocular drop.

So, here, even if it said consisting of topically administering a composition in the form of a tablet, you'd still need to look at the specification and prosecution history to determine whether that truly means one tablet or -- limited to only one tablet, or if it could mean one or more tablets.

And I'll go into the case law that supports that in just a moment, but I just wanted to make one last point on the plain English of the language here. So if the Patentee in this case wanted to claim, for example, an ocular ointment, the claim would read, consisting of topically administering to an eye of said human in need of said reduction of eye redness, a composition in the form of an ocular ointment, there would be no question that the ocular ointment would refer to the formulation, and not any particular amount of that composition. And the same is true here.

This is also evidenced by the way Dr. Galanis, Petitioner's expert, uses this term in his opening declaration, and how Judge Kirsch used the term in his PI decision, both of which were submitted in these proceedings before Patent Owner ever presented its strained, narrow interpretation of this phrase.

JUDGE YANG: Talking about experts, Exhibit 1014, which is the opening declaration from your expert, paragraph 54 said the two consisting phrases together limit the method to the single step of topically administering an ocular drop that contains brimonidine as the sole active ingredient in the ocular drop. Does that not mean a single drop?

MS. CIPRIANO: Dr. Galanis, if you look at his reply declaration,

I don't have the exhibit number handy, but I can get that for you. In his reply declaration he clarified that. His opening declaration was submitted before this issue was ever brought to light. Patent Owner didn't take this claim construction position until much later in the process.

JUDGE YANG: Because we asked for it in the DI.

MS. CIPRIANO: Well, yeah, and they did take this position in the litigation as well, but after all of these papers went in and after the preliminary injunction hearing in New Jersey. So Dr. Galanis explains that he was using that in the common parlance terms, that 'an eye drop,' you can buy a bottle of an eye drop, and that's not just a single drop, you're buying a bottle of 20 milliliters, or however much the bottle is. The bottle is the eye drop, but a single drop is a much different concept than buying an eye drop.

Now, Patent Owner, getting to the case law and the basis for Patent Owner's claim, Patent Owner seeks a narrow construction of the claim based on the combination of the consisting of, in the claim, with the word an, as we've been discussing. And for this argument, Patent Owner relies heavily on the Federal Circuit's decision in Norian. But Norian does not stand for the general proposition that the transition phrase consisting of limits all 'a' or 'an' in a claim to mean only one. Rather, the Federal Circuit in Norian confirmed that the claim must be analyzed in the context of the claim language, the specification, and the prosecution history.

So I've put some of the information from Norian on Slide 10. And on the left-hand side, I have put the claim that was at issue and the terms that were at issue and discussed in the decision in red.

So there, the dispute was whether the term, a sodium phosphate, on the lower left-hand side of the slide, was limited to a single type of sodium

phosphate, or could include multiple types of sodium phosphate. And the Court construed the claim to be limited to a single type, based in large part on two factors.

First, the specification only included examples that used a single type of sodium phosphate. There was no disclosure whatsoever of using multiple types of sodium phosphate in a single solution. Second, the Court found that the Patentee explicitly surrendered a broader interpretation of the claims.

And I'll note that there were two instances in the prosecution history that the Court noted, but I'll note particularly the comments that were made in an amendment. So when the Applicant in Norian amended the claims to replace a sodium phosphate solution with the words a solution consisting of water and a sodium phosphate, the language that appeared in the final claim, Applicant told the Examiner in its comments that the amendment limited the claimed kit to one in which the solution is made of water and a single solute, where the solute is either a sodium phosphate or a sodium carbonate.

So the Court in Norian did not just base its narrow construction on the consisting of language and the word 'a' in here. Rather, the Court in Norian looked at the entire prosecution history, the entire intrinsic record, as a court is supposed to do in any claim construction analysis and found that there was a basis for the narrow construction in that case. Here, however, neither the specification nor the prosecution history supports such a narrow reading of the claims. So I'll quickly go through a couple examples in the specification.

In the specification, ocular drop appears in two contexts. I've put

the first on the top of Slide 11, and that is instances where the specification describes embodiments and indicates that the embodiments are formulated as an ocular drop. Here, it's pretty evident that they're not formulating an individual drop of a solution; they're formulating a batch, a bigger solution that they're going to individually administer as drops, but they're calling it an ocular drop. The other way that an ocular drop is used in this specification is talking about the types of compositions, and I've put that in the bottom right-hand corner of Slide 11, and it states, the topical compositions include, but are not limited to, ocular drops, ocular ointments, gels, and creams. So, again, talking about this as the formulation.

JUDGE YANG: I have a question. There is this doctrine of claim differentiation, and we have two independent claims in the patent here. So, I understand Claim 8 has the comprising language, and I believe Patent Owner freely admits that there the claim is not limited to a single drop. So other than this single drop or multiple drops, in terms of scope, is there any other difference between these two claims?

MS. CIPRIANO: I believe so, Your Honor. If you look at the language of Claim 8, it reads, so we're on the same page, a method of reducing eye redness in a human subject having ocular hyperemia comprising topically administering to an eye of said human in need of said reduction of eye redness, 0.025 weight by volume brimonidine as the sole redness reducing active ingredient.

Here, that leaves open the ability to have other active ingredients as long as they're not redness reducing. So, for example, the combination of brimonidine and an allergy medicine or some other eye drop that is administered in combination with brimonidine.

Looking at the rest of the specification, the examples similarly lack any indication that the number of drops matter to the invention. Example 1, no mention of the number of drops. Example two explicitly states that one or two drops were used. Example four and five refer to the doses but don't specify. It doesn't seem like it matters how many drops are administered in these experiments. The only place in the specification where it expressly states that one drop, that a single drop was used, is in Figure 5C, there's a description of Figure 5C in the specification, and I've put some of this information on Slide 12.

The explanation of Figure 5C states that an additional drop of brimonidine was given to reverse the hyperemia observed after use of Visine, the product Visine. Patent Owner relies on this figure, there's been some debate in the papers about what this figure actually means, but we advance that the rest of this figure is really riddled with inconsistences. It does not allow us to draw a lot of conclusions about whether the number of drops is actually important to this invention.

So the Patent Owner in its sur-reply points to the annotations in Figure 5 that refer to brimonidine 0.012 percent x1, and that appears in three places, and Patent Owner's position as we understand it is that that should mean to a person reading the patent that only one drop of brimonidine was used in this experiment. But these annotations really don't give the clarity that Patent Owner suggests. So as I said, that annotation appears in three places on the figure, one near the top, under the right-hand side of Figure 5A, and then again between Figures 5B and 5C on both sides.

Now, Patent Owner asked the Board to ignore the other annotations and descriptions of this figure and assume that this brimonidine

annotation of the figure controls. But such an interpretation is arbitrary, truly, and is riddled with hindsight. Not only does the language that appears in the figure contradict what's in the description of the figure in the specification, the annotations in the figure use 0.012 percent, where the description and the specification uses 0.15 (sic) percent.

It also ignores the specific descriptions of the number of drops used in the example, which is above Figure 5B and above Figure 5C, there are both annotations of "ii gtts," and as Dr. Galanis explains, that means two drops.

So the reasonable reading of this experiment is that the number of drops of brimonidine that was administered is not of sufficient importance to make clear. It just really didn't matter to the inventors that wrote this experiment and drew this figure. Either one or two drops of brimonidine were used, and that is enough for us to not have support for a narrow construction of this claim in this situation.

Patent Owner seems to base its argument on the idea that Figure 5 provides sufficient disclosure to provide 112 support for a claim directed at use of a single drop, but that is not the proper question in claim construction. The question for this is whether the claim language and the intrinsic record show that the inventors clearly meant to limit the claims to administration of a single drop, and the simple answer is no.

The prosecution history similarly supports that the single drop concept was not in existence until this litigation. If you look at the prosecution history that I've put up on Slide 13, the Applicant -- this was comments made by the Applicant when they inserted the claim phrase consisting of, and the Applicant made it perfectly clear what consisting of

meant. They said it meant that brimonidine was the only active ingredient in the composition. They said nothing about the number of drops.

So, finally, I just wanted to touch on this idea that the application of this claim construction is inconsistent if we follow Patent Owner's proposed construction. So, according to Patent Owners, they have alleged that Lumify is a commercial embodiment of the challenged claims. On Slide 14, I have put up on the left-hand side the directions from the product Lumify. And Lumify instructions patients to instill one drop of the product to the affected eyes once every six to eight hours. Now, Patent Owner contends that each administration of Lumify every six to eight hours is a separate performance of a single drop administration.

Now, turning to one of the pieces of prior art that the parties discuss at length, in this case, the Gil patent. Example 1 of Gil describes a clinical study on human patients that receive radial keratotomy surgery, which is the precursor to Lasik. Example 1 explains that the patients received one drop of a study medication, brimonidine, at 0.03 percent every four hours while awake, yet Patent Owner takes the position that the periodic administration of the single drops in Gil is a multi-drop administration that is not covered by the claims.

JUDGE FLAX: Well, what if -- sorry to interrupt you, but what if every time they do it, and it's spaced it out every six hours, it does reduce eye redness? So, first time, one drop reduces eye redness. You wait long enough, here it comes back, I need another drop, does it again. Isn't that a separate -- let's call it an infringement, if you were doing it. Wouldn't each one of those be an infringement?

MS. CIPRIANO: I don't disagree that each -- if we're going to say

that claims are limited to a single drop, that, yes, that would be an infringement of performance of the claimed method, but so would the administration in Gil, and that is our point, that each time, let's say, as we know today, this amount of brimonidine reduced the redness in those patients' eyes. That administration, each of those administrations, would also be a performance of the claimed method. But Patent Owner has claimed that it is not, because it is part of a larger experiment, and kind of explains around why Gil is not a performance of the method. But we would argue that if Lumify is a performance of the method, then so would the administration in Gil.

So, unless there are other questions, I'll just leave it at the fact that Patent Owner's proposed narrow construction of the claims is not supported by the intrinsic record or the case law regarding how to interpret a consisting of claim. The limited construction is nothing more than a litigation-driven attempt to salvage the claims, and should be rejected. Thank you.

MR. FREDERICKSON: So, with that, I will go and address the core of what we see to be the obviousness issues before the Panel in these particular IPRs.

Judge Yang, to your earlier question, what are the other differences between the '742 IPR and the IPRs at issue in this proceeding. And one of the notable differences is that these patents were narrowed to limit the performance of the method to the use of brimonidine alone, whether through the language Ms. Cipriano talked about in Claim 8, or through the use of consisting of instead of consisting essentially of.

Now, we think the Board already addressed that factual issue, because it was part of the dispute in the '742, when it found that Norden and

Gil teach or suggest that brimonidine alone is effective in reducing eye redness. But we'll also go over why that was obviously the correct answer. And I put on the screen Slide 18. This is a collection of certain prior art references that have been cited throughout the petition that talk about kind of one thing pretty consistently and pretty repeatedly, that, by 2008, brimonidine was known to be a strong and potent vasoconstrictor.

We've included, not including the red outline boxes, Robin in 1998, Wikberg in 2001, Desco in 2005, and Hong in 2007. Those later two references, Desco and Hong, they built off the work of Norden. It was so well known and so widely accepted that brimonidine was a strong and potent vasoconstrictor that surgeons, eye surgeons, were using it off label to achieve that purpose.

JUDGE YANG: Sorry to interrupt. Let's say we agree with you at the time you mentioned it was known that brimonidine is a vasoconstrictor. My understanding is Patent Owner argues that not all vasoconstrictors would achieve reducing eye redness. It might constrict a bit, but not sufficient. There is a degree. Just because brimonidine is a recognized vasoconstrictor doesn't mean it will actually reduce eye redness. Could you address that?

MR. FREDERICKSON: Absolutely. So, I'll start with just the background context. The words that were being used to describe brimonidine vasoconstricting activity were words like potent, strong, as effective and powerful as the well-known vasoconstrictor phenylephrine. So, these are words and terminology that are being used to describe some type of effect that you need a certain high dose, or if you need to administer other doses. So, just the level of background state of the art was that this drug was known to be a vasoconstrictor.

Now, the other thing that's important is that vasoconstriction is the equivalent of eye redness reduction. Eye redness reduction in these patent claims are the result of what's known as ocular hyperemia, and all of the experts agree what ocular hyperemia is vasodilation of the blood vessels in the front of the eye. Everyone also agrees, and this goes back to the Federal Register, way back in the 1980s, if I have that correct, that talked about that the mechanism of action, this concept of vasoconstriction, that's the term used in those prior art products for purposes of achieving eye redness reduction. And that makes sense; if you're going to constrict the blood vessels in the front of the eye, you make them smaller, the smaller blood vessels are going to be less red and less visible. And so, certainly by 2008, when you have this background in the art about the effects of brimonidine and then you layer that on with the teachings of Gil and Dean. And we have that in Slide 20.

Gil, on the left-hand side, has a number of examples and references to uses of low concentrations of brimonidine for purposes of effecting reduced neurogenic inflammation. Patent Owner, like it did in the '742 IPRs, it dismisses Gil as being all about and exclusively about pain, but that's not accurate or a fair description of Gil. Gil talks about pain to be sure, but it also talks about this concept of neurogenic inflammation and includes ranges from 0.01 percent to 0.5 percent. Those appear twice in two separate sections, and then a specific estimate of the use of a low concentration of brimonidine at 0.03 percent. So we have one reference pointing towards lower concentrations of brimonidine for purposes of achieving reduced neurogenic information, an umbrella term that covers redness.

Dean gives more information about why the person of ordinary skill in the art wants to lower the concentrations of brimonidine. Everyone again agrees it's an undisputed fact in this proceeding that at the higher concentrations, brimonidine was known to have a number of serious side effects including sedation and allergic reactions. Dean acknowledged that, so did both sides' experts, Dr. Galanis and Dr. Noecker. At these higher concentrations you do see allergic reactions.

And Dean says, we want to unlock the vasoconstricting powers of brimonidine and use them, but we want to use them to take advantage of another drug in the treatment of glaucoma. So I agree with Patent Owner that Dean doesn't talk about redness reduction, but it does talk about and does inform a person of ordinary skill in the art that brimonidine at these lower concentrations can and should be used to achieve vasoconstriction of blood vessels in the front of the eye, and in the purpose of Dean, the reason for doing that was to increase the bioavailability of the second drug.

And so, again, we have all these references talking about the mechanism of action of brimonidine, the fact that at least Norden tested it to be effective, actually effective in reducing ocular hyperemia in patients that have undergone Lasik surgery, and then Gil and Dean pointing that person of ordinary skill in the art to use the lower concentrations.

And so all of that is pointing the lowest concentration, lower concentrations. Let's get away from these high concentrations that have these bad side effects; we want to use this drug as an everyday eye redness reducer, not one time during Lasik, not to treat a more serious condition.

And so on Slide 22, to round out the obviousness analysis, when you have that motivation to go lower, when you have a reasonable

expectation of success that it will work because it's a potent and strong vasoconstrictor, because Gil suggested that it would reduce neurogenic inflammation at those higher concentrations, because Dean suggested that you get a meaningful vasoconstricting effect at those lower concentrations, then it just becomes a matter of finding the optimal dose.

And we have on Slide 22 a series of admissions from Patent Owner's experts, Dr. Stamer, Patent Owner's witness Dr. Gil, and Dr. Gil's patent and Dean that all coalesce around the same thing: when it comes to finding the optimal dose for one of these eye drop formulations, that's a matter of routine experimentation. The art told you to go low, it told you that you should have a reasonable expectation of success of having eye redness reducing effect, and finding that specific point value, the 0.025 percent or the 0.3 percent, that's just a matter of routine optimization.

JUDGE YANG: So, I'm sure you're going to get to it, we'll just get to it sooner. The teaching away argument, the Alphagan trials?

MR. FREDERICKSON: Absolutely. Slide 24 provides a bit of a summary of the teaching away argument. And what I'll just say at the outset is that this is Patent Owner's primary argument, this series of labels does virtually of the work for Patent Owner. And what Patent Owner, you know, takes these three labels and asks the Board to reach a series of inferences. An inference on top of an inference on top of an inference to assert there is some teaching away.

And in fact, Patent Owner goes so far as to assert that these three different labels for three different products that were evaluated in three different clinical trials that had three different sets of protocols, that those three labels established, and a person of ordinary skill in the art would think

that the minimum effective amount of brimonidine for vasoconstriction and redness reducing is 0.2 percent. That's a pretty absolute statement to be drawn from three labels that have almost no data whatsoever.

I've put on the screen -- I'll skip over, the Board's already addressed this issue, because I know we cited it in our papers, on Slide 26, I've put the entirety of at least the first two labels, the Alphagan 0.5 label and the Alphagan 0.2 label, and the references to something called conjunctival blanching.

Inference number one the Patent Owner asked the Board to make is that the reference to transient conjunctival blanching and conjunctival blanching in the two higher dose Alphagans refer to moderate redness reducing. There is not a shred of evidence, other than Patent Owner's litigation expert assertions, that that is the same thing as the moderate redness reducing that you talk about when you talk about these over-the-counter eye drops. If anything, the undisputed fact is, when these labels talked about this thing called conjunctival blanching, it was identified as an adverse event, something that was unwanted, and something that investigators or whomever thought was not a good thing to be occurring in these patients.

Dr. Dana explained why that may be the case. Because if you have such excessive constriction of the blood vessels, such that your eyes are blanched and they appear to be unnaturally white, that could reflect much, much more serious problems. Now, it turns out to be the case that that wasn't true in the Alphagan, that people didn't withdraw it, it wasn't as serious as feared, but that doesn't mean that it wasn't still an adverse event.

JUDGE YANG: I'm looking at Petitioner's Exhibit 1009, the

Federal Register. There, page 9 of 18, the left column, it reads, the action of a vasoconstrictor, when applied to the surface of the eye, is described in the literature as blanching. Is that blanching different from the ones in the label, and the ones you are talking about?

MR. FREDERICKSON: Well, part of the problem, Your Honor, is we don't know how blanching was defined in these labels. But what I would submit is that Federal Register statement is actually entirely consistent with what I'm saying. Because that Federal Register statement says something to the effect of the vasoconstricting mechanism of action is described as blanching, bleaching, and whitening of the eye. And so there's no equating -- those are different terms to describe different amounts of whitening on different points on the spectrum in terms of whitening. There's nothing that equates this concept of blanching to moderate eye redness reduction that we're talking about when it comes to these over-the-counter eye drops.

So, I would submit that that's not inconsistent. Sure, blanching is absolutely a form of whitening, but it's a form of whitening that is to such a serious degree that it was identified as adverse in the clinical trials, and not probative of whether a person of ordinary skill in the art would think that these labels teach away.

JUDGE YANG: So, when Federal Register used the word blanching, it is not describing it as an adverse event, right?

MR. FREDERICKSON: The Federal Register was agnostic as to whether it's adverse or not. I think the Federal Register was taking a survey of the literature and saying, this concept of vasoconstriction, we've seen it be described using these different terms, but the context in which those terms

are being used could vary quite significantly across the literature. So, there's no definition that says blanching equals whitening.

But then, even if there were, even if you accept the proposition that blanching equals some form of whitening, I agree that it is some form of whitening, but we think it's the excessive whitening, because it was identified as adverse.

On Slide 27, I highlight some of the problems that Patent Owner is asking the Board -- the second set of inferences that the Patent Owner is asking the Board to draw. What the Patent Owner is doing is taking one line item that's the result of three different studies -- the third set of studies, third and fourth were the two later Alphagan products, are absolutely silent on the concept of blanching. So we have no idea, other than, again, some of Patent Owner's speculation in their expert declaration, we have no idea what actually happened in those Alphagan. We haven't had the protocols, there's no articles that describe what was measured, when it was measured, who it was measured.

So, it's two labels that reference blanching, one that's silent. The first label was a study of something -- of the use of brimonidine one time at a very high concentration, following a type of refracted surgery, argon laser trabeculoplasty. So that's one use, one set of experiments that was being done. The Alphagan two and Alphagan three studies are different indications, different usages of brimonidine over a different and much more extended period of time when there was both physician investigator observation and patient observation of certain events.

And so what we have, at best, is three different data points, two data points and the absence of data, and Patent Owner is asking this Board to

extrapolate that that forms some sort of dose response relationship between this adverse event. An adverse event that wasn't studied and wasn't part of the defined protocol, but something that they identified.

And so we think the Board was absolutely correct that it is a data point. The Alphagan labels are relevant, they talk about brimonidine. If anything, the Alphagan labels show that as you lower the concentrations of brimonidine, all of those bad side effects go down and lessen, and that's the motivation why you'd want to continue to lower the dosage. But to extrapolate and to put as much weight on those three labels from these three different studies as Patent Owner does, just simply doesn't follow and can't overcome the express disclosures in the prior art.

With the Board's position, may I go a little bit longer into some of my rebuttal?

JUDGE YANG: Yes.

MR. FREDERICKSON: Unless there were any other specific issues that you wanted me to talk about on the Alphagan trials or the teaching away argument?

So then the related argument when it comes to teaching away, and we put this on Slide 29, has to do with the concept of dose versus concentration. And, again, here's an argument that we think is just divorced from the science and from the literature and how persons of ordinary skill in the art think about eye drops. Unlike fixed dosage forms, like the question that was asked earlier about tablets, where you know exactly how many milligrams of a drug are in a tablet, that is largely unknown if not entirely unknown when it comes to eye drops. Virtually every piece of reference in front of the Panel, whether it's this patent, this specification, all the prior art,

they refer to eye drops consistently by terms of concentrations. Sometimes you see references to the number of drops, but sometimes you don't, and what you never see is any indication of what the volume of the eye drop is.

And so if Patent Owner is correct, if a person of ordinary skill in the art was going to be so hyper-focused on the absolute amount, the milligrams that were being administered and absorbed into the eye -- these eye drops wash away pretty quickly, they're administered by people usually in their home without the sensitivity or the degree of precision that probably doctors would like, but if persons of skill in the art were so sensitive and concerned about this absolute dosage question, then you would have to know both the concentration of the eye drop and the volume of the eye drop. And that volume is never really disclosed in any of the prior art, because that's not what persons of ordinary skill in the art think about when they think about administering eye drops or they think about dosing eye drops. It's all about the concentration.

And we submitted evidence, Dr. Galanis' reply declaration, that talks about studies that are being performed, that talks about the considerable variability that occurs in the administration and the deployment of an eye drop. Not all eye drops are created equal, not all eye drops are the same size.

And so for Patent Owner to come here and argue that this concept of dose has some particular significance that a person of ordinary skill in the art would ignore Gil and ignore Dean in their discussion of let's go to these lower doses, and somehow do basic arithmetic to add up the concentration on the assumption that two eye drops were administered at the same volume and had the same amount of absorption and all of that that goes into

administering a drug, that's just not supported anywhere in the record.

And so we would submit to the Board that this concept of absolute dosage and absolute amount of eye drops is just not how people in this field think about dosage and think about the formulations. They think about the concentration. And that's what the specification held out to be the invention here. There's nowhere that talks about the number of eye drops, other than references maybe in one of the examples that holds out the number of eye drops as being something that's specific, or part of the invention. It's all about the concentration. And as the Board found in the '742 IPR, as the art points to when we presented it in this case, that all points towards moving towards these lower concentrations of brimonidine for purposes of identifying eye redness reduction.

I'll just close briefly by talking a little bit about secondary considerations, maybe if not without reference to any particular slide, but there's two issues before the Board we see when it comes to secondary considerations and the objective indicia. The first is, what is the closest prior art? The Board found, we believe correctly, in the prior IPR, that Gil was the closest prior art reference. And Patent Owner advanced the argument there as it does here that, no, Visine, a different drug that's also approved for eye redness reduction, is the closest prior art. But the Federal Circuit has held that when it comes to identifying the closest prior art for a purpose and method of treatment, the best place to start is the drug itself.

And so brimonidine was certainly well-known. And then Gil disclosed a very specific formulation that's 0.005 of a percentage point in terms of concentration an unknown volume both in Gil and in Lumify. So we don't know whether or not they're the same or different, 0.005 of a

difference in concentration for purposes of being effective in reducing neurogenic inflammation, which is an umbrella term that captures eye redness. So, we would submit that that decision that the Board previously made that Gil, and not a completely different drug that happens to operate on a different adrenergic receptor, is the closest prior art.

And then the second issue is very related, it goes to this question of nexus, the commercial success and the alleged industry praise associated with Lumify. And the problem that Patent Owner runs into there, just like it did in the prior IPR, is that what it holds out to be the invention, what the specification says is the present invention is discovery of the uses of low concentrations of brimonidine for purposes of achieving eye redness reducing. Because Gil talked about using low concentrations for eye redness reducing, because Dean pointed in that direction, we again think the Board was absolutely correct the prior go-around in finding that there was no nexus that would elevate this alleged evidence of secondary considerations to overcome the express disclosures of Norden, of Gil, and of Dean.

And so, with that, unless the Board has any further questions, I will reserve the remaining amount of time for rebuttal.

JUDGE YANG: Counselor, would you like to reserve any time for your surrebuttal?

MR. DINER: Yes, Your Honor, I'd like to reserve 10 minutes. Before we start, let's go to Slide number 2, please.

Good afternoon. Bryan Diner, may it please the Panel. Now, we've just heard from Petitioners a lot of hypothetical arguments about what they believe the prior art meant. It's all hindsight. And, Your Honors, this record establishes that with credible, direct evidence, going to testimony, in

the form of testimony and the form of contemporaneously published prior art.

First, we have real-world evidence and testimony from Dr. Dan Gil. He was a leading expert in alpha-adrenergic agonists, including what we have here in terms of brimonidine or the alpha-1 agonist. He's the lead inventor on the Gil patent, and he worked for many years before the effective filing dates of these patents for Allergan, the owner of brimonidine, to try to repurpose brimonidine for other uses other than treating glaucoma. He never used -- as he testified, he never used brimonidine at a lower dose ever to treat redness relief, or to relieve redness. And, corroborating that testimony, he submitted certain contemporaneously published prior art references, one of which was a patent that basically was an Allergan patent. And when they were looking to develop new redness relievers, they went with the alpha-1 agonist. They did not even go with brimonidine. They didn't even mention brimonidine in their patent applications.

Second, we have a contemporaneously published review article, again with prior to -- or a review article looking back on the state of the art prior to August of 2008. And that review article was called "The Efficacy, Safety and Current Applications of Brimonidine." It talked about multiple proved uses, unapproved uses, and even future uses of brimonidine, but it never mentioned the use of brimonidine for reducing eye redness. We submit to Your Honor that the testimony in these references are examples to illustrate how, using hindsight, the Petitioners have basically cherry-picked pieces of prior art to reconstruct the invention, ignoring what the prior art as a whole taught or fairly suggested with regard to brimonidine's ability to reduce eye redness.

So, now I want to turn to the petitions themselves and what Petitioners argued. They basically advance four arguments in their petitions. One, that the Patent Owner should be precluded from litigating the findings of fact of the prior Board's final written decision; two, that Norden, Gil, and Dean teach brimonidine alone as the sole active agent in reducing eye redness; three, that the use of 0.025 percent brimonidine would have been prima facie obvious based on the theory of overlapping ranges; and four, that the use of 0.025 percent brimonidine would have inherently reduced eye redness.

Now, counsel for Petitioners mentioned the findings of fact in the final written decision of the Board. We submit that that could have no preclusive effect, even the findings of fact, in this proceeding. And that's consistent with the Google case, in fact, that they cite. Unless there is a decision from the Federal Circuit, neither the findings of fact or the conclusions of law from that prior decision have any preclusive effect.

Moreover, Patent Owner's appealed that final written decision, as Your Honors know, and appealed it on the basis of the claim construction position, and that it affected the obviousness analysis, including the findings of fact.

If the Federal Circuit were to vacate and remand, it wipes out that entire final written decision, including the findings of fact and the conclusions of law based thereon. Now, I'm not going to offer any personal opinions as to what occurred at the hearing last week at the Federal Circuit suffice it to say that it is a public record and if Your Honors are interested, you can listen to it before you issue your final written decision.

JUDGE YANG: Yes, I was interested, and I did listen to it, and I

have a question for you. So, the majority of the oral argument before the Federal Circuit focused on the consisting essentially of language of the claim construction. I just wanted to find out if the Patent Owner's appeal included the other issues. You had a wish list, you told the Court over there.

MR. DINER: Yes, Your Honor, absolutely. And as I just stated, we took the position that that erroneous claim construction infected the entire obviousness analysis, including the findings of fact. And when Judge Taranto asked counsel for Eye Therapies on appeal, if we assume that claim construction is wrong and we have to remand, is there anything else you would like to us to do in the context of issuing an opinion? And counsel for Eye Therapies answered, yes, we'd like you to look at certain factual findings: a, the closest prior art issue that has already just been discussed by counsel, and b, the teaching away of the Alphagan clinical studies, which I will get into as well.

So, it is possible that if Judge Taranto renders that opinion, and his track record is that if he does do that, we're going to have an opinion from the Federal Circuit in June or July. And so it could also bear on these issues of fact with regard to teaching away and closest prior art. Although, closest prior art, as it is, is governed by a legal construct. It may be a finding of fact, but it is governed by the legal construct, which I will get to.

Now, can we go to Slide 3, please? Irrespective of that final written decision, we submit that this Panel has to make its independent findings and conclusions of law. And you already heard that I believe, and we believe, that the record is very different. We'll go into more detail about that in a moment. But in addition, as Judge Yang, you mentioned before, we're dealing with very different claims.

The '742 Patent, as the prior board construed those claims, were open to permitting co-administration of up to 0.03 percent brimonidine with other active ingredients, even if they did reduce redness, and had no requirement of efficacy. That is, it was just an intent to reduce redness; it didn't have to actually affirmatively do so.

Taking a step down, and then in a narrower scope claim, you have the '600 Patent, which is part of this proceeding. And there, it's a low dose of 0.025 percent brimonidine. Claim 28, which is a challenged claim in the '600 patent, is directed to a bullet point amount of 0.025 percent brimonidine. It is open to multiple drops.

Now, with regard to the '245 Patent, it's even more narrow than the '600 Patent. The '245 Patent, Patent Owner submits, is directed to a single step of administering a single drop of 0.025 percent brimonidine as the sole active ingredient, it does have benzalkonium chloride in there as an inactive agreement, to actually reduce redness. It's not just an intent; it must actually be done. And as I will get to in a moment, the construction of single step, single drop, is, in Patent Owner's position and opinion, consistent both with the intrinsic record in terms of the specification in the claims, as well as dictated very clearly by the prosecution history.

Now, if I can, I would like to go to Slide 5, I believe. No, 4. So, before we get a little bit further down -- go to Slide 4, please. I would just like to bring to this Panel's attention that there were certain dependent claims in the '245 Patent that are relevant to the inquiries here. A couple wherein clauses at the first two bullet points we have here is that this invention, this patented method, induces a low incidence of rebound hyperemia. That's important with regard to the secondary considerations, particularly

commercial success. And the second bullet point is that the eye redness here that is being reduced is not associated with an ocular disease or a surgical procedure.

JUDGE YANG: Counsel, on that point, as you pointed out, this is a dependent claim. Does it not mean that an independent claim would be broader and could just include those?

MR. DINER: Yeah, it does mean that, on the basis of claim differentiation. I'm just pointing out to the Panel that these are additional claim limitations, and these claims stand alone, and would not necessarily stand to fall with the resolution of Claim 1. And they are supported, these two first bullet points, if you look at Claims 1, 2, and 4 of the '245 Patent, and ultimately Claim 4, which depends through 2 and back to 1, is basically capturing both the low incidence of rebound hyperemia and the fact that it's not associated with a surgical procedure or an ocular disease. So, it's an even more narrow claim.

Now, could we go ahead to the next slide, please? I would just like to introduce the Patent Owner's experts, because I think they're particularly relevant to the issues that are being discussed.

First off, we have Dr. Robert Noecker. Dr. Noecker, what you need to take from this is that he is the only expert in this case, for both of these IPRs, that was actually a clinical investigator in the Alphagan clinical trials.

And I alluded to Dr. Dan Gil as the person who is a lead expert in alpha-adrenergic agonists. He was the lead inventor on the Gil patent, and, as I mentioned before, he was responsible for many years at Allergan trying to repurpose brimonidine for other uses and never thought of using it for

redness relief.

And, finally, Mr. Karst is an expert in FDA law and practice, and he addresses the issue of adverse events, which I will get to when we discuss the Alphagan studies.

I'd like to turn to Slide 7, please. This is a very important point, and Petitioner's Counsel mentioned this and brushed it aside as something that is all about concentration. It's important to realize that dose and concentration may not, and are not, often the same thing. What matters? Dose matters for efficacy, for therapeutic efficacy, because dose is a function of, in the ophthalmic area, the concentration of the drop that is being put in and the dosage regimen, which could be how many drops are going to be administered as part of a particular dosage regimen. And that's --

JUDGE FLAX: So how do you control the dose, if your claim construction is correct and that you only administer a single drop to reduce eye redness, knowing the fact that every drop out of an eye dropper is not the same size?

MR. DINER: Well, because either the eye dropper -- and counsel alluded to this before, saying that there's no evidence in the record as to what the drop size is. There is indeed evidence in the record. It's Exhibit 1030, Petitioner's reference page 20, and it specifically says that the standard eye drop size or volume for brimonidine eye drop is 35 microliters.

So if there's going to be variation, from the FDA's perspective, it's got to be very minor. And so what we're talking about here, brimonidine eye drops -- and the prior art is very clear that the brimonidine eye drops go in at 35 microliters. And that's going to be very important when we start talking

about Gil and Norden in terms of what there is. But that's in the record, and that's in the prior art, without doubt.

Now, the fact that dose matters, even Petitioners recognized that in their petition at page 2 when they said a POSA would have been motivated to pursue low doses of brimonidine to reduce eye redness. The Board in the final written decision said the same thing; they all understood that it was involving low dose.

Now, I'd like to nip something in the bud here, if we can. Can I go to slides -- can you please tee up Slides 20, 22, and 31 from Petitioner's slides? I'd like to explain a few things.

I just want to illustrate, Your Honors, that it is about dose, and that dose matters, and concentration is not what drives efficacy, therapeutic efficacy.

JUDGE FLAX: Is there one that you want us to be looking at?

MR. DINER: Yeah, why don't we go to Slide 20 while my colleague tries to pull that up?

JUDGE YANG: Petitioner's, right?

MR. DINER: Yes, Your Honors. Slide 20 of Petitioner's slides. Let me know when you're there.

JUDGE FLAX: I can see it.

MR. DINER: You got it? Okay. At the top it says, POSA would have been motivated to use low concentrations of brimonidine to reduce eye redness. And they rely on Dean, on the right-hand side of that slide. What Dean actually says, if you come straight down into that paragraph, on the first box, second line from the bottom, it talks about lowering the overall dose of brimonidine. Dose is what matters. They said there's nothing in the

prior art that says dose matters or concentration is the be all and end all, this tells you that this is what they're looking for, POSAs understand that dose matters for efficacy.

Let me go to the next slide, if I will.

JUDGE YANG: Can I just, sorry, interrupt you there? Right there in front, the sentence before that, where Petitioner highlighted it, I just find it interesting, right? The first sentence says it's because of the relatively high drug concentrations that is causing the side effect, of course. In the same breath, or the next breath it says, lowering the overall dose. So, how much can we -- what kind of conclusion can we draw from these two sentences?

MR. DINER: So what you have here is the one time where concentration equals dose, and that's when you're putting in a single drop. In this paragraph, it's referring to and relating back to Alphagan 0.2, which was referred to in the first column of the Dean patent. And there, the Alphagan 0.2 was administered as a single drop, but that is a dose of 0.2 percent brimonidine. But when it's talking about lowering the dose, you have to figure out what it is and how much drug you're putting in the eye, because at the end of the day, how much drug you're putting on the eye is where you get efficacy.

Now, it's the same thing with the Gil patent. If we can go to Slide 22, and let me know when Your Honors are there.

JUDGE FLAX: We're looking at Petitioner's slides, is that right?

MR. DINER: Slide 22, I'm sorry. Petitioner's Slide 22. And we can look at the left-hand side of the slide, the box on the left, bottom left. Are you with me? It says the determination of the effective dose for any of the selected compound is well within the ordinary skill of the art. Okay,

we're talking about dose.

Now, they didn't put in that whole paragraph, but if you want to read the topic sentence of that paragraph, it says, "an effective dose, when it comes to topical ocular pain, is a matter of broad therapeutic effective dose requirements." They're talking dose, dose is what matters. And even further, up in column 3 of the Gil patent, it says the present invention relates to a method which comprises applying to the eye of said mammal an effective amount of brimonidine. It's all tied in in terms of how much you put on, not the concentration of the drop, but the dosage regimen, and what that dosage regimen dictates.

So that's very important, because it transitions us now back to Patent Owner's slide, the very next slide, if I may. So the steady and consistent message in the prior art is if you wanted brimonidine to have any effect on whitening the eyes and reducing redness, you had to dose high. Norden is a primary example of that, Norden doses two drops of 0.2 percent brimonidine. It's the equivalent of putting a single drop of 0.4 percent brimonidine onto the eye. Let's take a look at Gil. Now they rely on Gil which has two prophetic examples in it that they rely primarily on, 1 and 4. No data in those examples, but let's look at Example 1.

What Example 1 is, and we can just focus on just prior to surgery, which they don't highlight in their slides, they highlight other aspects of it. But just prior to surgery, it's prescribing a dose loading protocol that's going to do six to seven drops of 0.03 percent brimonidine in order, before the surgery begins, because this is a prophylactic installation, a dose of 0.2 percent brimonidine, or the equivalent of one -- a single drop of 0.2 percent brimonidine would be in terms of ocular delivery to the eye. And so that's

actually eight times higher than what's in the '245 Patent, Example 1 -- or Claim 1.

And so the message there is, if you want to have any therapeutic effect, in that case it was for ocular pain, you've got to dose high. And there should be no doubt that that's an amount that is equivalent to a drop of 0.2, because it's all prophylactically administered. So even before the surgery begins, in this radial keratotomy, the knife would come down on the cornea, you've got a loading dose in the eye that is equivalent to a drop of 0.2 percent brimonidine.

Now, let's take a look at the Alphagan clinical studies. These were studies that were done over a decade on hundreds of patients, and they are highly relevant and reliable human clinical studies, and they also taught to dose high. What they teach ultimately, and we'll get to this in more detail, is that there's a minimum effective dose that a person skilled in the art would have understood from these Alphagan clinical studies of 0.2. In other words, if you dose and it was believed that before August of 2008, if you dosed below 0.2, you would not induce sufficient vasoconstriction to manifest as redness reduction. That was idea of what those studies had conveyed to one of ordinary skill in the art.

And if we can go to the next slide, we have a slide here that depicts what would have collectively been understood by a person of ordinary skill in the art. By the way, the person of ordinary skill in this art is someone looking to develop a better redness reliever, and defining that person of ordinary skill in the art as someone who has six to nine years of experience in developing eye drop formulations for clinical trials and regulatory approval. They would have been highly interested in what these Alphagan

clinical studies would have said about conjunctival blanching.

JUDGE YANG: I just want to interrupt, and I do apologize for this one because it's going to get you off your track there. Did Patent Owner put out a POSA definition? And the reason I'm asking is, on Patent Owner's response page 10, it says the POSA definitions provided by the parties do not differ much. I have to admit I looked up and down, but didn't really see one provided by Paten Owner. Is there --

MR. DINER: I loved their definition. I think it's perfect.

JUDGE YANG: Okay, so there is no difference, you just adopted that?

MR. DINER: What is great about it is its focus on defining a POSA as someone who is keenly interested in clinical trials. And this is human clinical trial data, and this would have been highly relevant and highly reliable data that they would have looked to when trying to develop a better eye redness relief.

Okay. So, what we see collectively coming out of these studies -- and it's not just labels. My friend on the other side said it's just about putting together three labels. It's not. It all starts, actually, with Petitioner's Exhibit 1030. And Exhibit 1030 is the Alphagan NDA, and in it, it has all the clinical trial results for 0.5 and 0.2. And what we see in -- and then of course, they have to all be approved, and when they get approved and the FDA puts them on a label, it comes with an imprimatur of truthfulness and reliability, which we'll get to in a moment.

But what we see is that at 0.5 percent brimonidine, almost 50 percent of the patient subjects experienced conjunctival blanching. And I will get to the definition of conjunctival blanching. But then, when you just

drop the concentration down to 0.2, it drops like a rock all the way down to only about 3.5 percent of the patients experiencing conjunctival blanching.

And then, when they would have studied it in the Alphagan P studies, it didn't even show up. It would have been monitored, it would have been looked for, but it didn't show up. And what does one of ordinary skill in the art conclude from that? Is that below 0.2, there would not have been sufficient vasoconstriction to manifest as redness reduction, and that's the collective teachings of those studies. And then, when you have that, and the person of ordinary skill in the art has that in their mind, and then they go and look at the Dean patent -- next slide.

My friend on the other side acknowledged that Dean says nothing about redness. He has a data-less hypothesis in there that says, well, constriction of the front of the eye, not for reducing eye redness, but for increasing brinzolamides, that's the co-administered drug in that case, increasing its bioabsorption.

But even if you understood, like they would want you to, that you can infer vasoconstriction and redness reduction, it would be backstopped by the Alphagan clinical studies, which, pre-2008, August 2008, POSAs would have had that information before then, and would have understood what the minimum effective dose of 0.2 for brimonidine to induce whitening or blanching of the conjunctiva, that below that would have been insufficient to manifest -- insufficient vasoconstriction to manifest this redness reduction.

JUDGE FLAX: So with the understanding that vasoconstriction is required to reduce eye redness to some level, too much of it causes blanching? And you're saying blanching is equivalent to reducing redness?

MR. DINER: That's correct.

JUDGE FLAX: That is redness reduction? Blanching is redness reducing?

MR. DINER: That is correct, Your Honor, it is, and it's --

JUDGE FLAX: So before blanching occurs, you do not have any redness reduction, is that right?

MR. DINER: Well, if redness reduction is blanching, if you don't have blanching, then you're not going to see any redness reduction.

JUDGE NEW: Doesn't blanching as an adverse condition imply too much redness reduction? In other words, an abnormal amount, so that the eye appears abnormal to the clinician's view?

MR. DINER: No, Your Honor, we disagree with that, because if we can go to slide -- one second. Let's go to Slide 43, please. So, just because it is an adverse event doesn't mean it's undesirable for any purpose. Now, all adverse events, anything that is off target for what you're looking for in these clinical studies has to be reported, it's required by the FDA's regulations. And so an adverse event just means that it's an event on the ocular surface; it doesn't mean that it's undesirable.

Conjunctival blanching was not identified as a serious adverse event, and importantly no patient withdrew from that study because of conjunctival blanching.

JUDGE NEW: So it's your position then that conjunctival blanching and redness reduction are synonymous terms?

MR. DINER: That's correct. And if we can go to Slide 39, the box on the top left is the quote that comes out of Petitioner's Exhibit 1009, which is the Federal Register from 1988. And, Judge, you alluded to this before, and it's saying very clearly here that in the literature, it's understood

that blanching is just another way of saying whitening of a reddened conjunctiva. That's exactly what all vasoconstrictors do that are reported in the Federal Register 1988 document.

And, importantly, another one of Petitioner's references substantiates the same thing. If you look at Exhibit 1029, page 2, top left-hand column, it will tell you that conjunctival blanching is merely an A1 agonist effect. That's exactly what's happening and exactly what the A1 agonists are doing in the Federal Register. So it is the same thing, conjunctival blanching is in fact redness reduction. It's just saying the same thing a different way, and the literature recognizes this.

JUDGE YANG: So the same place you just pointed to, Exhibit 1029, page 2, it also mentions that a determination of conjunctival blanching is subjective. And another piece of evidence, this is Petitioner's Exhibit 1032, it actually states that in some cases, the conjunctival blanching was the surgeon's description of what, in fact, appears to be normal looking eye. So then my understanding is, sometimes it could be labeled as there is blanching; other people look at it and say, well, that looks normal, and therefore they didn't report. That is --

MR. DINER: One thing you're missing is that at the beginning of any of these studies they're going to do a baseline study, and they're going to look at what the degree of whiteness is of someone's eyes. And then they're going to conduct the experiment and then they're going to evaluate it. And even in Exhibit 1032, there, what the surgeon was saying is that, well, based on the baseline, it looks normal. And if there was -- well, what you don't know, was there redness before, and now it's reduced? There's not enough information in that document to know. But what we do know is that it's just

basically another way of saying, as the literature identifies, blanching is just a whitening of the reddened conjunctiva.

JUDGE YANG: Okay, I want to go back to the Alphagan P, right? That's the one that didn't report any blanching as adverse event. So do we know the baseline set up over there? Is this the same, substantially the same as the other Alphagan trials?

MR. DINER: Absolutely, Your Honor, because the FDA's requiring it. Let's go to slide -- we can start at Slide 45. Okay, first off, as a premise, all adverse effects have to be identified. It's a requirement, and you must describe the overall adverse reaction profile the drug based on the entire safety database. Importantly, what Mr. Karst says, then, is then when all this information is processed by the FDA -- and by the way, all these protocols, all these trials, they all have to be preapproved by the FDA, and the FDA periodically audits them. They want to make sure that if there's any subjectivity in the evaluations, I know Your Honor raised that, that they are minimized, and the variability between the centers where they test these products on various people, that it is minimized.

And so what we have here is when the FDA eventually puts it on a label and it says here prescribing information, a synonym for the label, it provides an indicia of truthfulness and reliability.

So now let's go to the next Slide 46. Remember, I told you Dr. Noecker's the only expert in this case that was actually a clinical investigator in the Alphagan clinical studies. And what Dr. Noecker says, and this is uncontested, is once a surface event is observed, such as an adverse event of conjunctival blanching, for a drug in a clinical trial, it will be recorded and monitored going forward.

Now, the next slide helps to answer even more of your questions. So if we -- this is out of Petitioner's Exhibit 1030, and we go to the bottom box there. It says, throughout the study, subjects were monitored for signs and symptoms of an adverse event. And here's the kicker, any adverse event occurring during the study was recorded by the investigator and graded for severity, and they described the scoring mechanism, trace, mild, moderate, and severe.

Now, to get back to your question, in terms of when it was monitored, the top box says, and this again is out of the same exhibit, it says you first evaluate the adverse effect for severity grade increase from baseline. So what happens is the patients come in, they get a baseline measurement for their degree of whiteness and everything else that they're looking at. And then when they come back for each visit thereafter, they're evaluated by ophthalmologists who are skilled and trained and know how to evaluate conjunctival blanching, and know how because the protocols approved by the FDA how to score it by trace, mild, moderate or severe, and then that all gets tabulated and statistically analyzed and sent to the FDA for approval before it even gets on the label.

So what we have from this slide is who, highly skilled ophthalmologists, who there's very little subjectivity in their evaluations based on these protocols, when did they do it? They do it at baseline and every successive visit after that, and how do they do it? They score it according to these trace, mild, moderate, and severe scores.

Now, if we can go to Slide 44, when Dr. Gil was asked this question about the Alphagan clinical studies about it being such an adverse event, he said there were no reports of blanching having contributed to the

termination of anyone from this study, it was more in the range of mild to moderate, which is really what you're looking for with a redness reliever.

And if we can go to Slide 48, Petitioner's expert, Dr. Dana, he was asked on cross examination during the PI proceedings, is it fair to say these protocols, that they led to consistency and reliability, whether they be for efficacy or side effects? Yeah, I would generally agree with that, he said.

So, next slide, please. So, what we have then on the next slide is the FDA's evaluation of all these adverse effects, which includes conjunctival blanching. And in there they said there was an adequate number of subjects, in the top box, in terms of doses and duration of exposures to adequately assess safety. In the next box, which is directed specifically to adverse events, they say the evaluation of the potential adverse events by the Applicant in this case, Allegan, was adequate. And then, going to Mr. Karst's point about the importance of the safety database, in 7.2.8 it says, the submitted safety database appeared adequate and complete.

There's one more piece of information that is in our sur-reply but not on this screen, and that is the idea in the Alphagan clinical studies. In another one of Petitioner's exhibits, it's Exhibit 1075, part 3, page 65, section 7.3, they compared the adverse events across clinical studies. In other words, they looked at what were the adverse events in brimonidine -- or Alphagan 0.2 and also in the Alphagan P studies.

So what we have here is the knowledge in the prior art for the POSA to know and to look at, that these studies, for any adverse events, if it was identified early on, say in the 0.5 or the 0.2, it would have been looked for in the lower concentrations at 0.15 and 0.1. And the fact that it wasn't

there means that it was monitored, it was looked for, but it didn't show up. And so that's why you can look at this -- let's go a couple more slides to the graph again, I think it's Slide 52.

You can look at this slide, and it is the culmination of not just a couple of labels, but all the clinical studies that went into it, which a lot of it is sourced out of Exhibit 1030, and what it says is that when you're at a high concentration of 0.5 and then you start to drop, it goes down rapidly, and then when it goes even to 0.015 and 0.1, it doesn't appear anymore. And so what a person of ordinary skill in the art would glean from that is that there wasn't sufficient vasoconstriction beneath or below 0.2 to manifest as redness reduction.

And there's more. There's corroborative evidence in another one of the Petitioner's exhibits, it's Exhibit 1029. This is the one that says there is a dose response relation between, for brimonidine and conjunctival blanching. It says that at page 5, and that's in the left column around the middle of that column. If you go to the right-hand column of page 5, more towards the top, you'll see that they group the 0.2 and the 0.5 together as experiencing conjunctival blanching, and then the dose that is below 0.2, they group it with the placebo established floor, as effectively implying that it's no better than placebo to reduce conjunctival blanching.

So, collectively, we have this understanding by a person of ordinary skill in the art, when they're looking pre-August 2008 of whether or not they're going to consider ever lowering brimonidine's dose to reduce redness. And the answer to that question is, the blaze marks are all over the prior art. If you went lower, you wouldn't have sufficient vasoconstriction to reduce redness. And that would be a teaching away, and that also segues

into the unexpected results, which I'll get to in a moment, but, effectively, if you don't have any expectation that it's going to work at a low dose, the fact that it did work is itself unexpected. And we know that with regard to the gold standard in the prior art at the time, the Visine studies, that it actually was almost 600 or 650 percent better at reducing redness.

But there's more. It didn't have the side effects of tachyphylaxis and rebound hyperemia. And that made it, under the case law of the Federal Circuit, not only an unexpected and incredible difference, but one that was a difference in kind, because you had both a terrific profile of safety and efficacy, and that would then transition into doctors recognizing it and it being picked up by customers and consumers and making it a commercial success, which I will get to in a bit.

So I hope that answers your question on whether or not -- how a person of ordinary skill in the art would have understood the non-reporting of conjunctival blanching at those lower concentrations with respect to vasoconstriction and redness reduction. They wouldn't. They would have seen it as insufficient vasoconstriction to reduce redness.

JUDGE YANG: I appreciate that. This question is mainly for my own curiosity. So were the data incorrect on the -- based on the challenged claims, it's not like you're doing anything else, right? You give 0.025 percent brimonidine and redness did get reduced. So how come at 0.1 percent, which is, what, 4 times higher, it doesn't work?

MR. DINER: That's why it's an unexpected and non-obvious invention.

JUDGE YANG: So it does not work at a higher --

MR. DINER: Well, what the person of ordinary skill in the art

understood from these human clinical studies, pre-August of 2008, it wouldn't work if you went below 0.2. The fact that it did makes it completely unexpected and non-obvious.

JUDGE YANG: Yeah, I'm not trying to set a trap here, I'm just saying -- I'm just curious. Did anybody go back and look at 0.1? Would it work or not? I guess we just don't know.

MR. DINER: I mean, I don't know if anyone went back and looked, but the fact is, people did look, they did a dose ranging study in Example 1029, and they saw that there was a dose response relationship in that, as you went below 0.2, they didn't see any kind of meaningful redness reduction, and so that's that makes it a nonobvious invention.

JUDGE YANG: All right. I have another question for you. So you liked Petitioner's definition of POSA, because you argue that a POSA would look at this, assessing the redness reliever for regulatory approval. I'm sure you know Petitioner's argument, but they cite case law and quote case law to say there is no requirement for the POSA to be motivated to develop anything based on the rationale that forms the basis for FDA approval. I'd like to hear some response to that.

MR. DINER: Yes, Your Honor. There are a number of cases that actually say, and you cited one to frame the analysis, you cited one in your institution decision, the Axonics case. And it basically says there that the person of ordinary skill in the art frames the obviousness analysis and the problem to be solved by the claimed invention. And then, Your Honor, the Endo case, Endo pharma case, in there it says, well, you know, a POSA is motivated to do things to achieve a certain -- in this case, a certain end result. And it was a pharmaceutical invention, and so they said it is proper

within the law -- and this is also in all of our reports, it is proper within the law to consider what a person would have been doing who tried to make a successful or commercially valuable pharmaceutical product.

And I'd like to just point to the slide, because I was looking for it and I was trying to remember which slide it was, and it's Slide 20 from Patent Owner's slides. For pharmaceutical inventions, the law approves considering as relevant what a person would have done to develop an FDA approved product. Even the cases that Petitioner cites, the Allergan v. Sandoz case, it said FDA approval may be relevant to the obvious inquiry, such as in determining whether one of ordinary skill in the art would be motivated to develop the drug product.

Now, I'm not saying that it's totally dispositive. What I'm saying is that it can be taken into account, and the fact that the person skilled in the art is defined as someone -- on the previous slide, please -- that has collectively six to nine years of experience in developing eye drop formulations for clinical trial and regulatory approval, that frames the reference as it's said in your Axonics case, the relevant artisan provides the perspective that governs the obviousness analysis.

I'm not saying it's totally dispositive; I'm saying you're taking into account this POSA, who is one of ordinary skill in the art trying to develop a better eye redness reliever, with this definition, would have been completely interested in what those Alphagan clinical studies said and collectively what they showed, which we already went through.

So if I can, I'd like to go back to -- let's take it to Slide 65. Sorry, go to Slide 63. 63, please. So I just wanted to regroup and talk a little bit about Norden and Gil and Dean again. So, Norden, as we said, is two drops

of 0.2 percent brimonidine, which is the equivalent of about 0.4 percent brimonidine from a single drop. That's 16 times higher than Claim 1. It teaches no more than the Alphagan clinical studies. And then, next slide please, if we come to Gil Example 1, and I want to spend a little bit of time on this so that Your Honors understand.

Gil Example 1 is about -- and I'm just going to focus on just prior to surgery, so the two hours prior to surgery where they administer 20 minutes apart one drop, then 20 minutes later another drop. You're looking at about six to seven drops of 0.03 percent brimonidine, to reach an accumulative dose in the eye of about 0.2, and that's prophylactically, that's before the knife even comes down. That's what the dose is in the eye. And that's not a single drop, that's a dosage regimen.

And this is an important point that counsel made with regard to claim construction, this is not a single drop, this is six to seven drops of a loading dose protocol to put about 0.2 percent, based on an equivalency between -- for in a single drop into the patient's eye.

Now, let's go to Gil Example 4. There's a lot that has been said about Gil Example 4, and that's Slide 65. Yeah. So first off, all experts agree that the rabbit model in Gil Example 4 is incapable of measuring redness or even assessing redness reduction. Here we have the admission by Dr. Galanis, Petitioner's expert. But what I want to focus on is what's really happening in that example. What they do is, they basically mutilate the rabbit's eye, they open it up and they put a chamber on that rabbit's eye. It's called a pharyngeal ring, something that's going to seal the tested brimonidine solution on top of the eye. And remember, rabbits can't blink, so everything that's staying on top of the eye, it's going into the eye.

And so what they say in Example 4, when you read it in context of Example 5, and Example 5 is the actual working example implementing the protocol of Example 4. And Example 5 at column five, lines 65 to 66, says that you fill that chamber with the brimonidine solutions you want to test at the various concentrations with one cc of brimonidine solution. That's one milliliter.

One milliliter, conservatively speaking, is about 20 to 30 drops, so you're basically resting on that rabbit's eye, who can't blink, and you're just putting it on top of the eyeball, 20 to 30 drops of whatever concentration you're going to test. So if you're going to test 0.01, which is the lowest concentration in the range, you're basically looking at 0.2 percent brimonidine, the equivalent of a single drop of 0.2 percent brimonidine going on the eye. You tick it up, as they did in Example 5, to 0.2 percent brimonidine, and you put 20 to 30 drops in that chamber, you're way, way higher than a single drop of 0.025 percent, that's indisputable.

And even Dr. Galanis agreed that when you take one cc or one milliliter of brimonidine solution, knowing that the standard drop of brimonidine is 35 microliters, that comes out to 28 or 29 drops. That's what taking place in that rabbit example that is incapable of measuring eye redness reduction.

JUDGE YANG: At some point I would like to hear your argument on the claim construction about the single drop.

MR. DINER: Let's go to it right now. I'm glad you asked. So if we could go to Slide 23, please. This is Claim 1 of the '245 Patent. And you heard my friends on the other side talking about it, the transitional phrase, consisting of, introduces the sole step in this method, which is a topical

administration of what they say a composition in the form of an ocular drop.

What I want to point the Panel to is, to your question earlier, Judge Flax, isn't it really just an ocular drop? Yes, it is, and all you have to do is look down at the further language in the claim at the bottom, third line from the bottom, it says the ocular drop. It doesn't say the composition; it says the ocular drop. And so the claim itself is telling the POSA that you're administering in the single step here an ocular drop. Now, they could have said in this claim, consisting of one or more ocular drops. They didn't.

JUDGE NEW: But doesn't the claim language and the phrase, "in the form of an ocular drop," directly relate to the composition? It's not a modification of the composition or a modifying term of the composition, rather it's modifying the term administering, which simply means to apply.

MR. DINER: It's already agreed by the parties here that the term administering means a single step. It's a single step, and the only question is, is it a single step of administering a drop or, as they say, a composition?

JUDGE NEW: Right, but the typical dictionary definition of the word administer, as a single step, merely means to present or to supply or to apply.

MR. DINER: Right, and what is presented or supplied here as the subject of what is administered is an ocular drop. There should be no dispute. It's said in the actual element and --

JUDGE NEW: Well, what's actually administered is the composition, right? And in the form of a drop modifies the term composition, not the term administering.

MR. DINER: Respectfully, Your Honor, I would disagree. I think when the POSA is reading this claim, they're understanding that this is a

single step as based on the language "topically administering," it means it's instilling what? You don't juts instill a composition; you instill the composition as something. And that "as something," the subject of this administration step, is an ocular drop. That's clear from the claim step itself, and that's clear from the language at the bottom of the claim where it says the ocular drop. It doesn't say the composition; it says the ocular drop.

And to understand even to a greater extent, if we can go to the next slide, the impact of the prosecution history on this --

JUDGE YANG: I'm sorry to interrupt, but I'd like to go back to the -- yes, thank you. So, you mentioned the wherein the ocular drop in the singular form sort of confirms -- that an ocular drop means a single drop. But I believe counsel for Petitioner earlier made a point that the specification also said the composition could be in other forms, for example, an ocular ointment. And so giving you this scenario, a composition in the form of an ocular ointment, you later would also say, wherein the ocular ointment. But there, we're not talking about any amount, right? We're not -- you could say a scoop, but nobody measures it that way. So, just because you have "the" to refer back, it doesn't mean it’s singular -- I'm trying to get a better handle on the --

MR. DINER: The "the" could go to the number of drops, because it's not plural, it's singular in that way. It's the ocular drop, it's not the ocular drops. And in terms of your question, is it the administration of a composition? One of ordinary skill in the art reading this claim, whether that language is there or not, is going to understand that that is an ocular drop that is administered. And it's belt-and-suspendered with the reference to ocular drop below.

But what I'm also saying is the legal impact of "consisting of" on this step is further emphasized in terms of the prosecution history. So during the prosecution history, if we can go to the next slide, the transitional phrase started out as "comprising;" comprising an ocular drop. It would have encompassed one or more steps and one or more drops. But in order to induce the patent grant -- if we can go to the next slide -- they introduce the transitional phrase "consisting of," thereby limiting it to a single step of a single ocular drop where the subject of that administration is the ocular drop.

And, in that context, you also have to look at Claim 8, and you referenced Claim 8 before. If the Patent Owner wanted to include in Claim 1 more than one drop, Claim 8 tells the person or tells the public that it could have done that. It showed that it knew how to do that, and actually it intentionally inserted the word -- or the transitional phrase "consisting of" to induce the patent grant, to make it a distinct claim in terms of drops from Claim 8, because Claim 8 is evidence about how it could have been written to actually cover more than one drop.

Another way it could have been written is "consisting of at least" or "one or more ocular drops," and that was not done. And so when you look at the prosecution history in the context of this claim, and you see what the Patent Owner gave up, they essentially gave up anything beyond a single step and a single drop. And that was the whole idea --

JUDGE FLAX: Counsel, can you explain what -- there's a lot of dependent claims in this patent that say the drop is administered for long-term use. What do they mean in terms of one drop?

MR. DINER: Well, in terms of --

JUDGE FLAX: How do you administer one drop long-term, I

guess is my question?

MR. DINER: What that means is that you have one drop -- let's just take Lumify, okay? You have Lumify, you can administer one drop, it works in one minute, lasts for eight hours, but after that therapeutic effect wears off after eight hours, you can decide later at night, you're going to a party, you're going to a wedding, you want to put another drop in. And then you do it the next day in the morning when you wake up, and you put another drop in. And then you wait eight hours, and you put another drop in in the evening. That's kind of the continuous product --

JUDGE FLAX: So that continuous use seems to suggest that it's the formulation that's the drop, not that the application is the drop, because it's saying that you've got a bottle full of drops, thousands of drops, and that bottle is administered long-term, rather than --

MR. DINER: A bottle can't be administered. What has to be administered --

JUDGE FLAX: Well, what's in the bottle is administered long-term.

MR. DINER: And what comes out of the bottle is an ocular drop. And that's the whole point of this claim: it is directed to an ocular drop, instilling an ocular drop.

JUDGE FLAX: But no individual drop is administered for long-term use, which is what you're saying Claim 1 requires, a single drop into the eye. That cannot be long-term use.

MR. DINER: One drop gives you eight hours of whitening --

JUDGE FLAX: Is that long-term?

MR. DINER: That is one treatment. Long-term, I believe, in the

context of the claims and the specification, means that you can use it for longer -- you can use it regularly. You can use it more than four days in a row, you can use it more than several weeks in a row. In fact, there was a clinical study in the NDA for this product that basically said you can administer for 28 days, and you won't have any effect of tachyphylaxis or rebound hyperemia.

JUDGE FLAX: But how could one drop be administered for long-term use, which is what Claim 18 says? I don't mean to argue with you, but I just don't understand how grammatically that's possible.

MR. DINER: Well, it's not one drop that's administered for 18 days; it's one drop that could be administered once in a day and then again the next day and then again the next day. That's what it means to be able to use it for long-term use, because the prior art products, they suffered from these side effects, and you couldn't use them regularly or for a longer period of time. Now, this whole point about the specification, if I may?

JUDGE FLAX: But is that referring to the same drop? So, the dependent claim says "the drop." That antecedent basis refers to the drop, an ocular drop, in Claim 1. Talking about Claim 18, which is X'd through, so I guess it's not part of this proceeding anymore, but what does that mean? That it's referring back to an ocular drop in Claim 1, and saying that that drop, the drop, is for long-term use?

MR. DINER: In the context of that claim, what that means, then, is that you can use that once, and maybe just once a day and you'll get your reduced, but if you wanted to use it another day --

JUDGE FLAX: That same drop?

MR. DINER: No, it would be a different drop. You would get a

different treatment. It's a separate treatment. A separate drop in the context of Lumify will give you a separate treatment.

I'm going to hold there with about four minutes left for rebuttal, unless there are any more questions.

JUDGE YANG: Just want to confirm with you, it's 14 minutes?

MR. FREDERICKSON: That seems about right, yeah, I went a little long. Thank you, Your Honor. I'll start where that line of questioning just left off with Judge Flax, and it really highlights the problem of this single drop interpretation or construction, and this larger notion that the dose matters. And I'm not saying that dose doesn't matter. Of course, the amount of drug that gets administered to a particular part matters, but it's not how persons of skill in the art think about administering eye drops.

And as Ms. Cipriano explained, it creates and injects all of these concepts about words we've heard from Patent Owner's Counsel and Patent Owner's experts about dosing regimens and what the intent of the doses in Gil following surgery were, versus the intent of the use of Lumify and whether that's somehow probative of whether this claim speaks to one drop or multiple drops, or whether this claim speaks to the number of drops that are topically administered at any given point in time. And it just creates an interpretation and a view of how this art has been described that is just inconsistent with what we've seen in both the patent and the prior art.

Now, the principal argument that we heard -- and this was in Patent Owner's, their Slide No. 9 -- I won't put it up on the screen; I understand you all have it in front of you -- with respect to the Alphagan studies. And the Alphagan studies in Slide number 9, the Patent Owner's, is where they purport to assert that those three studies, three points, two points

from the two higher doses and then the absence of a point, creates a dose response curve. Now, no expert has actually said that there's a dose response curve from these three disparate studies. This is an extrapolation that they're drawing. But it goes and it shows, it illustrates, I actually think, quite well the lengths that Patent Owner is going to construct this view of these Alphagan studies that just did not exist, contemporaneously or otherwise, in any of the prior art.

No article or person of skill in the art or publication has strung together these three studies in the way that Patent Owner has. And we know that because -- if we can go to Slide 28 of Petitioner's slides, please. We know that this concept of 0.2 being the minimum effective dose, that's what the person of ordinary skill in the art would have understood and assumed, that's Patent Owner's argument. We know that's incorrect, because in 2007 Hong published a study where not only did Hong go lower than 0.2, went to 0.15, but also reduced the number of drops to one drop.

And so if what Patent Owner was saying is true, in these clinical studies -- no one's questioning the reliability individually of any clinical studies; we're sure they were well-run and went through the FDA regulatory process -- but where we do have an issue is the extrapolation and the stringing together of this inference, this conclusion that Patent Owner is trying to draw that is inconsistent with contemporary journal articles that said, huh, we saw what Norden did, we want to replicate a study in a different refractive surgery, but we're going to make a couple of changes. We're going to reduce the amount below the 0.2 percent concentration that Norden used.

So, the notion that that is the minimum effective amount, or

someone would actually think that prior to 2008, is wrong. And we're going to reduce the number of drops from two to one. And what Hong reported --

JUDGE FLAX: It stopped working.

MR. FREDERICKSON: I'll pause. Would it be possible to get our slides up?

MR. DINER: It's working. It hasn't been working.

JUDGE YANG: Correct. We'll give you a couple more minutes back, how about that?

MR. DINER: Five minutes? Fine.

MR. FREDERICKSON: And what Hong concluded in doing this lower dose, lower drop study, was that brimonidine was just as effective and powerful as the well-known vasoconstrictor phenylephrine. And so, again, this notion that minimum effective amount, and a person of ordinary skill in the art would draw that conclusion, is just inconsistent with the actual contemporaneous evidence.

Now, Patent Owner has suggested that its experts somehow know more than Petitioner's experts by virtue of Dr. Noecker being a participant in the Alphagan clinical trials and Dr. Gil's status as the author of one of our prior art references. Now, the problem with those arguments is twofold.

First, the secret knowledge of these people who happened to participate in these studies is not the type of knowledge that's available to persons of ordinary skill in the art. But, second, we asked Dr. Noecker -- and we pointed this out in our reply on pages 19 and 20 -- we asked Dr. Noecker, what were these study protocols? How were these studies actually conducted? And what was the redness measuring that was being done? And he wasn't able to answer. He said he needed to see the protocols. And that's

what we're missing.

And so while we don't doubt that, in some capacity, someone identified something that was being described and characterized as conjunctival blanching in the two higher concentration studies, what we don't know is how that blanching was actually defined. We don't know what the severity grades were, other than sort of very generic, mild, moderate, or severe. And what we don't know is the relationship between the spectrum of eye redness reduction.

And so what I mean by that is what Dr. Galanis said: one way that you can reduce eye redness is to decrease hyperemia. So you have a red eye, and you decrease hyperemia. The NDA and the labels that Patent Owner relies on and points to suggest that only increases in severity were being captured. So what happened to those patients who had red eyes and then decreased the redness? They lessened the hyperemia, maybe it wasn't blanching, but it certainly was still red, but there was some decrease in redness. That's just unknown.

And so I agree with one thing my friend on the other side said about this idea of blanching, is that there's a lot of people that seem to have a lot of views about what it means to be blanching. And to draw an extrapolation that that automatically means that lower concentrations of eye redness -- brimonidine wouldn't affect as an eye redness reducer, it's just not supported by the record. Turn to Slide 22, please.

There was also some discussion about the terminology, a lot of terminology being thrown around and the relationship between dose and concentration, and if there was something significant about when a prior art reference uses dose in one context but uses concentration in another context.

And, again, that doesn't seem to comport with what the specification actually says in Gil, when Gil talks about, on the left-hand side of Slide 22, exact dosing data have not been determined, but it is anticipated that a topical formulation having between 0.01 percent and 0.5 percent weight by volume of brimonidine.

So when Gil talks about dose, he's referring to concentration. Gil doesn't talk about the number of drops or the volume of those drops anywhere in the disclosure.

When Dean talks about dose, what Dean says is that, he'll talk about not only on the right-hand side, the concentration, but Dean actually identifies the number of drops to be administered. And he says expressly, to achieve this vasoconstricting property of brimonidine, of these lower concentrations, let's use this low concentration range which overlaps with the claimed 0.025 percent, and let's use one to three drops of brimonidine. So, even under this hyper-narrow construction of let's only use one drop, it's disclosed in Dean. And whether or not a person who has a particularly severe case of eye redness needs one drop, or two drops, or three drops, that's well within the routine skill of the treating physician or the pharmacologist that's going through and doing the dose response study finding.

And so there's no great significance to this notion or this artificial divide that the Patent Owner is trying to make between dose and concentration. And again, it's one of these situations where you start with sort of a general principle that dose matters when it comes to any sort of pharmaceutical ingredient, we're not saying otherwise, but when it comes to talking about dose in administering these eye drops, persons of skill in the

art talk about the concentration and rely on the concentration.

There was some brief discussion about some of the dependent limitations, this was on one of Patent Owner's earlier slides where my friend from the other side talked about low incidence of rebound hyperemia, maintaining normal interocular pressure, and the cause of the eye redness not being associated with any tertiary disease, and suggested that there's some meaningful daylight between those dependent limitations and those dependent claims and the independent claims. We submit to you that there's not, and certainly not any expert testimony on the Patent Owner's side that would suggest there's any meaningful difference or meaningful challenge to those limitations.

With respect to low incidence of rebound hyperemia, we submitted an unrebutted declaration about the claim construction of what it means for there to be a low incidence of hyperemia, rebound hyperemia, and that's a population-wide assessment. And so it's not something that measures in any individual patient. Either the brimonidine is going to have that statistical property or it's not going to have that statistical property. And so it's inherent in the actual administration, which as Patent Owner's Counsel said, is inherent. Brimonidine at low concentrations does not cause rebound hyperemia, that's just a property and a result of the administration. And there's no meaningful challenge to that inherency argument there.

The same is true for the normal interocular pressure limitations, and that of course makes sense, because when you want to talk about minimum effective doses, there was an understanding that a minimum effective dose for brimonidine to lower interocular pressure was much, much higher than the low concentrations claimed here. And so by administering a

drug that there isn't enough of it to achieve a particular effect, of course that's an inherent property with the drug.

And then, finally, this concept of not being associated with surgery or diseases, we submitted the largely unrebutted testimony from Dr. Galanis who says that the cause of eye redness, the claims are agnostic to it. The claims require a method of reducing ocular hyperemia. Ocular hyperemia is the vasodilation of the blood vessels in the eye, and that's caused because something happened to the eye, whether it's trauma, whether it's allergens, whether it's a cold or a virus. That condition, that event, is going to start a biological response, your inflammatory response. And as part of that -- again, whether it's caused because of a Lasik surgery, caused because someone poked you in the eye, or caused because there's too much pollen in the air, that inflammatory response is going to cause your blood vessels to dilate and cause eye redness.

Now, the brimonidine, it doesn't treat the cause, it doesn't cure your allergy, it doesn't affect the trauma that's caused by Lasik. What it does, and what it acts on, is the alpha-2 agonist receptors in the blood vessel. So it treats the blood vessels itself, not the thing that caused the blood vessels to swell and enlarge in the first place. And so again, this notion that the surgeries or the disease have any significance to the obviousness of these claims is just inconsistent with both the science and also the specification which relies in large part on an example using Lasik to say, this is how well our drug works, we caused this trauma and the brimonidine group did so well.

So, with that, unless the Board or Panel has any other questions, I didn't need any of my extra five minutes, so I'm happy to answer any

questions.

JUDGE FLAX: Thank you very much.

MR. DINER: How much time do I have?

JUDGE YANG: You had four minutes, but since there was some technical issues, we'll give you an extra two.

MR. DINER: You're giving me an extra two minutes? Okay, very good.

JUDGE YANG: Well, let's see how it goes.

MR. DINER: Okay, very good. Well, let me just start off with regard to the claim construction issue. At the end of the day, what it is still is a low dose, okay? And everyone agrees that it's a low dose, and from that perspective what is administered as a low dose in the claimed invention for Claim 1 of the '245 Patent is going to be significantly lower than what is administered in Norden or Gil for the reasons that I mentioned.

Now, my friend discussed the Hong reference. I'd like to spend just a moment on the Hong reference. The Hong reference wasn't to measure hyperemia or any reduction in hyperemia. What they were looking at was to prevent hemorrhage. And there's a difference. If you think about it, with regard to vasoconstricting in order to reduce hemorrhage and subsequent bleeding complications, you're looking at trying to reduce the blood vessel caliber of a blood vessel that's not very dilated or swollen at all.

So if you think about it in the context of a balloon example, if you constrict a normal blood vessel that doesn't have a whole lot of -- it's not engorged with blood and doesn't have a ton of blood rushing through it, all you're doing is just making that a little bit thinner, so that when it comes into the surgery it's less prone to damage.

However, when you're looking at trying to reduce hyperemia in the context of vasodilated hyperemia, and you have a blood vessel that is engorged, you've got to actually exert enough vasoconstriction on that balloon. If you think of a balloon filled with water, you've got to exert enough vasoconstriction on that to even have any meaningful visible effect in terms of redness reduction.

And the fact that Hong is looking at 0.15 percent brimonidine in a single drop, it's still six times higher than 0.025 percent brimonidine. He didn't measure hyperemia, he only looked at whether or not it could reduce subconjunctival hemorrhage. For the reasons I mentioned, it doesn't necessarily tell you enough about whether it would work for reducing vasodilated hyperemia.

On top of that, we're backstopped by, again, the Alphagan clinical studies, which I'll say a little bit more about, which, pre-August 2008, generally the POSA didn't expect -- and these are clinical studies that are done on hundreds of patients for more than a decade -- didn't expect from that data that you would have sufficient vasoconstriction to actually manifest as redness reduction. And that is further backstopped by Exhibit 1029, which is a peer-reviewed journal in the Ophthalmology Journal, it's in Petitioner's exhibits, and that's where it says at 0.2 and 0.5 you get vasoconstriction, you go below that, you're not getting enough of vasoconstriction to be any better than what you see with a vehicle or a placebo.

And so that is a very powerful message that one skilled in the art takes. When they look at that in the context of what my friend said about Hong and the Alphagan clinical studies, I think there is a very big difference.

Now, on the Alphagan clinical studies, again, they're not just an assembly of separate studies. As I said, the clinicians in the Alphagan clinical studies were regularly looking across those studies and comparing adverse events. And if the clinicians in the Alphagan study were doing it, so too would the person of ordinary skill in the art, especially that person who has six to nine years collectively of experience in formulating eye drops for clinical trials and regulatory approval.

Now, I'd like to spend a few minutes on -- two minutes, I guess, on the closest prior art. So, on this point, the closest prior art, they said, oh, well, you chose brimonidine. Or you didn't choose brimonidine, you chose Visine, and it doesn't have brimonidine in it. And they said, well, the law says you want to pick, at least for the closest prior art, something that has the compound in it. What they cited for that was the BMS case. The BMS case is not a method of using an old -- it doesn't claim a method of using an old compound. What it claims is a compound, per se. And so it's a structural obviousness analysis. So, clearly, in that case, you're looking at what is structurally similar.

Well, when you're looking at a process claim or a method of use claim, in this case we're looking at a method of reducing eye redness. It has already been held by this Board in the prior decision that Example 1 -- which is not, by the way, directed to a single drop of 0.03 percent brimonidine; it's a dosing regimen of putting in approximately equal to a single drop of 0.2 percent brimonidine -- that is not a method of reducing eye redness.

And so if the reason that this claim exists is because, as the prior Board held, in terms of its novelty, it was novel and not anticipated by

Example 1, the first step is, do I have what I'm claiming here as a method of reducing eye redness? That question was answered in the In re Merchant case.

It also had a situation whereby, in Merchant, you had a method of removing hydrogen fluoride gas, hydrogen fluoride from HCL gas. And it used a dry technique. The closest prior art, according to the Board, which would ultimately be reversed by the Federal Circuit, was a method of removing hydrogen fluoride from air and using a dry technique. That's like analogous to brimonidine here. And the CCPA said on appeal, no, that's not the closest prior art. Just because it has the dry technique, like you're claiming by analogy, what we're claiming in our method, brimonidine, doesn't make it the closest prior art. You have to start with what the claim is covering, and the claim there was directed to a method of removing HF from hydrogen chloride gas. The closest prior art also, according to the CCPA, was also directed to a method of removing HF from hydrogen fluoride gas, even though that closest prior art used a wet technique and not the dry technique. And that's on all-fours, essentially, with our case.

The second problem with 0.03 being the closest prior art is, that's what the prior Board considered to be obvious. You can't compare the closest prior art for purposes of unexpected result against what you think is obvious. That would mean you would have to test the invention, ultimately, against the invention itself, and that's never been the law. And that's also something that we detail in our Patent Owner's response. The point is, is that, with regard to Millennium, if you were going to take 0.03 from Example 1 as the closest prior art, again, it's not a single drop, it's six or seven drops just prior to surgery. It's in the context of RK surgery, and it's

also administering many other active ingredients.

So you're effectively dismantling, deconstructing Example 1, and saying, I want you to compare against what I think is obvious, which is a single drop of 0.03 against your Lumify product in a redness-relieving test. That is not the law, that's never been a law. That runs headlong in opposition to the Millennium case. And that's why -- that's why what Petitioner is arguing is the closest prior art cannot be the closest prior art as a matter of law.

And when you look at the Merchant case, in that factual scenario, what they said you want to do is basically try to see how many of your elements in your claim match up with the closest prior art. And in our comparison between Visine we have redness reduction, we have 0.025, we have alpha agonists, and we have actual redness reduction. We have alignment straight through.

You're looking at me like I'm going over now. Am I too long?

JUDGE YANG: You are going over. And all these points I know, as a matter of fact, are in the briefs. If you need another sentence or two to finish up, you may go ahead.

MR. DINER: I'll just say, namaste. Thank you very much.

JUDGE YANG: Very good, thank you. Well, thank you to counsel for both parties. This argument is actually very enjoyable. I like it. Unfortunately, you cannot both win. You guys can still negotiate and settle, then that would be win-win. But at the Board, somebody will lose. But your clients should be very pleased with your performance. I think you did a great job. We will look at the briefs and issue final decisions. Hopefully, we'll get some guidance from the Federal Circuit. These cases are submitted

and we are adjourned.

(Whereupon, the above-entitled matter went off the record at 4:09 p.m.)

IPR2024-00467 (Patent 11,833,245 B2)
IPR2024-00563 (Patent 11,596,600 B2)

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