IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ALLERGAN, INC.	*	Civil Docket No.
	*	2:09-CV-97
VS.	*	Marshall, Texas
	*	
	*	August 4, 2011
SANDOZ, INC.	*	1:15 P.M.

TRANSCRIPT OF BENCH TRIAL
BEFORE THE HONORABLE JUDGE T. JOHN WARD
UNITED STATES DISTRICT JUDGE

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P R O C E E D I N G S

COURT SECURITY OFFICER: All rise.

THE COURT: Please be seated.

Proceed.

MR. DENNING: Thank you, Your Honor.

ROBERT J. NOECKER, M.D., PLAINTIFF'S WITNESS, PREVIOUSLY SWORN

DIRECT EXAMINATION (CONTINUING)

BY MR. DENNING:

Q. Good afternoon, Dr. Noecker.

A. Good afternoon.

Q. The next reference that the Defendants looked at with their experts yesterday that I want to show you

is DTX155.

A. 155.

Q. I believe this is the Airaksinen article?

A. Yes.

Q. And this is one in which they compared two different concentrations of the Timpilo drug to -- to Pilocarpine; is that correct?

A. Yes.

Q. And you already testified about Timpilo and Pilocarpine and the effects of -- the adverse effects of Pilocarpine on the eye, correct?

A. That's correct.

Q. Was -- did the addition of Timolol to Pilocarpine and Timpilo make it better?

A. It did not seem to be. Did not seem to.

Q. If we could look at the graph on Page 589, please, and we see on the left-hand side on the top, looks like the -- a Timpilo with .5% Timolol and 2% Pilocarpine; the middle one is .5% Timolol and 4% Pilocarpine; and then the bottom is Pilocarpine by itself.

Do you see that?

A. I do.

Q. And what does this graph show you?

A. Poor control of intraocular pressure. It's

important -- so this graph we have to be a little bit careful with, because unlike the other graphs we looked at earlier, which are frequently across times of day by hour, this drop on this graph is mean average.

So in this study, they put a drop in of the medication and then they checked -- they checked the eye pressure, put a drop in, and then checked the eye pressure two hours later. And then this data is mean IOP of those two morning timepoints.

So this is a study where they only collected morning data, so it doesn't tell us anything about the effect on afternoon data.

And then they had a run-in period on the beta-blocker. And this is over a three-week -- this is days, 21 days to 42 days of average IOP. So, once again, it should be capturing the best timepoint, and then the morning -- the morning, you know, less effective timepoint.

So it doesn't tell us anything about afternoon pressure. But when you look at this, the eye pressures are all over the board. So this is even day-to-day. So this is not some fluctuation we were talking earlier about within the day.

You know, this patient started, if this was a patient in my practice, once again, Patient Mrs. Jones'

pressure is in the 20s, we put you on this drug or two drugs. We don't know what your eye pressure is going to be the next time you come in.

Maybe one time it's 18, kind of below the overflow limit. The next time, it's above on the next visit. So this is not somebody we say, okay, see you in six months. I'm sure everything will be fine.

So this is poor eye pressure control, and we -- you know, we wouldn't use this, because it's showing the poor IOP control of this combination drug.

Q. Thank you, Dr. Noecker.

And just to -- before we move on, what does Airaksinen teach a person of ordinary skill in the art about combining Brimonidine and Timolol in a fixed combination drug?

A. Nothing. And it might give you pause about combination drugs in general.

Q. Thank you, Dr. Noecker.

Let's move on to Defense Exhibit 148, which was the Clineschmidt article.

MR. DENNING: Thank you, Mr. Exline.

Q. (By Mr. Denning) This is the article in which they were comparing Cosopt on the one arm versus BID Timolol and TID Dorzolamide monotherapies; is that right?

A. That's correct.

Q. And if we turn to Table 3 of this study --

MR. DENNING: Which appears on -- on Page 1955, Mr. Exline.

Q. (By Mr. Denning) -- what time periods are they measuring with this study?

A. They're looking at the pre-dose in the mornings of 8:00 a.m., putting the drop in, and then two hours, once again, at the time we'd expected to be the most efficacious. So morning time points, two hours apart.

Q. Okay. Does this show anything about that afternoon trough at all in this paper?

A. It doesn't give us any afternoon information.

Q. Okay. Well, let's look at what it shows for -- for the morning pressure.

MR. DENNING: If we could go and, Mr. Exline, highlight on the bottom for month 3 and the change, the second to the rightmost column, and then highlight for the combination and for Dorzolamide -- I'm sorry -- second to the right, Mr. Exline.

There you go. Right there.

Q. (By Mr. Denning) So what -- what do we see here as the comparison between Dorzolamide as a monotherapy and then the Cosopt combination?

A. So the combination of Cosopt combination drug had a -- a mean change of minus 4.4, kind of the best -- best timepoint, the 10:00 a.m. timepoint.

Q. Would you -- and compared to 2 points lower for Dorzolamide; is that right?

A. Correct. So about 2 milliliters of mercury better. So when determining how much benefit Timolol is giving us, adding on top of the Dorzolamide, it's about 2 millimeters is what we see in this study.

Q. And what -- what impact does it have that this is at hour 2 versus if it were at hour 8?

A. Once again, this is the best timepoint, because it only goes -- gets worse from here. So this kind of tells us a best-case scenario, that two hours post-dosing is as good as it's going to get. So we -- by inference, we would suspect that it will be less of a beneficial effect in the afternoon.

Q. Okay.

A. We don't know exactly how much, but that's -- it's going to be the best. That's all we can tell you.

Q. Okay. And at hour 0 up above for the same -- for the same 2 in month 3, we see a difference from 2.8 to 1.4; is that right?

A. That's right. It's about 1.4, 1-1/2, yes.

Q. Okay. Earlier when we looked at the

demonstrative from opening that showed the afternoon trough, do you remember that?

A. Yes.

Q. And there was a -- the afternoon trough was about 3.25, I think, in that demonstrative.

Do you remember that?

A. I think it was 3.5.

MR. DENNING: Mr. Exline, are you able to pull that up?

A. You're talking about the difference between TID Brimonidine and BID Brimonidine?

Q. (By Mr. Denning) That's -- that's exactly right. That's what I was talking about.

A. I recall it being 3.5 millimeters of mercury. That's 3.25 --

Q. I think you may remember from Ms. Batoosingh's testimony when they looked at the actual underlying document. It was -- it was different.

A. Perhaps.

Q. But in any event, does -- the 1.5 to 2 millimeters of mercury benefit that we just saw from the Clineschmidt paper with regard to Cosopt, would that be enough to make up any afternoon trough in the difference between Brimonidine BID and TID?

A. Like I said, it doesn't give us really any

information regarding Brimonidine, but if you were to make the inference about what's the benefit of adding the Timolol in terms of eye pressure reduction, the most these other papers indicate it might be in the best, best-case scenario only at the morning is 1-1/2 to 2-ish, so not at the magnitude.

But, really, the inference I think you can draw is that magnitude may fall short. It's not going to be -- adding Timolol is just not going to be adequate.

Q. Okay. So what would one of -- what, if anything, would one of skill in the art learn from Clineschmidt about the ability to reduce the number of doses of Brimonidine from three doses to two doses by adding Timolol in combination?

A. That it would not be adequate to make up for the deficit we see in the afternoon -- that afternoon dip in IOP control.

Q. Okay. You may set that exhibit aside.

Dr. Tanna also looked at DTX200, and let's look at that briefly, if we could, please. This is the Boyle reference?

A. Yes.

Q. Now, again, this is a study looking at Cosopt, correct?

A. Correct.
Q. And Cosopt, meaning the combination of Dorzolamide and Timolol, correct?
A. That's correct.
Q. Okay. What does that teach you as a person of skill in the art about combining Brimonidine and Timolol?
A. It doesn't teach you anything, because different -- Dorzolamide and Brimonidine are different drugs.
MR. DENNING: And, again, if we can -- Mr. Exline, if you could look at Table 2, which is on Page 1948.
Q. (By Mr. Denning) Again, the only time measurements made with -- in the Boyle paper were at hour 0 and hour 2; is that correct?
A. That's correct.
Q. So does that tell us any meaningful information about what the midday IOP control would be, even for this combination?
A. All you can do is surmise that it's not going to be as good in terms of eye pressure lowering.
Q. Okay. And does the Boyle paper about Cosopt and the 0- and 2-hour measurements, what does that teach a person of skill in the art, if anything, about the --

combining Brimonidine and Timolol and the effects that that might be, if they were in a combination drug together?

A. Nothing specific to the Brimonidine/Timolol combination, but, once again, specific to the addition as Brimonidine -- or Timolol as a tool, it will fall -- it may fall short or probably will fall short in the afternoon.

Q. Okay. And if you could look at Table 5 in this paper as well.

This -- this one deals with the ocular and local adverse experiences. Do you see that?

A. Yes.

Q. And can you tell me, are there any -- did the combination in this study experience any reduction in adverse experiences than the individual therapies?

A. It didn't -- it didn't reduce any. It may have stung a little bit more.

Q. It may have stung a little bit more.

Okay. Thank you. You can set -- you can set that to one aside.

And the last one of the articles that they showed yesterday that I'm going to show you is DTX201.

MR. DENNING: If you could pull that up?

Q. (By Mr. Denning) This is the Hutzelmann

reference.

A. Yes.

Q. And this study, again, compared Cosopt on the one arm versus Dorzolamide BID/Timolol BID concomitant therapy, correct?

A. Yes.

Q. And, again, if we look at -- if we look at Table 2, which appears on Page 1251 --

A. Yes.

Q. -- we can see that they, again, took the measurements only at hour 0 and hour 2; is that right?

A. That's correct. Yes.

Q. I'm sorry. So, again, it tells us nothing about the afternoon trough; is that correct?

A. Right, same story.

Q. Okay. And if we look at the mean change.

MR. DENNING: I'm sorry, Mr. Exline. Please go back to that table.

Thank you.

Q. (By Mr. Denning) If we look at the change column, second from the right, at month 3, we see the combination and the concomitant are both at the exact same pressure reduction; is that right?

A. Right. So in terms of efficacy, it's neutral for the morning.

Q. Okay. So based on what you read in Hutzelmann, Dr. Noecker, what does it teach, if anything, one of skill in the art about combining Brimonidine and Timolol in a single combination treatment for intraocular pressure?

A. There's certainly nothing here specific for Brimonidine. And in terms of the addition of Timolol in a fixed combination, it doesn't seem like it's going to solve efficacy problems.

Q. Okay. So you can set that one aside as well, Dr. Noecker.

We've been through most of the art that the Defendants relied on yesterday at trial. Have you reviewed all of the art that Dr. Tanna and Dr. Laskar talked about yesterday?

A. Yes.

Q. And in your opinion, Dr. Noecker, as one of skill in the art, do these references -- would these references motivate a person of skill to develop a single composition drug of 0.2% Brimonidine and 0.5% Timolol?

A. No.

Q. Why not?

A. I have not seen compelling information that would lead me to -- looking at the -- all this prior

art, that there's a benefit to doing so. Basically, looking at Timolol to solve efficacy problems that are associated with Brimonidine.

Q. And in your opinion, Dr. Noecker, do these references provide a motivation to one of skill in the art that making a fixed combination of 0.2% Brimonidine and 0.5% Timolol could allow you to reduce the number of dosage of Brimonidine from three doses a day to two doses a day without losing efficacy?

A. No, I don't see any evidence here that would lead me to believe that, that you could successfully reduce the dosing interval from three times a day to twice a day --

Q. Okay.

A. -- of Brimonidine.

Q. Thank you, Dr. Noecker.

We need to do one more -- one more run through the claims now in light of all of these references.

MR. DENNING: So, Mr. Exline, if you could please pull up AGX512. And I think we can be even more efficient than last time.

Q. (By Mr. Denning) So here we have --

MR. DENNING: Do we have the other 512, Mr. Exline?

There we go. Thank you.

Q. (By Mr. Denning) Here we have all of the asserted -- all the claims at issue of the four patents that we're talking about. And, again, we have highlighted all of the limitations that relate to the .2% Brimonidine and .5% Timolol.

And my question -- those limitations appear in Claim 1 of the '976, 1 and 7 of the '258, 4 of the '149, and 1 and 4 of the '463.

My question for you, Dr. Noecker, on the obviousness analysis, is there anything in DeSantis/Timmermans, in light of all of the other references that you've seen in this Court, that would have taught one of skill in the art to choose the specific combination of 0.2% Brimonidine and 0.5% Timolol in a single combination?

A. I don't see any teaching in this prior art that would lead me to do so.

MR. DENNING: Okay. If we could pull up the AGX513, please, Mr. Exline.

Q. (By Mr. Denning) Now, we have put up only the claims that have the preservative BAK in it as well as the concentrations. And I want to direct your attention to Claim 2 of the '258, 8 of the '258, 2 of the '463, and 5 of the '463, each of which additionally claim the limitation of BAK preservative, Benzalkonium Chloride

preservative, at 0.001% to 0.01%.

And looking at those four claims, Dr. Noecker, is there anything in DeSantis/Timmermans, in light of all of the other references that you have seen in this courtroom, that would teach one of skill in the art to choose a specific combination of 0.2% Brimonidine and 0.5% Timolol in a composition with 0.001% to 0.01% Benzalkonium Chloride?

A. No.

Q. And with respect to claims 3 and 9 of the '258 and 3 and 6 of the '463, each of which include the limitation of BAK at a concentration of 0.005%, my question, Dr. Noecker, is, is there anything in DeSantis/Timmermans, in light of all of the references that you've seen in this courtroom, that would teach one of skill in the art to choose a specific combination of 0.2% Brimonidine and 0.5% Timolol with a preservative concentration of 0.005% Benzalkonium Chloride?

A. No.

MR. DENNING: And finally, if we could go to 514, Mr. Exline.

Q. (By Mr. Denning) We have Claim 4 of the '149 patent displayed, and this is the one that talks about a method of reducing the number of daily topical ophthalmic doses of Brimonidine administered topically

to an eye of the person in need thereof for the treatment of glaucoma or ocular hypertension from three to two times a day without loss of efficacy.

And with respect to that limitation, Dr. Noecker, my question is, is there anything in DeSantis/Timmermans, in light of all of the other references that you've -- you've seen in this courtroom, that would teach one of skill in the art a method of reducing the dose of Brimonidine from three doses to two doses without reducing efficacy in the treatment of glaucoma or ocular hypertension?

A. No.

Q. And why not?

A. Many of the -- much of the prior art does not really address the key timepoint, which is that afternoon trough, which is what's led to the labeling of Brimonidine. So we really don't have a lot of information or reason to believe that the addition of the Timolol to the Brimonidine would allow us to reduce the dosing interval without losing efficacy.

Q. So now, looking back at 512, 513, and 514, my ultimate question, Dr. Noecker, is, in light of the DeSantis/Timmermans reference and all of the other prior art that you've seen in this courtroom, is it -- what is your opinion regarding whether these claims of these

four patents would be obvious to one of ordinary skill in the art in 2002?

A. They would not be obvious.

Q. Now, in addition to -- to doing your anticipation and -- and obviousness analysis, have you also considered what are called objective considerations of non-obviousness?

A. Yes.

Q. Okay.

MR. DENNING: If you could -- if you could please pull up AGX111R.

Q. (By Mr. Denning) Okay. This is the -- this is the graph we've seen a couple times in your examination, and this is where you show the afternoon trough and the difference between Alphagan TID and Alphagan BID, correct?

A. Yes.

Q. Okay. With that in mind, if you could please grab PTX77 from your PTX binder.

A. Okay.

Q. And this is the Sherwood paper as it's been called, correct?

A. That's correct.

Q. And what are the treatment arms in this study?

A. This had Combigan, which was twice daily fixed

combination Brimonidine/Timolol. And then we had monotherapy with Timolol twice a day. And then we had Brimonidine monotherapy used three times a day. Those are three treatment groups.

Q. Okay. So we're comparing on the one hand Combigan in which patients are getting Brimonidine twice a day. And on the other hand, we're giving this concomitant -- concomitant therapy in which they're getting Brimonidine three times a day; is that correct?

A. They're getting monotherapy three times a day.

Q. Thank you for correcting me.

So there are three arms in this study. On the one hand, they're getting Combigan, which has Brimonidine, two times a day. On the second hand, they're getting Brimonidine three times a day. And then on the third hand, they're getting Timolol without any Brimonidine; is that correct?

A. That's correct.

Q. Okay. Thank you for correcting me.

MR. DENNING: If we could look at Figure 3 of this -- of this study, which appears on Page 1235 of the journal.

A. Yes.

MR. DENNING: One more page. There you go, Mr. Exline.

If you could blow up that figure in the top right corner.

Q. (By Mr. Denning) Can you tell us what this -- what this figure is showing, Dr. Noecker?

A. This is a result of the -- a graph of the result of this study in which they evaluated the -- the eye pressure, the eye pressure lowering of each of these three treatment regimens at four different timepoints during the day.

So in the morning before the dose, the eyedrop administration at 10:00 a.m., which is this peak best timepoint; 3:00 p.m., which is the problematic timepoint; and then 5:00 p.m., which is the final, end of the day for everybody, I guess, in the study.

So what we see is, once again, 10:00 a.m. the pressure is a little higher in the morning before everybody gets their medicine. 10:00 a.m. is kind of the expected peek efficacy of these drugs. So the lines go down; the points go down, and we see kind of the best-case scenario at 10:00 a.m.

And then we start seeing the afternoon, we see the change in pressure. We see that the timepoint that we worry about, once again, is this 3:00 p.m. timepoint. So the circles are the Combigan, the triangles are the Timolol, and the squares are Brimonidine.

And so being lower on the graph is better. We see Combigan occupies the lowest position in terms of IOP-lowering; Timolol next; and then Brimonidine at the -- at the top.

And then it goes back down later on in the day after dosing. So we see -- we see good or the best efficacy with the combination formulation.

Q. And particularly, if we look at the 3:00 p.m. and 5:00 p.m. timeframes, that's the afternoon trough we've been talking about, correct?

A. That's correct.

Q. And in both of those instances, the -- the subjects who were on the Combigan treatment, Brimonidine only twice a day, had lower mean IOPs than those patients who were getting Brimonidine three times a day in the Brimonidine monotherapy arm, correct?

A. That's right. Somewhat surprising.

Q. And that's even after the folks who were on the Brimonidine three-times-a-day therapy had their second dose of Brimonidine at 3:00 p.m.?

A. Uh-huh.

Q. And by 5:00 p.m., that had kicked in.

A. Right.

Q. Their pressures are still higher than those people who were on the Combigan treatment and haven't

taken any eyedrop since 8:00 a.m. that morning; is that correct?

A. Right. Even with the additional dose, it's still numerically better to be on the combination.

Q. Is this something that you as one of skill in the art would have found surprising in 2002?

A. Yes.

Q. And why is that?

A. I think, based on our experience, we'd expect that it would be kind of a neutral effect, that we wouldn't see this beneficial effect from adding the Timolol onto the Brimonidine to be able to be -- have a positive effect.

We suspect that it might have some positive effect, but that magnitude is really what's rather striking. It really eliminated that -- that difference we saw in those other studies, which was the TID dose, three-times-a-day dosing, and twice-a-day dosing.

Q. Okay. Thank you, Dr. Noecker.

Let's also -- let's change subjects slightly and talk about side effects. We've heard about ocular allergy a couple of times, and I don't mean to belabor the point, but did you bring some pictures to -- to show the Court what ocular allergies really are?

A. Yes.

MR. DENNING: And, Mr. Exline, if we could please bring up the first of those. I think it's called 510.

Q. (By Mr. Denning) What are we seeing in AGX510, Dr. Noecker?

A. A bad-looking eye. So what we see here is the eye is red. So the conjunctivae of vessel, the kind of clear covering that has the blood vessels, they're very engorged. So this would also show up in study reports as hyperemia. We've looked at tables reporting that side effect. So eye redness or vessel engorgement.

We see that the skin of the eyelid around the eye is kind of thickened and red and scaly. The color is not the best on this picture, but they kind of get this rubbery, flaky appearance on the skin that's really, really itchy. You can kind of see from across the room.

And then what we're trying to show here is the eyelid is pulled down, and we're trying to show the inner surface of the eyelid. It doesn't come out so great here, but you get these bumps called follicles. We were talking earlier about folliculosis. It looks like little fish eggs in there. So it's these little blister-like bubbles, hundreds of them on the inside of the eyelid, which kind of tells us that this is allergy

due to Brimonidine. So these people are miserable.

MR. DENNING: And if we could go to AGX511, please, Mr. Exline, the second of the two pictures you brought.

Q. (By Mr. Denning) What do we see here, Dr. Noecker?

A. So this is a patient of mine who's receiving -- we have another picture of Alphagan allergy in one eye, in her right eye -- this is the left one in this picture, she's getting nothing. So kind of normal-looking eye.

In her other eye, you see, once again, the vascular engorgement, the hyperemia, the kind of pinking around the eyelids, the eyelid changes. That's basically what you see on this. And a complaint of extremely itchy eye.

And this particular patient, who actually was one of my favorites, and she was somebody -- she came from Indiana, Pennsylvania. So she came from 80 miles away to see me, because she was on this drug and just miserable. She said, look, I walk around town and everyone tells me I look like a vampire.

And I helped her. I stopped the drug. I changed her therapy around because she was allergic. I said you have an allergy, and we stopped it, and she was

one of my happiest -- I know her well. I can tell you everything about her. She was my most loyal patient. Referred a hundred other people from this little town to come in and see me just because we recognized her allergy. We stopped it and made her a very happy person.

Q. In your experience, Dr. Noecker, are allergies common with Brimonidine as a monotherapy?

A. Over time, yes. We don't see them right away, but the longer patients are on the drug, they -- they tend to occur. The original Alphagan, why clinicians grew not to love it is because the rate would approach 25 percent, and over a longer period of time, probably a little bit higher than that.

Q. When you say the original Alphagan, you mean the Alphagan .2%?

A. The .2% formulation.

Q. Okay. In your experience, are allergies as common with Combigan, which also has .2 percent Brimonidine?

A. No, it's dramatically less.

Q. Was that surprising to you as one of skill in the art?

A. Definitely.

Q. If you could please, sir, pull up PTX9A, one

of the PTX exhibits. And we can see this is the clinical study 12T, the Combigan conducted as part of the Phase 3 studies -- sorry -- that Allergan conducted as part of the Phase 3 studies for Combigan; is that right?

A. Yes.

Q. Okay. And if you could turn to Table 12.2.2, which is on Page 89 of this clinical study, there's a table.

MR. DENNING: Mr. Exline, if you could please blow that up for us.

Q. (By Mr. Denning) And what does this table show us, Dr. Noecker?

A. These are adverse events that were recorded in this clinical study divided by organ system.

Q. And it shows on the left the -- the results with the combination therapy or what is Combigan, in the middle with Brimonidine as a TID monotherapy, and then on the right is Timolol; is that correct?

A. That's correct.

Q. Okay. And what -- what do you notice in the difference between the first two columns, the combination and the Brimonidine?

A. That -- that the, I guess, adverse -- we'll use the term adverse event, since this is in a study

protocol, allergic conjunctival folliculosis is much less in the combination group. Eye pruritis, which is itching, is much less in the combination group. The blepharitis rate, which you can presume may be allergic blepharitis, is lower. The allergic conjunctivitis rate is lower with the combination drug. Those are the things that pop out first.

Q. Now, the people getting the combination therapy were only getting Brimonidine two times a day versus three times a day for those in the Brimonidine monotherapy.

Were these results surprising nonetheless to you as one of skill in the art?

A. Yes. And I think it's -- I think it's -- part of it is why allergy occurs with Brimonidine, and I can explain that.

Q. Please do so.

A. So it really -- and we -- we've learned a lot of this basically because of the subsequent generations of lower concentration Alphagan. So with Alphagan P .15% and Alphagan P, what we saw on patients on those drugs is that their allergy rates dropped precipitously. It's because they were getting less drug exposure.

Why allergy occurs with Brimonidine is kind of interesting. So it has nothing to do with the way the

drug lowers eye pressure. So a lot of times these patients have great eye pressures. The bad thing is they have a red, itchy eye that's driving them nuts. So what happens with Brimonidine, it gets oxidized. Alpha-agonists are easily oxidized medications. And so just by being exposed to the air, oxygen is there; it turns it into this new compound, which is what people get allergic to. So the more drug that's kind of not going into the eye and hanging out on the surface until it gets washed away, increases the chance that they're going to get an allergy. So it's how much is in that time, in that two-minute period where there's drug on the eye. That's when the oxidation occurs.

Now, the bad thing in terms of allergy that Alpha-2 agonists do is they shrink cells. So other drugs don't do that. So you have this allergenic stuff hanging on the surface, and then the gap, the drug-shrunk cells increases the space between cells so that allergenic compounds get underneath the surface where all the immune cells are. And then people's eyes kind of blow up.

Clinically, we would see people would get allergic conjunctivitis and have come off the drugs during allergy season, probably because their allergic to the pollen, too, and that space made it easier for

the other stuff to get under there as well. So you have these biannual, bi-seasonal -- whatever the word is -- twice-a-year spikes in the spring and fall where allergies would tend to spike of people on Alphagan. So that -- that's why it's particularly bad with Brimonidine Alpha-2 agonists.

Q. Okay. And so does it surprise you that -- were these results surprising to you, even though the doses of Brimonidine in the combination therapy, too, were less than the doses of Brimonidine in the Brimonidine arm, which were three?

A. Yes, initially, until we figured out why.

MR. DENNING: If we could -- if you could pull up PTX9B, and we'll go through this one a little more quickly.

Q. (By Mr. Denning) But this is the 13T study from the Combigan clinical trials.

MR. DENNING: And, Mr. Exline, if you could go to the third page of this where it says clinical study -- back one, please -- forward one, please.

I think we have the wrong document, Mr. Exline. If that's 9B, then I wrote down the wrong number. I could do the ELMO, if that's easy.

Okay. That must have been my mistake

writing down the wrong (sic) for you.

Q. (By Mr. Denning) Okay. This is the -- the 13T study; is that correct, Dr. Noecker?

A. That's the title on this page, yes.

Q. Okay. And this was comparing the combination of twice daily with -- with Alphagan three times daily; is that right?

A. That's right.

Q. Okay. And if we look at the data on the next page, we can see that the combination arm is on the -- the left-hand column, and the Brimonidine arm is in the middle; is that right?

A. That's correct.

Q. Okay. And did we see a reduction in allergy in the 13T study like we did in the 12T study?

A. Yes.

Q. For example, I see eye pruritis has gone from 13 occurrences to 3 occurrences; is that right?

A. That's right.

Q. Foreign body sensation from 10 to 2?

A. Yes.

Q. And conjunctival folliculosis from 9 to 2?

A. Yes.

Q. Okay. And before you understood what was happening through this study, were those results

surprising to you?

A. Yes, not predicted at all.

MR. DENNING: If we go to JTX, Mr. Exline, please, and if we can go to Column 7, Lines 6 through 11, please.

Q. (By Mr. Denning) Did the inventors disclose in the patent the -- the allergic benefits to this combination drug?

A. Yes.

Q. We see here it says: The incidences of oral dryness, eye pruritis, foreign body sensation, and conjunctival folliculosis were statistically significantly lower with the combination than with the Brimonidine, while burning and stinging were statistically significantly higher with the combination than with Brimonidine; is that right?

A. Yes, it is.

Q. Okay. Yesterday -- we're going to turn to another reference, one of them that Dr. Tanna looked at yesterday, which was the Goni reference, DTX23.

MR. GOLOB: Your Honor, he doesn't discuss the Goni reference in his report at all nor does he talk about the study that goes with it.

MR. DENNING: Your Honor, if I may. I don't intend to ask his opinion. I just want to look at

some of the data in the Goni reference.

THE COURT: Let's see where he goes.

Q. (By Mr. Denning) Dr. Noecker, do you have the Goni reference in front of you?

A. What was the DTX number?

Q. It was DTX23.

A. Yes, I have it.

Q. Okay. And what drugs were being evaluated in the Goni reference; do you know?

A. This is a 12-week study comparing the fixed combination Brimonidine/Timolol with the individual components --

Q. Okay.

A. -- use.

MR. DENNING: And if I could -- Mr. Exline, if you could go to Page 583 and blow up the top paragraph in the upper left, the study design paragraph, please.

Q. (By Mr. Denning) Okay. Is that where it says this was a 12-week study --

A. Yes.

Q. -- Dr. Noecker?

And how long were the 12T and the 13T studies that we just looked at?

A. A year.

Q. A year?
A. Yes.
Q. Okay. Dr. Noecker, you can set the Goni reference aside.
A. Okay.
Q. And I want to look at one more, which is PTX123, which is the Motolko reference, Dr. Noecker.
A. Yes.
Q. This is a comparison of patients receiving Brimonidine monotherapy versus a fixed combination of Brimonidine and Timolol, essentially comparing Brimonidine to Combigan?
A. That's right.
Q. Now, in this instance, both arms of this study had Brimonidine BID; is that correct?
A. That's right.
Q. So there was no difference in which the people taking Combigan were only getting Brimonidine twice a day and the people doing Alphagan were getting three times a day, here in this Canadian paper, they were two times a day in each arm, correct?
A. That's right.
Q. Okay. And what's being measured in the Motolko paper?
A. Ocular allergy.

Q. Okay.

MR. DENNING: If you could turn to Page 3 of the study and blow up Figure 1 in the upper right-hand corner, please, Mr. Exline.

Q. (By Mr. Denning) Now, this study shows 18 months of data; is that right?

A. That's right.

Q. Is there a reason why 18 months is important in examining allergies?

A. Well, in this particular case, just when the -- when the allergy becomes more prevalent or the incidence rises, it's time-dependent. So the longer we look for it, the more that we'll see. And it tends to be a side effect that only gets worse with time. It's not like you can ride it out and it will get better. It's a one-way trip. The longer you're on the drug, the more likely you are to be getting it.

Q. Okay. So if you're assessing the allergy effects of a drug, would you look at an 18-month or a year-long study or a 12-week study?

A. For this particular drug, definitely 18 months.

Q. And we see here in the dark circles, the Brimonidine dosed twice a day, and then in the open circles, we see the Combigan dosed twice a day, correct?

A. Yes.

Q. And what does this data show you?

A. So it shows that the -- the rate of allergy in patients who are only getting Brimonidine is -- is much, much higher than those who are getting Combigan. So that -- and this is a side effect of, once again, you can see as time goes on, it's becoming more and more prevalent.

So it's a time that we're seeing side effects. So the rate -- when you have the Timolol in there, it seems to be -- the rate -- it lowers it significantly.

Q. And was that something that was a surprise to a person of ordinary skill in the art in 2001/2002?

A. Definitely, until we figured it out.

Q. Okay. Set aside ocular allergies now. We also heard earlier in this trial from Dr. Whitcup about sleepiness. Do you remember that?

A. Yes.

Q. What is the nature of sleepiness observed with Brimonidine?

A. So it tends to be related to the dosing. So somnolence that's reported upon is really dose-dependent. So the story we get in our patients is that we say, okay, take your eyedrop twice a day or three times a day. So they take their 7:00 a.m. drop

and about a half an hour later, they get really sleepy and fall into their cereal. So it's not really -- it kind of goes away.

So it's not like taking Benadryl or an antihistamine where you're kind of drowsy all day long. It really tends to be very much related and short-term related to the dosing. So you get it very shortly after dosing, kind of when you see the peak effect of the drug, peak absorption.

Q. Okay. Do you see that high rate of somnolence with Combigan?

A. Surprisingly, no.

MR. DENNING: If you can turn to JTX9E, and we can put it up on the screen.

Thank you, Mr. Exline.

Q. (By Mr. Denning) This is the Allergan 24T study, a Phase 3 study with Combigan; is that correct?

A. Yes.

Q. And if you could turn to Page -- that ends in the Bates No. 22630, and there's a safety assessments conclusion paragraph.

Do you see that sir?

We'll put it up on the screen for you.

A. Yes. Yes.

Q. And what's discussed in the first bullet point

under the safety assessments conclusion?

A. So this study, which was looking for sleepiness -- I mean, so it wasn't kind of an incidental finding in the study. They were kind of seeking out this side effect.

There was a highly favorable statistically significant difference between the treatment groups favoring combination with 9.2 percent responders in the combination group, and 19.3 percent responders in the concurrent group.

The risk ratio was 2.10, indicating a greater than twofold risk for sleepiness with concurrent or the combination.

Q. So somehow combining the Timolol with the Brimonidine cut the sleepiness side effect in half?

A. That's right. The Timolol is protected for that Brimonidine-based side effect.

Q. Okay. And you said that was a surprise. Why was that a surprise?

A. Because we -- it was something we've never observed with using these drugs for patients who happen to be on both drugs together. And it hadn't been reported in any other situation. So it was -- it was unique.

Q. Finally, Dr. Noecker --

MR. DENNING: If we can pull up PTX1, the '149 patent, and if we could go to Column 1, please, and Line 7 to 28 at the top, just that first paragraph.

Thank you.

Q. (By Mr. Denning) Do you see starting about Line 16 in the '149 patent, Column 1, Dr. Noecker, it says: There is, moreover, a long-felt need for an effective and safe topical ophthalmic pharmaceutical composition, including Brimonidine and Timolol, which has increased stability and requires a lower effective concentration of preservative as compared to the individual agents alone.

Do you see that?

A. I do.

Q. In your opinion, did that long-felt need exist in the industry in 2002?

A. It did.

Q. And then it says: Finally, there is a need to increase the efficacy of many topical ophthalmic agents without increasing the systemic concentration of such topical agents, since it is well-known that many of the topically applied ophthalmic agents cause systemic side effects, drowsiness, and heart effects.

Do you see that, sir?

A. I do.

MR. GOLOB: Your Honor, he did not opine on this. He opined that there was a long-felt need for a combination product. He did not mention Brimonidine and Timolol. He does not speak about systemic concentrations or anything like that. He just talks about a combination, a fixed combination period.

THE COURT: I don't know where the report is. Let me see it.

MR. DENNING: I'd be happy to modify my question, Your Honor, if that speeds up the process.

THE COURT: All right.

Q. (By Mr. Denning) Dr. Noecker, did you think in 2002 there was a long-felt need in the industry for a fixed combination drug to treat glaucoma?

A. Yes, because, once again, statistically, about a third of our patients needed more than one therapy. So while we had the prostaglandin analogs on the scene, we still had patients who would end up on multiple therapy. And some of those patients would be on Brimonidine and Timolol, and this would -- a fixed combination drug would help simplify therapy to decrease dosing and to decrease costs, fulfill a need in terms of compliance, et cetera.

Q. And did any other company develop a .5% Brimonidine and .2% -- I'm sorry -- a .2% Brimonidine

and .5% Timolol combination before 2002?

A. No.

Q. Did any other company develop a fixed combination drug with .2% Brimonidine and .5% Timolol before Allergan filed this patent application in 2002?

A. No.

MR. DENNING: One second, Your Honor.

Nothing further, Your Honor.

THE COURT: Okay. Cross-examination?

CROSS-EXAMINATION

BY MR. GOLOB:

Q. Are you ready, Dr. Noecker?

A. Yes.

Q. Good afternoon. I thought we were going to say good morning, but it's good afternoon.

I want to get a clarification on something, if I could right off the bat. I thought I heard your counsel ask you about whether you were giving an opinion on Claims 1 through 3 of the '149 patent.

And I believe you are not, correct?

A. Between Claims 1 through 3, no. Claim 4.

Q. Okay. So you're not giving any opinions on Claims 1 through 3 of the '149 patent?

A. No.

Q. With respect to invalidity?

A. No.

Q. Okay. In your rebuttal report, you cite the standard for obviousness, right?

A. Yes.

Q. And there was no U.S. requirement in the definition of your obviousness standard, right?

A. No -- I'm sorry?

Q. There was no requirement of it being somebody in the United States, right?

A. Right.

Q. Okay. And you also discuss an ordinary -- a person of ordinary skill in the art as well, right?

A. Yes.

Q. And your definition doesn't include a limitation of the United States as well either, right?

A. Didn't use the words United States, no.

Q. Okay. Now, you talked about some drugs earlier today that were available around the world. I think we talked about some combinations like Xalacom and Probeta and a few others.

Do you recall that?

A. Yes.

Q. Okay. So does the drug have to be available in the United States to be considered prior art?

A. No.

Q. All right. So I think you had a lot of discussion, but I just want to get some dates and make sure I'm pinning it down here.

You're agreeing that Cosopt was available on the market and publicly available prior to April 2002, right?

A. Yes.

Q. And so was Timpilo prior to 2002; it was available?

A. Not in the United States.

Q. No. It was available somewhere in the world?

THE COURT: Okay. I've been asleep up here. You think I don't write this down, that I don't know which one at this stage of this ballgame. And if you really think I'm that bad, you need to disqualify me. I'm obviously incompetent.

MR. GOLOB: No, we don't, Your Honor.

THE COURT: Why don't we move on then.

MR. GOLOB: Okay. All right.

THE COURT: I mean, if you want to lump them together for something, let's go, but come on.

MR. GOLOB: Okay. All right. I'll move on, Your Honor.

Q. (By Mr. Golob) So in your report, Dr. Noecker, you talk about all these fixed combinations, right?

That you talked about earlier, you talked about them in your report, right?

A. I talked about some fixed combinations, yes.

Q. But you don't give any timeframes with respect to their relation to any FDA analysis, right?

You do an FDA analysis, right? And you talk about the FDA and what -- that it would be very difficult to get through the FDA, and then you talk about all these other products, right?

A. We've talked about the drugs that failed at the FDA.

Q. Right.

A. Yes.

Q. But you don't give any timeframe for when they failed at the FDA or maybe they haven't even failed yet, right?

A. I don't think there were any dates of failure.

Q. Okay. And there's certainly no date of failure prior to April of 2002, right?

A. For which?

Q. For any of those combination products that you talked about?

A. Are you speaking for Xalacom, the post --

Q. I don't want to list them unless I bunch them altogether.

THE COURT: Go ahead and list them. That's not what your question was. Go ahead, Mr. Golob.

MR. GOLOB: Okay.

THE COURT: You've got cross-examination. You'd better use it as effectively as you can.

Q. (By Mr. Golob) So you talked about several fixed combinations that were available outside the United States but weren't available in the United States, right?

A. Yes.

Q. And you also talked about that they weren't available in the United States, because they didn't get through the FDA, right?

A. Correct.

Q. But you didn't talk about any timeframe for whether they were known to be failed before April 2002 or after April 2002, right?

A. I did not provide specific dates, correct.

Q. Okay. So you stated that most people in the industry were surprised by Combigan getting FDA approval, right?

A. Yes.

Q. And, again, that was way after the patents were filed, right?

A. Several years.

Q. It's good to be turning pages.

THE COURT: I don't want you to do anything -- fail to do anything you think's necessary.

MR. GOLOB: I understand, Your Honor.

THE COURT: But I don't need to be told things I've been told eight to ten times. That's what I'm hoping we don't do.

Q. (By Mr. Golob) So I want to move just very briefly to Timolol and Brimonidine just very briefly.

You would agree with me that .5% Timolol was the most prescribed beta-blocker for treatment of glaucoma and ocular hypertension prior to April 2002, right?

A. Yes.

Q. And you would agree with me that .2% Brimonidine was known prior to 2002 for treating glaucoma and ocular hypertension, right?

A. Yes.

Q. And both of them were preserved in BAK as you well know, right?

A. The .2% formulation and some of the .5% formulation and some .25%.

Q. Okay.

A. They're alternative formulations available.

Q. Right. But the most widely prescribed one was

.5% Timolol, and it was preserved in BAK, right?

A. Of the Timolol -- yes.

Q. Now, you said something today on direct, and you said that there was a .2 -- .25% Timolol that was actually preferred, which is different from what you just said to me now.

I just asked you if .5% Timolol was the most prescribed, and you said yes, but earlier in your direct, you said .25 Timolol was preferred.

A. Yes. That's what I said, for initial therapy.

Q. Okay. And all the studies you looked at up here earlier today, they were all .5% Timolol, right?

A. Yes.

Q. Now, I think we heard in opening -- you were here for Ms. Brooks' opening?

A. Yes.

Q. Okay. You heard that Allergan made gallant efforts to try to get .2% Brimonidine to be dosed twice a day, right?

A. Yes.

Q. And you know that outside of the U.S., Brimonidine at .2% is approved for use two times a day, right?

A. Yes.

Q. Okay. And I believe in your deposition, we

asked you if you yourself had dosed .2% Brimonidine less than three times a day, and you said yes, right?

A. Sometimes, yes.

Q. Okay. Now, I believe you also said that -- on direct a few times, that the .2% Brimonidine had some problems, and you actually thought it was kind of in disfavor by 2001; is that -- I don't want to mischaracterize your statement, but that's kind of what you said, right?

A. Yes. We were -- clinicians were getting tired of the allergy rate.

Q. Okay. And the FDA approval for Alphagan P .15 was August 2001, right?

A. I think so.

Q. So it would have just come out just prior to the patents in this case being filed, right?

A. Yes.

Q. All right. If you could turn to Exhibit DTX276. Well, if I can find it.

MR. GOLOB: Of course -- I apologize. I'm skipping around a little, Your Honor, so I'm looking for the document, but it's up there.

Q. (By Mr. Golob) That's an article that you authored, right?

A. Do I have this in a binder?

Q. You should. It's 276.
A. Oh, I have it here. I see it now.
Q. Okay. Is that an article that you wrote?
A. Yes, it is.
Q. And it's dated March/April 2002?
A. Yes.
Q. And you're the sole author, right?
A. Yes. There's a number -- there's a group along with that whose names are listed elsewhere, but, yeah, I was the author on this.
Q. Right. It looks like you get all the credit on this one, right?
A. Lucky me.
Q. Now, do you recall doing this study?
A. I don't. This is a long time ago.
Q. So that would be a no?
A. Not the intricate details.
Q. Okay. But this is a study, as it says, about Brimonidine .2% as a replacement for beta-blockers in geriatric patients with glaucoma, right?
A. That's correct.
Q. And at the expense of getting the wrath of the Court for both of us, we're not going to ask what the definition of geriatric is, right?
THE COURT: I probably qualify for that,

too.

A. I'll pass.

Q. (By Mr. Golob) So if you could turn to the page that is the sixth page, and it is just above the acknowledgments, the paragraph there. And it says: In many elderly patients, therefore, long-term use of topical non-selective beta-blockers may not adequately lower IOP.

Replacement therapy with Brimonidine twice daily significantly reduced IOP and improved quality of life. Brimonidine was also safe and well-tolerated in this large geriatric population.

Do you see that?

A. Yes.

Q. And it was the .2% Brimonidine that you were recommending here, right?

A. Yes.

Q. Thank you.

Now, I -- I don't want to belabor the point, but you were well aware of BAK as the preservative of choice, basically, in the 2001/2002 timeframe?

A. I'm not sure I would use preservative of choice.

Q. It was the overwhelmingly most -- most overwhelmingly used preservative at that time?

A. Probably not in artificial tear preparations or dry eye therapies --

Q. Doctor --

A. -- but in glaucoma therapies, yes.

Q. Yeah. So we're talking about glaucoma, in glaucoma for sure, right?

A. Yes.

Q. So I want to spend a little bit of time on DeSantis, and I know the Court has probably heard what he thinks all he needs about DeSantis, so we're going to try to --

THE COURT: I didn't say that now.

MR. GOLOB: No. I've heard all I want to hear about DeSantis.

Q. (By Mr. Golob) But let's talk about the patents for one second here, Dr. Noecker.

The patents in this case are directed to a fixed combination glaucoma product, right?

A. Yes.

Q. And the claims have three ingredients in them, right?

A. Yes.

Q. So the claims have Timolol, right?

A. Timolol is there, yes.

Q. Brimonidine?

A. (No response.)
Q. Is that a yes?
A. Brimonidine?
Q. I'm talking about the patents in this suit.
A. Oh, patents-in-suit.
Q. The four --
A. I thought we were talking about DeSantis. I'm sorry.
Q. No. We're talking about Allergan's four patents.
A. Okay. Yes.
Q. They are directed to a fixed combination glaucoma product, right?
A. Yes.
Q. And they have three ingredients in the claims, right?
A. Yes.
Q. They have Timolol, right?
A. Yes.
Q. Brimonidine?
A. Yes.
Q. And BAK?
A. Yes.
Q. There's no other ingredients in the claims, right?

A. I'd have to check closely, but we'll go with no for right now.

Q. Okay. So let's talk about DeSantis. So DeSantis was directed to treating glaucoma and ocular hypertension, right?

A. Yes.

Q. And DeSantis is a fixed combination glaucoma product, right?

A. Could you be more specific? Are we talking in the claims or --

Q. Anywhere in the patent. It talks about a fixed combination of a therapeutically effective amount of one or more Alpha-2 agonists and beta-blocker, right?

A. Yes.

Q. Okay. And as we've seen, Timolol is both in the title and in the claim as a beta-blocker, right?

A. Timolol does appear in the title, and Timolol does appear in the claim.

Q. Okay. And I think, if I understand your argument about Timmermans, you said the word Brimonidine is not in there, right?

A. Correct.

Q. Okay. But when you look at the structure, you know, as somebody skilled in the art, that that's Brimonidine, right?

A. After a fair amount of thought, yes, we can identify it. If we look up what Brimonidine looks like and look at in the paper and attach the groups together, yes, we can -- we can figure that out.

Q. So when I asked you at your deposition if you agreed with me that Brimonidine was disclosed in Timmermans and you said yes, you didn't have any of that qualification, did you?

A. I'll go with that answer.

Q. Okay. And, in fact, in DeSantis, when Brimonidine is -- is identified in the text, it's identified as the -- the U number, but it's also identified as the tartrate, right?

A. In Timmermans, you're talking about?

Q. In Timmermans, yes.

A. I'd need to look at that specifically.

MR. GOLOB: Can you put -- no. Timmermans, 124. So if you go to Page 20 -- the 28th page, or maybe it's the 12th page maybe. Go to the next page, please.

I believe it's the paragraph that says -- the third one down and the fourth one down. It may be one more up. I'm sorry. You know what? I'll come back to it, and I'll find it for you.

I'm sorry, Your Honor.

Q. (By Mr. Golob) All right. So let's get back to DeSantis.

A. Okay.

Q. So DeSantis incorporates Timmermans by reference, right?

A. Timmermans is listed in the references, right.

Q. Right. And, again, Timmermans is not listed for its purpose of being cardiac drugs; it's listed for showing clonidine and clonidine derivatives, right?

A. It's included in that big list of clonidine derivatives, yes.

Q. Right. Okay. Now, let's talk about the alpha-agonists, because you made this -- you had this chart where you had this 2.6 million number, something like that?

A. Potential combinations, yes.

Q. Right. So when you read, as one of skill in the art, DeSantis and you see Alpha-2 agonists, you're telling the Court that as one of skill in the art, you are looking at whatever that number was, 197 plus 56, and you're not thinking to yourself, well, what are the possible ones I could choose and know there's only three that are even remotely available on the market?

A. What do you mean remotely available? There's more than that available on the market. Which market

are you talking about?

Q. So in the U.S. market, how many Alpha-2 agonists were available in April of 2001?

A. Are you talking about ophthalmic --

Q. Yes.

A. -- eyedrop medications?

Q. I'm talking about ophthalmic eyedrop medications.

A. Okay.

Q. There was .2% Brimonidine, right?

A. Yes.

Q. What else?

A. In terms of alpha-agonist?

Q. Yeah.

A. Apraclonidine 1.1%.

Q. Okay. That was in disfavor, I believe you said, right?

A. For -- for -- I don't know if I used the word disfavor, but --

Q. That's the word you used in your deposition --

A. Okay.

Q. -- okay?

A. I'll go with that.

Q. Clonidine was the other one, right? And it's not available in the U.S.?

A. And Apraclonidine .5%.
Q. Okay.
A. So there's two different concentrations. And then we had Alphagan P .15%.
Q. In 2001? In April 2001?
A. April 2001. So Alphagan P may have come out after that.
Q. But the --
A. But it was known.
Q. So there were a very limited number that were known to you, right, that were commercially available in the United States?
A. As glaucoma medications.
Q. Yes.
A. But there's many -- in medicine, there's many other, you know, blood pressure medications, such as Timolol originally was a blood pressure medication, so...
Q. But if you're sitting there as somebody skilled in the art, you're going to think about making a combination glaucoma product, and you're reading DeSantis, your first thought isn't to think about, well, what are the Alpha-2 agonists that are on the market that might work?
That's not how you're thinking. You're

thinking, oh, my, there's 172 of them; I better check them all out?

A. Well, in some ways, we want to do better, because as I said before, we weren't like -- we don't look at those drugs as perfect drugs, and I think when you're coming out -- trying to come out with a new therapy, you'd like it to be better.

So I think you do take a look at, you know, what could be better. We do have some of these compounds which do exist as antiblood pressure medications, which is a long history of crossover from blood pressure medications becoming glaucoma medications. So I don't think -- I'd look at others to try to do better.

Q. How many combination products are available for glaucoma around the world where the base product isn't previously approved?

A. (No response.)

Q. So you have two actives in the fixed combination, right?

A. Yes.

Q. How many fixed combinations are you aware of that are available somewhere that have as one element of their fixed combination a drug that's not been approved in that -- in wherever it is?

A. (No response.)
Q. None, right?
A. I'm not aware, but I'm not sure of the -- outside the U.S., to be honest with you.
Q. You're not aware of any, right?
A. (No response.)
Q. Xalacom, you're not aware -- those two drugs are approved, right, Latanoprost and Timolol?
A. Approved for?
Q. Well, they're individually approved as monotherapy in the place where Xalacom is approved, right?
A. Yes.
Q. Okay.
A. I think I understand.
Q. So -- right. So no company that you're aware of has made a fixed combination glaucoma product in any country where the two actives weren't formerly approved as monotherapy, correct?
A. With the active ingredient itself, yes.
Q. Yes.
A. There's certainly different, you know --
Q. It's a yes or no?
A. It's a yes.
Q. Thank you.

So -- and as we said, DeSantis discloses BAK, correct?

A. Benzalkonium Chloride?

Q. Yes.

A. Yes.

Q. Okay. So -- and you knew -- we don't have to say it 50 times, but you knew and you talked about .2% Brimonidine was available and .5% Timolol was available as of April 2001, right?

A. Yes.

Q. I want to talk about an exhibit that you used.

MR. GOLOB: And, Mr. Exline, I know you're not employed by us. I'll give you 20 bucks, if you want. But could you put up AGX516?

Q. (By Mr. Golob) So this is a slide we used earlier, right?

A. Yes.

Q. And this slide showed basically that DeSantis was cited in the '258 patent, right?

A. Yes.

Q. Okay. So -- and Counsel asked you if the inventors submitted it to the Patent Office, right?

A. Yes.

Q. Do you know when it was submitted to the Patent Office?

A. Not off the top of my head.
Q. Well, would you be surprised if it was submitted in June of 2009?
A. Would I be surprised? No.
Q. Okay. And, in fact, would you be surprised if it was submitted by the inventors after the Defendants in this case gave it to Allergan in its infringement -- in its invalidity contentions?
A. No.
Q. And how many of the patents that you're opining on had issued already by June of 2009?
A. I have to check the dates.
Q. All of the others. '149 issued in 2006. You can look in your book. You have 1, 2, 3, and 4 as your JTX, but I'll submit that to you.
A. Okay.
Q. '976 issued in 2008, and the '463 issued in 2008. None of them have DeSantis cited in them, right?
A. Of the others, no.
Q. I'm getting corrected. It was added after the Defendant sent Paragraph 4 letters, not after they sent their invalidity contentions.
A. I'll take your word for that.
Q. Okay.
THE COURT: It was good that he corrected

that, because, otherwise, somebody else was going to correct it.

MR. GOLOB: Absolutely.

THE COURT: They're getting all excited at that table.

MR. GOLOB: And if it was Ms. Brooks, you know she said she loves to be right, so that would be definitely something she would do.

THE COURT: All right. We all got that out of the way. Now let's move along.

Q. (By Mr. Golob) Now, you talked a little bit about Claim 4 of the '149 patent, which is JTX1.

MR. GOLOB: Could you put that up for me, please, Savi?

If you can go to Claim 4, please. I'm sorry. That's the wrong claim. I need the method of manufacture claim in the -- in the '463. Exhibit JTX3, please.

Q. (By Mr. Golob) So you see this claim is about an article of manufacture comprising package material and a composition within, right?

A. Yes.

Q. Okay. So prior to April 2002, drugs were available in articles of manufacture, right?

A. Yes.

Q. They came in a bottle?
A. Came in a bottle, yes.
Q. The bottle came in a box?
A. Yes.
Q. They had a package insert in them?
A. Yes.
Q. They had indication on the package insert?
A. Yes.
Q. Earlier you talked a lot about a drug called Timpilo. Do you recall that?
A. Yes.
Q. And you made a lot of comments about four times a day was better than the combination; is that right?
A. Could you be more specific?
Q. I think you talked a lot about the fact that, you know, the Pilocarpine was better alone than when you -- it still needed to be four times a day, even though you were adding the Timolol to it?
A. I think we were talking about efficacy data at specific time points, if I'm not mistaken.
Q. I thought you were talking about that the four times a day was -- yeah. Okay. So you were talking about the four times a day was actually better, right?
A. In terms of efficacy at specific time points?

Q. In terms of in general.
A. Well, I'm not sure I said that.
Q. Okay. So -- because you realize that Timpilo is supposed to be dosed twice daily when it's the combination product, right?
A. Yes.
Q. Okay.
MR. GOLOB: Now, I do have that Timmermans, so I'll actually just put it on the, ELMO, if that's okay. Oh, okay.
A. Which -- which number is it for me to look up in my books?
Q. (By Mr. Golob) This is 124.
Do you see the UK-14,304-18 is Brimonidine, right?
A. Is it DTX124?
Q. DTX124.
A. I just like to look. And what page are we on?
Q. It looks like 13.
A. I'm there.
Q. Okay. You see the paragraph that I have on the screen? It says -- it mentions UK-14,304-18, and it's the tartrate form, right?
A. There's tartrate in parenthesis, yes.
Q. Right. So that's Brimonidine Tartrate, right?

A. Yes.
Q. Now, I want to move to -- you talked about a few things that you were surprised about.
A. Yes.
Q. Now, when you were talking about -- and I guess this goes toward your unexpected results analysis, right?
A. Can you be more specific?
Q. Well, you said that you were -- there was unexpected results with respect to -- at least in your report -- the reduction in ocular side effects, right?
A. Yes.
Q. And also the reduction in oral dryness?
A. Systemic side effect, yes.
Q. Okay. And general systemic side effects, right?
A. Yes.
Q. And when you talk about these reductions, you said you were surprised, right?
A. Yes.
Q. Okay. But you didn't produce to us any baseline data from which you would then be surprised of it, right?
A. Did I -- I'm not sure what you mean baseline data. I think I gave you my clinical experience.

Q. Let me ask it this way: So all of these comparisons were done where there was one less dose of Brimonidine, right?

A. Not all the comparisons.

Q. Well, the comparisons that you use in your report, the 12T and the 13T and the 19T, right?

A. Okay. Those studies, yes.

Q. Yeah. Those are the ones you used to say: I was surprised --

A. Okay. Yes.

Q. -- right? Those are all situations where you're comparing the combination drug, and the comparison is to some other kind of format, but that format has Brimonidine three times a day in it, right?

A. Yes.

Q. Okay. So -- and you testified that you would expect that you'd have some reduction in side effects because of the less dose of Brimonidine, right?

A. I think that's a theoretical thing, but that -- maybe. Maybe, maybe not, because the concentration didn't drop.

Q. It's more than --

A. The dosing interval dropped; the concentration didn't.

Q. But it's more than theoretical, because that's

what the results of the studies were, right?

A. Right, but that wasn't predictable.

Q. The conclusions don't say it was because of the drop in Brimonidine?

A. Can you point me to a specific sentence?

Q. Sure.

MR. GOLOB: If we put up DTX33, please. Yeah, this is not going to work.

COURTROOM DEPUTY: It's done.

MR. GOLOB: Oh. Thank you.

Q. (By Mr. Golob) So this is the clinical summary report that's already been used at DTX33, right?

A. Right. Which one is this?

Q. It's DTX33. Do you see it's the -- titled the Clinical Summary?

Do you see that?

A. I see the DTX number.

Q. Okay.

A. Which clinical study is it?

Q. So if you go to Page 3, do you see in the middle, it says Phase 3, 12T, 13T, 19T?

Do you see that?

A. Yes.

Q. Okay. So on the next page, it says: Overview Results.

Do you see that?

A. Yes.

Q. It says: Since patients receiving combination treatment had a reduced exposure to Brimonidine due to the BID dosing -- in other words, the combination product was only two times a day, but Brimonidine was three times a day in the other arm, right?

A. Yes.

Q. It was expected that the combination treatment would have a better safety profile compared to Brimonidine monotherapy.

Do you see that?

A. I see that sentence, yes.

Q. Okay. So it was expected that there would be a reduction in the side effects, right, because of the reduction in Brimonidine? You have one less dose; there's a third less, right?

A. I understand the logic. I'm not sure that that's reality, because one less dose -- when you look at which side effect you're talking about, a lot of it is concentration dependent. Once again, we talked about the transient appearance of the drug.

Q. Okay. But -- so my question is to you: You didn't provide any data to say: If we did this study, maybe the allergy conjunctivitis would go from 5.2% to

3.2%, but it went down to 1.4%, and that's why we're surprised.

You gave us no baseline data. All you're giving me is your subjective belief that you were surprised, correct?

A. Based on the decade of clinical experience, yes.

Q. But you didn't give me any baseline data to say: This is what I would have expected based on my 15 or so years of clinical work, and this is where it came out to be, correct?

A. Well, we have -- we have studies in the literature that we can cite that, you know, document the side effect profile of Brimonidine fairly well.

Q. What I'm saying is, you didn't do it. You didn't provide to us anything in your expert report where you said anything but your subjective belief that you were surprised, correct?

A. Yes.

Q. Now, as to unexpected results in general, you recall at your deposition we asked you if you had compared Combigan -- or the claimed invention -- I'm sorry -- if you had compared the claimed invention to the closest prior art.

Do you recall that?

A. Yes.

Q. Okay. And you, in fact, asked -- you didn't even know what closest prior art meant. Remember that?

A. In my deposition?

Q. Yes.

A. Yeah. It was 5:00 o'clock in the afternoon on Sunday in New York City. It was -- correct. I didn't answer.

Q. Well, it wasn't our fault that it was Sunday, right?

A. No.

Q. Your schedule didn't permit anything else, did it?

A. No.

Q. So -- but when we asked you, you didn't know what closest prior art meant, right?

A. At that time, I couldn't come up with a good answer.

Q. And you didn't actually do an analysis of what the closest prior art was, did you?

A. I think -- yeah, we took into -- I took into account what existed, yes.

Q. I didn't ask you that. I asked you if you put in your report: I did an analysis to determine the closest prior art, and here's what it is.

A. I don't think I included that statement.
Q. Okay. So you did not come up with what you thought was the closest prior art and do an analysis of that to the claimed invention, correct?
A. I don't think I included that statement in my report.
Q. Okay. In fact, you compared the claimed invention to several different therapies, right?
A. Yes.
Q. So you didn't pick one and say: This is the one, and I'm going to do the comparison, right?
A. Yes.
Q. And now, I want to talk a minute about your long-felt need analysis.
The statement in the patent, you would agree with me, that that might have been a little self-serving, recognize a long-felt need?
You saw -- your counsel put up a statement and said: Oh, there's a recognized long-felt need. That was in the patent, right?
A. Yes.
Q. It was a little bit self-serving, wouldn't you say? I mean, the inventors are saying it's a long-felt need, right, for a combination product? Is that what they're saying?

A. That's what they said, yes.

Q. Okay.

A. And I agreed.

Q. In your report, you say: There was a long-felt need for a fixed combination product for the treatment of glaucoma for many years, and in my opinion, the inventions of the patents-in-suit satisfied a long-felt need in the art.

A. Yes.

Q. Okay. So -- but you've acknowledged that there were other fixed combinations on the market prior to that time, right?

A. Yes.

Q. Cosopt?

A. Cosopt.

Q. You also state in a separate portion of your report that, quote: Indeed given that Combigan and Cosopt are the only fixed combination products on the market in the U.S., that long-felt need still exists.

A. I think it partially filled it, yes.

Q. But it still exists.

A. I think there's a long-felt need in general. I think Combigan certainly solves it for that subset of patients who, you know, take -- the possibility of the taking Timolol and Brimonidine exists, which is not all

patients. It's not the entire universe of patients we treat. But it satisfied a need for those patients without a doubt.

Q. But it didn't satisfy a long -- I mean, you can't have it both ways. You said it does and it doesn't. So -- you know what I mean? One time you say it does, and one time you say it still exists, right? Let's just take a yes or no to that.

A. I think in general terms --

Q. Wait. Wait. Can I get a yes or no first?

A. I don't understand your question.

Q. In one part of your report, you say it solved a long-felt need, right?

A. Yes.

Q. And in the other part of the report, you say the long-felt need still exists, right?

A. I think those are two different long-felt needs.

Q. Can I get a yes or no?

A. Those statements appear in the report, yes.

Q. Right. Exactly. Thank you.

Now, when you were doing all those numbers for DeSantis and got up to that 2.6-million-dollar number, one of the things you were talking about was --

THE COURT: I don't think he said

dollars. Am I confused on what this case is?

MR. GOLOB: Did I say dollars?

THE COURT: I thought you did.

THE WITNESS: Yes, you did.

MR. GOLOB: Oh, I'm sorry, Your Honor.

THE COURT: I'm used to those kind of numbers being thrown around, but I thought I'd really missed something.

MR. GOLOB: Okay. Sorry. I'm used to it being about dollars, too. I've never been in a patent case where somebody says there's 2.6 million possibilities for a combination.

THE COURT: Well --

Q. (By Mr. Golob) But -- so talking about that slide where you've got 2.6 million possible combinations -- do you recall that slide?

A. Yes, I do.

MR. GOLOB: Thank you. I was going to thank -- thank you, Savi.

Q. (By Mr. Golob) Okay. 2.68, right?

A. Yes.

Q. Okay. One of the -- there's three concentrations each you talk about, right?

A. Yes.

Q. And you said that that's because the FDA

requires you to test in the early stages three different concentrations, right?

A. That was the logic we were following, yes.

Q. Okay. And how is that relevant to obtaining a patent, the three possible different combinations that you might have to test at the FDA?

A. Well, I think it was actually that -- the FDA is thrown in there for -- to give context. I mean, theoretically, I guess -- I mean, I think this number is very conservative, because what you want to do in choosing different com -- you don't want to throw out an active ingredient or a formulation because you underestimated the amount of active ingredient you needed.

So it's -- it's basically pointing out that it's standard practice, especially in early phase studies, to do a spectrum, kind of a high, medium, low, to make sure that you don't miss, just because you got the concentration -- the active ingredients were good, but you missed because the concentration was wrong or the formulation was wrong. Maybe you changed something different.

Q. So let's try my question. But that has nothing to do with whether you can get a patent on a combination alpha-agonist, beta-blocker, and a

preservative, right?

A. I think it puts it into the context of what -- what information is available.

Q. Dr. Noecker, can I get a yes or no?

A. I'm sorry.

Q. And then if you need to say something --

A. I apologize.

Q. -- your counsel is going to stand up and get -- give you all the chance you want on redirect.

A. I apologize. What was the question?

Q. No problem.

Whether or not you need to test different concentrations for FDA approval has nothing to do with obtaining a U.S. patent.

A. Correct.

Q. Okay. So you can get a patent on a composition that doesn't get FDA approval. That's what DeSantis shows, right?

A. You can get a patent on that, yes.

Q. Okay. And, in fact, as we just discussed, the first patent in this case, the '149 patent, issued in 2006, right?

A. Yes.

Q. And it didn't get an FDA approval till 2007, right?

A. Yes.

Q. So they got a patent without getting FDA approval, right?

A. Yes.

Q. All right. So one more thing about DeSantis. So I believe earlier in your testimony, you said Brimonidine was a great drug.

Do you recall that?

A. Great at some things.

Q. Okay. And Timolol was the most widely used beta-blocker around at this 2002 timeframe, right, before the patents were filed?

A. I think it's still the most prescribed beta-blocker.

Q. Right. And the great drug, Brimonidine, you're talking about, we're still talking about in that April 2002 timeframe, right?

A. Which Brimonidine? Brimonidine .15%?

Q. No. Brimonidine .2%.

A. I like .15% better.

Q. But you said Brimonidine was a great drug, right?

A. Had several favorable attributes.

Q. Okay. And BAK was overwhelmingly used in ophthalmics, right?

A. I'm not sure about that. In glaucoma medications, maybe --

Q. I'm sorry.

A. -- but in other -- there's a growing realization that no new products contain BAK.

Q. In glaucoma medications, BAK was the overwhelming choice, right?

A. I would not say it was the overwhelming choice. I'm saying it was used. I don't think we liked it, but we used it.

Q. Okay. It was the most often used? Can we go with that?

A. We'll go with that, yes.

Q. Okay. So then you see -- you already told me that DeSantis discloses Timolol, right?

A. Yes.

Q. Okay. And DeSantis, through Timmermans, discloses Brimonidine, right?

A. Yes.

Q. Okay. And DeSantis discloses BAK, right?

A. Yes.

Q. And DeSantis is a fixed combination ophthalmic drug to treat glaucoma and ocular hypertension, right?

A. Are you reading --

Q. No. I'm just looking at you and asking you a

question.

A. It disclosed a fixed combination of Apraclonidine and Timolol, yes.

Q. It disclosed a fixed combination of an Alpha-2 agonist and a beta-blocker, right?

A. Yes.

Q. For treating glaucoma?

A. Yes.

Q. Yet you saw nothing in there, right? That's what you said. Nothing. A needle in a haystack, right?

A. I said needle in a haystack, yes.

MR. GOLOB: I pass the witness, Your Honor.

THE COURT: Redirect?

REDIRECT EXAMINATION

BY MR. DENNING:

Q. Dr. Noecker, would it surprise you if the Alphagan P .15% was approved by the FDA on March 16th, 2001?

A. No.

Q. And counsel for defense said August 2001. Would it surprise you if it was actually March 2001?

A. Actually, it makes A lot more sense. I actually should remember that, because other drugs were approved on that date. Now that you jogged my memory,

you're correct.

Q. Okay. And that was more than a year before the inventors filed for these patents-in-suit, correct?

A. That's right.

MR. DENNING: No more questions, Your Honor.

MR. GOLOB: No redirect, Your Honor.

THE COURT: You may step down.

THE WITNESS: Thank you, Your Honor.

THE COURT: Who will be your next witness?

MS. BROOKS: Your Honor, with that, the Plaintiffs would rest their rebuttal case.

MR. GOLOB: Your Honor, we have JMOLs on quite a few different points, if I could point them out.

THE COURT: Are you going to have any surrebuttal?

MR. GOLOB: We will. But they have not put up any evidence with respect to Claims 1 through 3.

THE COURT: Well, you know, this Court granted a summary judgment as to Claims 1 through 3. I don't think they're relevant at this stage. I think we mooted those, Counsel, at your request. I took them out of the case.

MR. GOLOB: I understand that, Your

Honor. We DJ'ed them, and just for completeness of the record for appeal, we just wanted to --

THE COURT: Well, you can make your motions, but I just want it clear that you took them out of this case as far as this Court's been concerned. At your request, I granted the summary judgment.

MR. GOLOB: Okay. Would you like us to wait until the end of all of the evidence?

THE COURT: I'm happy for you to do whatever you want to to preserve your record.

MR. GOLOB: Okay. So we will make a judgment, notwithstanding the verdict, that Claims 1 through 3 of the '149 patent are invalid for anticipation, obviousness, lack of written description, and lack of enablement.

We'll also make a JMOL that all of the claims of the remaining patents that are asserted are invalid under both anticipation and obviousness.

THE COURT: Denied.

I'll see y'all at 3:15.

COURT SECURITY OFFICER: All rise.

THE COURT: Be ready to go with your surrebuttal.

(Recess.)

COURT SECURITY OFFICER: All rise.

THE COURT: Please be seated.

All right. Who will be your first witness?

MR. DAVIS: Your Honor, before we call our first witness, the attorneys would like to proffer our deposition designations into evidence. We've prepared binders for each party, and we'd like to put those in evidence.

THE COURT: All right. Have y'all got it in electronic form so that you can put it in as an exhibit?

MR. DAVIS: Yes, Your Honor.

THE COURT: Okay. Just as the docket -- whatever the next docket -- whatever the docket number is in the file, and the Court has got a hard copy as I requested. Thank you.

(Witness sworn.)

THE COURT: Let's proceed.

JOEL W. HAY, Ph.D., DEFENDANT'S WITNESS, SWORN

DIRECT EXAMINATION

BY MR. MCTIGUE:

Q. Good day, Dr. Hay.

Would you please introduce yourself to the Court.

A. Afternoon, Your Honor. My name is Joel Hay.

Q. Dr. Hay, who are you currently employed by?

A. Currently employed by the University of Southern California.

Q. And what is your job title at USC, Dr. Hay?

A. I'm a professor and founding chair of pharmaceutical economics and policy.

Q. How long have you been at USC?

A. More than 20 years.

Q. I'd like to direct you to DTX273 in your notebook. Do you recognize this document?

A. Yes. This is the report I prepared for this case.

Q. Dr. Hay, can you please just briefly describe your educational background, experience, prior to joining the faculty at USC?

A. Yes. I got my bachelor degree from Amherst College in 1974; got a master's degree and Master of Philosophy from Yale University; and then I got my Ph.D. in economics from Yale University in 1980.

Q. Doctor, after you finished graduate school, what was the next thing you did in research?

A. After graduate school, I became an assistant professor first at the University of Southern California and then at the University of Connecticut Health Sciences Center. And both of those positions, I was

working on health economics and pharmaceutical economics.

Q. And when did you finish up at the University of Connecticut?

A. I believe that was around 1982. At that point, I then moved to Project HOPE Center for Health Affairs --

Q. What is that?

A. -- in Millwood, Virginia.

That's a -- Project HOPE is a global non-profit charity that provides American healthcare services and education to less developed countries around the world and also health policy services.

Q. Where did you go after Project HOPE, Dr. Hay?

A. After Project HOPE, I went to the Hoover Institution at Stanford University. That's a think tank that looks at a variety of both international and domestic policy issues. I was the health and pharmaceutical economist at Hoover.

Q. Is it correct, Dr. Hay, that throughout your career, you have studied economics and economical issues associated with healthcare?

A. Healthcare and pharmaceuticals, yes.

Q. Do you have any areas of specialty within the field of economics?

A. Well, my primary focus is on pharmaceutical economics.

Q. What is pharmaceutical economics?

A. Pharmaceutical economics is the application of economic theory, principles, methods, and investigation techniques to pharmaceutical markets, pharmaceutical industry, pharmaceutical R&D, intellectual property, the value of different pharmaceutical products.

Q. Are there any areas of particular interest for you in your research?

A. Well, I certainly, along with that, look at issues of outcomes research, econometrics, quality of life evidence, health policy, evidence-based medicine, but it's all generally in the rubric of pharmaceutical economics.

Q. Doctor, have you published peer-review articles in these areas?

A. Absolutely. I've published over 300 scientist abstracts, posters, and presentations and over 150 peer-reviewed scientific publications in the scientific literature on these topics.

Q. Are you an editor of any of these peer-reviewed journals?

A. I was founding editor and chief of Value in Health, The Journal of the International Society of

Pharmacoeconomics and Outcomes Research.

Q. That's a mouthful. I'm going to call it pharmaceutical economics. It's the same thing, right?

A. Yes.

Q. Have you ever worked in the private sector or as a consultant on pharmaceutical economics?

A. Yes, I have. I've worked for a number of different government agencies, federal, state, local. I've worked for international agencies. I've worked for non-profits.

I've done consulting in the pharmaceutical industry for most of the big pharmaceutical companies. And I've done legal expert consulting, again, for pharmaceutical companies, both generic and brand name.

Q. Doctor, have you ever testified in a patent case as an expert on the topic of commercial success or a pharmaceutical product in general?

A. Yes. I've testified in federal court in two commercial success patent cases for pharmaceutical products. In one case, I testified for the plaintiffs; in the other case, I testified for the defendants.

Q. Have you ever been disqualified as an expert in the area of commercial success?

A. No.

MR. MCTIGUE: Your Honor, Defendants

present Professor Joel Hay as an expert in the field of pharmaceutical economics, including the analysis of secondary indicia of non-obviousness, such as commercial success.

THE COURT: Allow him to testify according to the disclosures of his expert report filed in this case.

Q. (By Mr. McTigue) Dr. Hay, what is your opinion as to whether or not Combigan is a commercial success?

A. My opinion is that Combigan is not and hasn't been a commercial success. The clear weight of the evidence shows that it's not a commercial success.

In addition, I see no nexus between any indicators of commercial success shown for Combigan and the claims of the patents-in-suit.

Q. Dr. Hay, did you review any reports from the other experts retained in this matter?

A. Yes. I reviewed the reports of Dr. Noecker and Dr. Tanna.

Q. As part of your analysis, did you review the patents-in-suit?

A. Yes.

Q. And other than the patents-in-suit and the various expert reports, what Allergan documents did you review in forming your opinions?

A. I reviewed a number of Allergan documents. I looked at business plans, marketing research, market documents, financial documents, a number of different Allergan documents.

Q. Doctor, were you in the courtroom this morning when Mr. LeCause testified?

A. Yes, I was.

MR. MCTIGUE: Savi, would you please put up the gross sales slide that Mr. LeCause testified to today?

Q. (By Mr. McTigue) Doctor, this is a demonstrative slide counsel used in their opening, and obviously, they switched it today to make an adjustment to -- I know you have some issue with your color, but there is a green line, and they adjusted that, so it's no longer trending down; it's almost flat.

But other than with that representation to you, this is the gross sales slide that was used this morning.

A. Yes.

Q. Dr. Hay, does this indicate commercial success to you?

A. No.

Q. Why not?

A. This -- this chart only has these two lines,

gross sales and marketing spend, and there's some very important things that are missing from this chart.

Q. Do you agree in using gross sales in the commercial success analysis for Combigan?

A. Absolutely not. If you want to determine commercial success, you have to look at what kinds of rebates, discounts, coupons, and charge-backs are included to get those gross sales.

Q. Dr. Hay, did Mr. LeCause take into account these rebates, coupons, and/or price discounts for Combigan in his determination this morning?

A. No.

Q. How does this affect your analysis?

A. It definitely would change the slopes, change these lines.

Q. Did you prepare any demonstrative slides in response to this demonstrative slide?

A. Yes, I did.

MR. MCTIGUE: Please bring up Hay 1.

Q. (By Mr. McTigue) Now, we have put the -- again, the blue line and the green line. The blue line here represents gross sales, correct, Doctor?

A. Yes.

Q. And the green line with that one representation that it's now trending flat is what

Plaintiffs used this morning.

Did you add anything to this, Doctor?

A. Yes, I did. Using the data from that financial P&L, profit and loss, document that Mr. LeCause looked at this morning, I added in the net sales and the sum of all marketing and discounts.

I extended it out through 2011, because there was also data for the first quarter and -- and so I just did a simple straight extrapolation of that.

Q. So if I understand, this red line is a combination of what Mr. LeCause looked at, which used to be the green line, and what you've determined is the rebates, discounts, coupons, or charge-backs, correct?

A. Right. It's the sum of the marketing expenditures and all the rebates and discounts.

Q. And then the blue line, which I'll submit to you is the second line, what is that again?

A. That's now the net sales. And as you can see, the net sales that flattened out as of 2011 are actually starting to decline.

Q. Professor, this goes to the end of 2011. We're not at the end of 2011, so how did you do your analysis?

A. Well, even the first quarter of 2011 shows a decline in annualized sales for 2011. And so that's how

I compute it. I just annualize the first quarter of 2011.

The important thing to look at in this slide, though, is that the gap between net and gross sales continues to widen from time period to time period. And, in fact, if you just look at even the first quarter of 2011, there's a 50 percent increase in rebates and discounts in that one time period.

So we're seeing really all of the increase in gross sales being accounted for by increased discounts, rebates, and coupons.

Q. Dr. Hay, what's the source of the information for the graph that you've created here?

A. Well, as I said, this is from that profit and loss financial statement, and I've got some concerns about that data. It's -- it's not audited. There are a lot of discrepancies in that data.

There are a lot of entries, which I'm not sure what exactly they mean, but this was what I had to work with, in terms of -- of looking at net sales and -- and rebates.

Q. Did you do any analysis on your own, outside of Plaintiff's profit and loss statement, to render your opinion, Dr. Hay?

A. Well, I certainly looked at a number of other

data sources. In particular, I looked at the IMS data.

Q. What is IMS data?

A. IMS Health is a major third-party data collection service for the pharmaceutical industry. They collect information on pharmaceutical sales, pharmaceutical prescriptions, marketing expenses, detail expenses, journal advertising, contacts, free samples, all of the things that go into marketing and promotion. And it's widely used by the industry, because they want to keep track of how effective their marketing efforts are.

Q. And so did you utilize this IMS data to do any comparisons yourself?

A. Yes, I did.

Q. Okay.

MR. MCTIGUE: Okay. Could you bring up Hay 2, please.

Q. (By Mr. McTigue) Doctor, if you could orient myself and the Court to what we're looking at here, please.

A. Okay. So this is IMS Health data, which we could only get back to 1998, for the entire class of drugs in the glaucoma IOP category. And these are all the drugs that have been launched in the last 15 years still on the market. And so there's one drug that's --

that's off of here, because it was withdrawn from the market.

But basically what this shows is that if you adjust for time from launch -- and you sort of have to do that, because Combigan is, I think, about the most recent drug launched into this market -- you can see that from year of launch forward, Combigan is that lowest line down in the bottom. I think that's a gold color.

It's performed the worst in terms of any of these drugs, in terms of garnering market share over time. So that by year four from launch, it's way below any of these other drugs.

Q. Doctor, if you included another drug within this -- the one that you said wasn't on the market anymore, would it change your opinion?

A. No. That would be just another drug that didn't do well.

Q. Dr. Hay, these four years are not the same four years, are they?

A. No, no. For example, Xalatan, which is way up there on the top, I believe was launched somewhere around 1996. And that's why I only had two years of data on it, because my set only goes back to 1998.

But you can see that one did extremely well,

in terms of garnering market share in the first four years.

Q. Well, I want to talk about the relevant market and why, for instance, you included Xalatan.

Dr. Hay, why did you select these products?

A. Well, I read the expert report of Dr. Noecker, and I couldn't find any definition of the relevant market in -- in that expert report. Nothing from the other side gave me a definition of the -- of what the relevant market is. So I didn't have anything specifically to rebut in terms of a relevant market.

So to decide what are the appropriate comparators, which is what an economist does -- this is what economists in this area specialize in, is defining what is in the relevant market -- we look at what drugs are reasonable substitutes for each other.

And all the evidence that I could see in this case suggested that all of these drugs and maybe other things belonged in the relevant market. For example, maybe even laser treatments, maybe even surgery, maybe even some other types of interventions might belong in the relevant market.

So I -- I didn't define the outer limits of the market, but it was pretty clear from what I saw in this case that all of these drugs are in the relevant

market.

Q. Doctor, just -- again, what is the source of the data in this chart?

A. The source of this data is IMS Health sales revenue -- gross sales revenue, as reported for each of these drugs going back over time. And it's adjusting for the fact that the market is actually changing over time. The market, I think, is growing over time.

So we're not trying to penalize Combigan because it was a bigger market; we're saying, out of all the drugs available at each point in time from time of launch, what percentage of the market did each of these drugs get.

Q. Doctor, there's been talk of monotherapy, concomitant therapy. What, if any, consideration did you give to initial monotherapy medications as being in the relevant market?

A. Well, I heard Mr. LeCause this morning, as well as his deposition testimony, indicate that Combigan is sometimes used as initial therapy. Certainly I've seen nothing to suggest that Allergan wasn't concerned about initial therapies, as well as adjunctive and combination therapies.

And so -- in fact, they don't even break out their sales for Combigan by initial versus second line

versus third line, nor do they do that for any of the other products. So I think it's reasonable to conclude that all of these drugs are in the relevant market.

Q. So if all the IOP lowering agents are in the relevant market for Combigan, what does this do to Combigan's share?

A. Well, what it says is that by 2010, Combigan's share was only about 5.4 percent of the entire market.

Q. Professor Hay, did you consider any other assertions by Allergan's marketing executives in determining the relevant market?

A. Yeah. I saw the testimony of Mr. Bogard, who's a senior director of global marketing research for Allergan, and he stated that Combigan is a -- definitely a small share of the glaucoma market.

Q. Okay. I want to switch gears from what the market is to what are some of the metrics you used.

Doctor, first explain to us, what does the term cumulative revenue mean to you?

A. Cumulative revenue would be the dollar sales that a product garners year on year on year. So, for example, if in the first year they sold a hundred dollars worth, second year $200 worth, third year $300 worth, then the cumulative revenue over three years would be $600.

Q. Okay. Now that we know what it is, why is it relevant to your analysis?

A. Well, again, it's a measure of how rapidly a product is able to garner sales, and obviously, faster is better.

Q. Did you prepare a table on your analysis of the cumulative revenue of Combigan?

A. Yes.

Q. Okay.

MR. MCTIGUE: Please pull up Hay 3.

Q. (By Mr. McTigue) Again, Dr. Hay, if you could orient us to the table.

A. Okay. So here, as I did with the previous slide, I tried to keep things on a level playing field by taking every drug from the year of launch, not to penalize Combigan, and you can see that, nevertheless, by five years out of launch -- and this, again, is annualizing the Q12011 data -- Combigan, which is the third line down -- but these are the alphabetic, so that doesn't mean it's No. 3 -- is actually the worst performing of all of these drugs by year five from the year of launch.

For example, Xalatan by year five had achieved $900 million plus in cumulative revenue.

Alphagan P, by year five from launch, had

achieved $865 million dollars.

Combigan, which performed the worst, had only achieved about $350 million by year of launch.

Q. Doctor, Combigan launched in late 2007, correct?

A. Yes.

Q. So at least for year one, what did that do to Combigan's revenues?

A. Well, it kept those revenues somewhat small, because it launched in October of '07. But even if you look at -- at Combigan compared to the other drugs in year four, it doesn't do as well as the -- as any of the other ones.

Q. You said Combigan was one of the more recent launches, correct?

A. Yes.

Q. Did you adjust for inflation in this chart?

A. No. And if I had adjusted for inflation, Combigan would look even worse, because most of these drugs, like Xalatan, Alphagan P, Cosopt, et cetera, launched much earlier, and so the numbers would actually be much larger for them.

Q. Did Allergan's expert or the testimony you heard today indicate that Allergan examined cumulative revenue for any of their glaucoma medications for

purposes of their Combigan commercial success analysis?

A. I didn't see any evidence that Allergan's expert or -- or any of the testimony of the Allergan people, like Mr. LeCause, even considered the performance of Combigan in terms of sales, or anything else for that matter, relative to any of these other IOP drugs.

Q. Okay. We've talked a little bit about financial performance. I'm going to switch gears with you, and I want to talk about the second part of your analysis.

Beyond your opinion that Combigan has not been a commercially successful product in the glaucoma market, do you have any opinion on whether the sales of Combigan are driven by factors other than the claimed invention?

A. Yeah. I think the evidence that I've seen overwhelmingly suggests that the sales of Combigan are driven by marketing, discounting, rebates, coupons, the kinds of things we saw in those two lines that I added to the initial chart there.

Q. What are some of the materials that you reviewed to determine that aspect of your commercial success analysis?

A. Well, again, IMS provides information that

allows you to look at marketing expenditures and other things. They don't allow you to look at discounts and rebates. So for that, I had to use this same profit and loss financial statement that we've already talked about a couple times.

Q. And did you prepare a slide on this analysis?

A. Yes.

MR. MCTIGUE: Can we bring up Hay 4, please?

Q. (By Mr. McTigue) Dr. Hay, I think this is a chart on marketing and promotional expenditures. It is -- got a lot of numbers on it. So if you could explain for the Court what this chart is telling us.

A. Yeah. Okay. Well, this is only part of the chart, and there's a lot of other numbers on here, which I had problems with as well.

But in any case, if you take this chart at face value, what Allergan says internally is that cumulatively over the 2007 to 2010 period, they were spending 35 percent of their gross sales on marketing, even more, their net sales.

Q. So if I understand you correctly, this is out of Allergan's profit and loss statement as they've asserted to us, correct?

A. Yes.

Q. And you just bifurcated it and shortened it down in your expert report, right?
A. Correct.
Q. Okay. So what numbers on this chart are yours, and what numbers are Allergan?
A. All the numbers are Allergan's except for the bottom row, where I computed the percentage of gross sales, which is represented by the sum of all of the marketing and promotion expenses, for example, the 5099, the 5041, and the 5299.
Q. So cutting to the chase, this 35 percent number, what does that number represent, Doctor?
A. What that says is that for every dollar of gross sales, 35 cents was spent on marketing and promotion --
Q. And did you --
A. -- not to mention the discount.
Q. And did you analyze that 35 percent relative to the market?
A. Yeah. I looked at IMS data, which also only has gross sales. So that's why I couldn't compare to net sales for the IMS data.
But for gross sales on the IMS data, I looked at the entire pharmaceutical industry. And what they show is that on average, a branded pharmaceutical

company only spends about 6 percent of its gross sales on marketing and promotion.

So what we're seeing here is that Combigan spent five or six times as much as the average brand name pharmaceutical.

Q. Doctor, I want to turn to share of voice. Can you tell us what a share-of-voice analysis is in a commercial success setting?

A. Yeah. Share of voice is, out of all the money that's spent for a certain therapeutic category, in this case, glaucoma medications, all the money that's spent by all the drugs in that class on marketing and promotion, what percentage of that was spent by a specific product, in this case, Combigan.

Q. Did Mr. LeCause or Allergan's expert analyze whether any of Combigan's sales were driven by share of voice?

A. No. They didn't even look at marketing expenditures or share of voice.

Q. Did you?

A. Yeah. What I found was that in -- cumulatively through 2010, Combigan spent 11.5 percent of the $1.4 billion spent on marketing and promotion for this class. They had more than 10 percent of that. They had 11.5 percent, and they only garnered 3.2

percent of the market over that same period.

Q. Did you prepare a table on your analysis, Professor Hay?

A. Yes, I did.

MR. MCTIGUE: Can you bring up Hay 5 for me. Thank you.

Q. (By Mr. McTigue) Again, this is out of your expert report, is it not?

A. Yes.

Q. Okay. Could you orient the Court and myself to this chart.

A. Yeah. This looks at year four post launch, which is the only complete year that we have for Combigan, and what it shows is the cumulative marketing spend for all of these drugs alphabetically is the ones that are brands that have been launched in the last 15 years.

And what you can see in the first column is the cumulative amount of money they spent on marketing.

What you can see in year four is how much of the market they've gained, they've garnered through that marketing spending.

And in the last column, what you can see is how effective their marketing is in converting people to buy their product. So it shows how many millions of

dollars each of these products had to spend to get 1 percent of the market share.

So what you can see is that Combigan is by far the worst of any of these products. They had to spend $24 million for each 1 percent share of the market, whereas you look at the one right above them, Alphagan P, they only had to spend $3.4 million for each 1 percent share of the market.

Cosopt, the one right below them, they only had to spend $4.8 million for each 1 percent share of the market.

So -- and all of the rest of them had to spend a lot less than Combigan did for each 1 percent share of the market.

Q. And so based on this analysis, Professor, does Combigan's 24.02 million per share point tell you anything about the nexus with the claims of the patent-in-suit?

A. It tells me that they're -- that what's driving sales here is marketing. They can't convert people to -- to buy this product, except by spending an inordinate amount of money on marketing and promotion.

Q. Doctor, I want to turn to profit now.

Did you hear Mr. LeCause say this morning that Combigan was profitable?

A. Yeah -- well, he said it had a positive net income.

Q. Do you have an opinion about whether Combigan has a positive net income?

A. Yeah. I don't think it does.

Q. Why not?

A. For several reasons. But in particular, I -- I looked at the same document that Mr. LeCause looked at. That was the only one I had.

MR. MCTIGUE: Could we bring up PTX136, please?

Q. (By Mr. McTigue) Dr. Hay, do you have any particular concerns with PTX136 that you'd like to share with the Court?

A. Yeah. I think I have a lot of concerns with this document. I think, if we look at very last column -- or we can look at this one right here. We can stay right where we are -- they're claiming that they're selling a lot of Combigan in '07 through 2010, and yet there's no distribution or freight charges.

They're getting to distribute this for free? I don't know how you distribute a drug for free. And yet every year the distribution cost is zero. So that's a big problem.

Q. Is that just one example?

A. That's one example of many.

In addition to that, where do they get the marketing numbers in this chart, the marketing costs in this -- they just roll a ratio of Allergan's entire eye care market, 19.4 percent. That seems to be pulled out of a hat. It's not based on any rigorous auditable estimate of the cost of marketing Combigan.

G&A, that's just rolled out at 2 percent of sales, which makes no sense. And if you look at the last column, everything is zero for 10 years, 1996 through 2006, except what they call R&D.

Now, this morning it was unclear to me, based on Mr. LeCause's testimony, what is thrown into R&D. He seemed to say, well, all that's marketing back in '06. That's part of R&D, which doesn't make any sense.

Legal, back in '06 through 1996, that's all part of R&D which, again, I find a little perplexing.

Q. Doctor -- Doctor, if expenses are tied to a percentage of sales --

A. Uh-huh.

Q. -- and Combigan hasn't been launched yet, would this chart show any expenses for sales?

A. No, not if there's simple percentage of sales. That's why I find it perplexing. I don't think it's a realistic assessment of the actual marketing costs,

certainly prior to launch of the product.

And then another big problem with this P&L sheet is, if you look at net income before taxes --

Q. Where is that, Doctor?

A. That's down there at the bottom. That's one of the things that Mr. LeCause talked a lot about, the last --

Q. Then I'll let the record reflect that's 70,065 or 70 million, correct?

A. Yes. Over the cumulative time period, that's 7 -- $70 million, a little bit more than that. And what you see is that before income tax, the numbers identical to after income tax.

So they're claiming it's a profitable product, and yet they're not paying any income tax on it. They must have strange ways of doing their tax filing.

Q. Did you prepare any analysis of those lines from Allergan's profit and loss statement, Professor Hay?

A. Yes, I did.

MR. MCTIGUE: Please bring up Hay 7 now. No. Hay 7.

VIDEO TECH: Hay 7?

MR. MCTIGUE: Table 4 of his report.

THE WITNESS: Probably the next page.

MR. MCTIGUE: There we go. Sorry about that.

Q. (By Mr. McTigue) Now, Professor, the net income after taxes that's the top line, is that your line, or is that Allergan's?

A. That's taken right out of the P&L chart that we were just looking at. Every -- all of those numbers are right out of that chart.

Q. Okay. And the source here is the P&L chart, correct?

A. Yes.

Q. But the bottom line, is that out of Allergan's chart, or have you done some analysis on that?

A. No. What I did was adjust the numbers in the top line for the fact that you have to deal with the cost of capital.

Q. What is cost of the capital?

A. Well, it's time discounting that -- that any finance person does, any economist does. And what it basically says is that a dollar in the future -- a risky dollar in the future is not worth as much as a certain dollar today.

And so you have to adjust for that using a discount factor, which is standard in the industry as weighted average cost of capital.

Q. Doctor, the profit and loss statement had a 51-million-dollar charge for clinical trials, and it was in a bucket from 1996 to 2006. How did you account for that $51 million?

A. Well, clearly, not all $51 million in the R&D costs, if that's what they were, occurred in 2006. We've already heard testimony that they were doing clinical trials, you know, in 2000, probably in the 1900s as well. And so some of that 51 million is -- in fact, I would guess probably most of it goes back much earlier.

So I simply averaged it over the prior 10 years in that column and then did a simple time discount adjustment, and instead of 51 million, it's actually $170.761 million.

Q. And not going into your WACC analysis, but, Professor, ultimately, what did you come to as the net income adjusted by WACC for 2011?

A. If you just do that simple WACC adjustment, the 53-million-dollar net income that Mr. LeCause presented is, in fact, a 52-million-dollar net loss.

Q. If there was a 52-million-dollar net loss or maybe a carryforward loss, Allergan wouldn't be paying any income taxes on it, correct?

A. That would be one explanation for why they're

not paying taxes.

MR. MCTIGUE: I pass the witness, Your Honor.

THE COURT: Okay. Cross-examination.

MR. SHEAR: Thank you, Your Honor.

My name is Chad Shear, and I'm an attorney with Fish & Richardson representing the Plaintiff.

CROSS-EXAMINATION

BY MR. SHEAR:

Q. Dr. Hay, good afternoon.

A. Good afternoon.

Q. I'd like to start where you began with the demonstrative that you put up where you added the additional lines to the -- to the demonstrative that Mr. LeCause had this morning.

Do you remember that?

A. Yes.

Q. And the first four years on that demonstrative, that was actual data, right?

A. Yes.

Q. Thank you very much.

A. It was data from the P&L statement.

Q. Sure. Okay.

And -- and the numbers that you have for 2011,

those are your -- those are estimated numbers, right?
A. Taken from the 2011 Q1 data annualized.
Q. Okay. And you estimated that at the end of 2011, the sales would be 140 million for Combigan?
A. I believe so, yeah. The gross sales?
Q. Yes.
A. Something like that.
Q. And did you -- did you hear -- you were in the courtroom today when Mr. LeCause testified; is that right?
A. Yes.
Q. And did you hear Mr. LeCause say that internally within Allergan, they're projecting the sales for 2011 to be 155 million?
A. I don't specifically recall that, no.
Q. But if Mr. LeCause is right, and those numbers are correct, then your graph is wrong; is that right?
A. Well, it depends on what the discounts are to get to the hundred. Maybe they're discounting even more than they did in the first quarter.
Q. But you'd agree 155 million is higher than the 140 that you estimated here.
A. Right. And the discounts could be even higher.
Q. Okay. Now, Dr. Hay, I think -- I think I

heard you testify that you had some trouble understanding Allergan's P&L; is that right?

A. There were a lot of perplexing entries in that table, yes.

Q. Okay. And -- and in light of the fact that you had some troubles understanding Allergan's P&L, you still feel comfortable offering the opinion today in Court that Combigan was not a commercial success?

A. Well, in the totality of everything I've looked at, that was just one set of information I looked at. I looked at a number of other things and --

THE COURT: Why don't we answer the question he asked you. He didn't ask you what else you looked at. I'm not going to put up with it, Dr. Hay. You've testified too many times in too many courts, and you answer the question on cross that he asked you, and don't start giving me a lecture.

We got that clear?

THE WITNESS: Yes, sir.

THE COURT: Good.

A. Yes.

Q. (By Mr. Shear) Now, Dr. Hay, I'd like to talk about your experience a minute, if you don't mind. And I want to make sure I get it right. I think you said that your title -- you're the professor of

pharmaceutical economics and policy; is that correct?

A. Yes.

Q. And -- and so I -- is it fair, then, that -- that you -- is it -- start over. Let me see if we can get this comprehensible.

You've spent a lot of years studying the pharmaceutical industry, right?

A. That's correct.

Q. And -- and from that work and your work in the Hatch-Waxman cases that you've been involved with, you understand that drug development is an expensive process, right?

A. Yes.

Q. There's a lot of costs associated with developing a product.

A. Yes.

Q. There's research and development expenses, right?

A. Yes.

Q. There's the cost of Phase 1 clinical trials.

A. Yes.

Q. There's the cost of Phase 2 clinical trials.

A. Yes.

Q. There's the cost of Phase 3 clinical trials.

A. Yes.

Q. And then there's the expense of FDA approval.
A. Yes.
Q. And -- and it's all a risky proposition. You're not guaranteed it's going to work, right?
A. That's correct.
Q. And the reward for an innovator like Allergan is, in the end, they might get a patent out of it, right?
A. That's the business model, yes.
Q. Okay. And that patent gives them a -- a period of exclusivity in which they can try to recoup everything they have just spent bringing that drug to market, right?
A. Yes.
Q. And, Dr. Hay, you would agree with me, that it's our patent system that has allowed the creation of more new drugs and more new biomedical innovations in this country than any other country in the history of the world.
A. Yes, that's true.
Q. Now, Dr. Hay, I don't remember. Were you in the courtroom for opening statements?
A. No, I wasn't.
Q. Okay. So you didn't hear -- counsel for the Defendants said that -- that Combigan was the worst

performing brand name glaucoma medication launched in the last 15 years.

A. No, I didn't.

Q. Well, Dr. Hay, you are aware, though, that represented over here next to me are four of the largest generic drug companies in the world, right?

A. I don't know that specifically.

Q. But you are aware they're all here.

A. I don't -- I don't keep track of generic companies, to be honest. I don't know which ones are big and which ones aren't. Sorry.

Q. That's -- that's fair enough. But you would agree with me that there are four generic drug companies represented over here vying for the right to sell a copy of a drug which you say is a commercial failure.

A. That's correct.

MR. SHEAR: No further questions, Your Honor.

THE COURT: Redirect?

REDIRECT EXAMINATION

BY MR. McTIGUE:

Q. Quickly, Dr. Hay.

Counsel mentioned the cost of FDA approval can be high, right?

A. Correct.

Q. Was there anything in Allergan's profit and loss statement that reflected regulatory costs for FDA approval?

A. Not that I can see.

Q. And there are four generics. Is the model for generics different than the business model for a branded pharmaceutical company?

A. Absolutely not. Just because a product is or is not profitable for a brand name company has nothing to do with whether or not it's profitable for generics. They -- they're different business models. As we said, the brand name companies engage in certain kinds of clinical trials and certain kinds of other marketing activity that generics don't have to do.

For example, generics have mandatory substitution laws in the United States, so they don't have to do marketing.

So the fact that a product is commercially successful or is not commercially successful for a brand product says nothing about whether it could be commercially successful for generic companies.

Q. Thank you.

MR. MCTIGUE: No further questions.

THE COURT: All right.

MR. SHEAR: No questions.

THE COURT: You may step down, Dr. Hay.

THE WITNESS: Thank you, Your Honor.

MR. RUZICH: Good afternoon, Your Honor. We call -- Defense calls Dr. Laskar.

THE COURT: All right.

MR. RUZICH: And good afternoon, Your Honor. Rich Ruzich again for Sandoz and the rest of the Defendants.

THE COURT: He's still under oath. You might put that on the record.

Doctor, you understand you're still under oath.

THE WITNESS: I do.

THE COURT: All right. Let's proceed.

MR. RUZICH: Thank you, Your Honor.

PAUL A. LASKAR, Ph.D., DEFENDANTS' WITNESS, PREVIOUSLY SWORN

DIRECT EXAMINATION

BY MR. RUZICH:

Q. Dr. Laskar, you heard Dr. Noecker admit that he is not a formulator, correct?

A. Yes, I heard that.

Q. And are Dr. Noecker's opinions in keeping with his admission that he is not a formulator?

A. Yes, I believe that to be the case.

Q. Dr. Laskar, how many expert formulators have testified during this trial?

A. I've been present throughout the week, and to my -- up until now, only myself.

Q. And have you ever testified in court before?

A. No, I have not.

Q. Okay. Dr. Laskar, Dr. Noecker testified that he was surprised that you, as an expert formulator of more than 30 years, would believe that Brimonidine would be your sole choice as the alpha-2 agonist in formulating a fixed combination glaucoma product containing an alpha-2 agonist as of 2002.

Do you recall Dr. Noecker's statement to that effect?

A. Yes, I do.

Q. And what's your reaction?

A. I'm surprised that he would make that observation.

MR. RUZICH: Can we pull up AGX112, please?

Q. (By Mr. Ruzich) Now, Dr. Noecker repeated that DeSantis disclosed hundreds of thousands, as a matter of fact, millions of different possible combinations of a glaucoma containing an Alpha-2 agonist.

Do you recall that right here (indicates)?

A. Yes, I certainly do.
Q. Now, Dr. Laskar, would a person of ordinary skill in the art, in formulating a fixed combination glaucoma drug with an Alpha-2 agonist, be reading DeSantis as disclosing so many combinations?
A. A person of skill in the art would -- upon reading DeSantis, immediately would envision that that list is truncated to a very narrow list of both alpha-agonists and certainly beta-blockers.
Q. Okay. And so this whole analogy about this needle in a haystack really comes down to a strand -- a single strand of straw in the eyes of a person of ordinary skill in the art?
A. Absolutely, with a big flag on it.
Q. Let's turn now to beta-blockers and DeSantis. Dr. Noecker testified that DeSantis disclosed more than 50 beta-blockers, correct?
A. Yes. According to this, 56.
Q. Okay. Now, Dr. Laskar, would a person of ordinary skill in the art, in formulating a fixed combo of glaucoma drug -- of a glaucoma drug with an alpha-2 agonist, have any hesitation whatsoever with choosing Timolol as its beta-blocker, along with Brimonidine, after reading DeSantis?
A. Absolutely not. Even if one, as sometimes

people do, skips the title and goes to the body of the -- of the patent, even reading the list of those -- that 56 beta-blockers, there's only a small set that have any history of use in the eye for the control of ocular hypertension.

And if they would then merely look at the title, then that small number becomes one, Timolol. They read the claim, it becomes one, Timolol.

Q. Okay.

A. And by virtue of the fact that Timolol, as being most prevalently prescribed, would identify Timolol Maleate as a form of Timolol to be used in formation -- formulation -- excuse me -- of a fixed combination of an alpha-2 agonist and Timolol.

Q. To wrap up, Dr. Laskar, did anything that Dr. Noecker testified about, as well as Mr. LeCause testified about, have any way or any impact as to your opinion that the '463 and the '258 patents are rendered invalid and obvious?

A. No, not at all. I maintain everything that I testified to yesterday.

Q. And any impact on your opinion that the '258 and '463 patents are invalid as anticipated?

A. No. My opinions stand as discussed yesterday.

Q. Thank you, Dr. Laskar.

MR. RUZICH: I pass the witness, Your Honor.

THE COURT: Cross?

CROSS-EXAMINATION

BY MS. BROOKS:

Q. Good afternoon, Dr. Laskar.

A. Good afternoon, Ms. Brooks.

Q. I just have a few questions for you.

Disclosed for you today, although Counsel didn't use it, was a piece -- or a page from Remington's. You're familiar with Remington's, are you not?

A. Yes, absolutely.

Q. Certainly as a formulator, you are; is that right, sir?

A. Yes. Yes.

MS. BROOKS: And if we could pull up, please, DTX -- let's see if I can find the exhibit number on it -- you know, fortunately, my copy of Remington's does not have the exhibit number, so I'm just going to put this on the ELMO.

Q. (By Ms. Brooks) Attached to your exhibit report as Exhibit A, Dr. Laskar, was this page from Remington's regarding salt formation; is that right?

A. Yes, it was. I recognize Table 2, yes.

Q. And, in fact, you only had two exhibits attached to your reply expert report that was in response to Dr. Noecker's report, correct?

A. I believe my reply report was both to Dr. Noecker and Dr. Stella.

Q. Dr. Stella, that's right. And one of the things in one of the two exhibits attached was this page from Remington's talking about salt formation; is that right?

A. Yes.

Q. And you've agreed that Brimonidine is Brimonidine Tartrate, correct?

A. Yes.

Q. Timolol is Timolol Maleate; is that correct?

A. Yes.

Q. And those are two different salts, are they not?

A. Yes, absolutely.

Q. And you agree, would you not, with the statement in Remington's that salt-forming agents are often chosen empirically by the pharmaceutical chemist primarily on the basis of the cost of raw materials, the ease of recrystallization, and the percentage yield?

Would you agree with that statement?

A. I believe that statement is somewhat dated

in -- in light of current medicinal chemistry practices.

Q. Would you agree with the next sentence, however? Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound in dosage forms.

A. I would agree with that, yes.

Q. And that still applies to this day; is that correct?

A. Yes. I'm not qualifying that statement whatsoever.

Q. And you would agree that when you make a combination product where you put them together in one bottle, in this particular case, you would then be putting together two different salts into an aqueous solution, correct?

A. If the salt forms were, in fact, different, then yes.

Q. And you would also agree, would you not, that when one combines certain salt forms in an aqueous solution -- strike that -- two salt forms in an aqueous solution, there can be what's called a salt exchange, correct?

A. Yes, strictly speaking. I -- I would modify that by saying, so long as those two salts remain soluble, then they basically exist as separate ions that

each float as a cloud with the negative ions surrounding the positive, or vice versa.

Q. You can't predict how that -- what's going to happen when you put those two salts together in an aqueous solution until you actually do so, correct?

A. For the most part, you're correct, yes.

Q. And now Combigan, there's Brimonidine in Combigan, correct?

A. Yes, there is.

Q. And the Brimonidine, there are nitrogen atoms which are secondary amines in the Brimonidine; is that right?

A. Yes, as there is in Timolol.

Q. And you would agree that they could act as what are called nucleophiles capable of attacking electron-poor or electrophilic sites, correct?

A. Yes.

Q. And now the Timolol has carbon nitrogen double bonds, correct?

A. Yes.

Q. And these carbon nitrogen double bonds could be susceptible to nucleophilic addition, couldn't they?

A. Yes, they could be.

Q. And, therefore, they could react with the nucleophilic amine group of Brimonidine, correct?

A. Yes, they could.
Q. And, of course, that wouldn't happen if they were kept in two separate bottles; is that right?
A. That's correct.
Q. Now, if we go back to DeSantis -- I don't want to reinvent the wheel, but the last time you were on the stand, you agreed that the only formulation that is listed in DeSantis at Column 6, the example, is a formulation for containing Betaxolol; is that right?
A. Yes.
Q. And you are aware, are you not, sir, that there have been studies on the effect of Betaxolol as it relates to the lowering of intraocular pressure?
A. I'm aware of it as a beta-blocker used in the amelioration of glaucoma and ocular hypertension, yes.
Q. And now, Betaxolol is a different mechanism than Timolol, correct?
A. It is a somewhat more selective beta -- beta-blocker, yes.
Q. Exactly. In fact, it's a cardioselective beta-blocker, preferentially inhibiting the beta-1 adrenoreceptors, correct?
A. I don't have that text in front of me, but I would believe that you're reading correctly.
Q. Whereas Timolol is not a selective

beta-blocker, is it?

A. That is correct, yes.

Q. And one of skill in the art would know that Timolol could cause brachycardia, arrhythmia, and even congestive heart failure by blocking beta-1 adrenoreceptors of the heart, correct?

A. Yes. That is known about Timolol.

Q. And the Timolol is contraindicated in patients with pulmonary disease as inhibition of beta-2 receptors in the bronchi and bronchials results in contraction of smooth muscle of the bronchial tree from unopposed parasympathetic activity leading to bronchospasm in respiratory obstruction, correct?

A. I don't know from what you're reading and -- but, yes, as a non-selective beta-blocker and understanding the impact of a beta -- beta-antagonist on the respiratory tree, that sounds correct.

Q. And, in fact, Timolol also crosses the blood brain barrier and blocks serotonin receptors in the central nervous system and may cause depression, weakness, fatigue, memory loss, decreased libido, and impotence, correct?

A. If you're -- I trust that the reference that you're reading from is a reliable one.

Q. And, in fact, because Timolol is a

non-selected beta-blocker, it should be used with caution in patients with diabetes mellitus, correct?

A. Yes, if that's what the text says.

Q. And, in fact, there have been several reports demonstrating that the use of these non-selected beta-blockers, like Timolol, may negatively impact the patient's quality of life by causing exercise intolerance, sexual dysfunction, and respiratory difficulty, correct?

A. I trust that the -- the reference you're reading.

Q. Whereas Betaxolol, the only beta-blocker disclosed in a formulation in DeSantis, doesn't suffer from these problems, does it?

A. That I -- I'm not a pharmacologist. I'm not a physician. And so I would -- I would not position myself to make a judgment about that.

Q. So you would have difficulty opining as one of the skill in the art whether one of skill in the art would look at DeSantis and knowing that Betaxolol doesn't have these same negative characteristics as Timolol would choose Betaxolol in their formulation. You're not able to tell us that one way or another; is that right, Dr. Laskar?

A. What I can say is that the DeSantis patent

explicitly identifies Timolol in the title, explicitly identifies Timolol in the claim. And for that reason, it leads one skilled in the art to identify Timolol as a first candidate in the formulation of a fixed combination of an Alpha-2 agonist and a beta-blocker.

Q. I'm sorry. Are you finished with your answer. I didn't want to cut you off.

A. I'm done. Thank you.

Q. My question, sir, was you aren't able to tell us whether one of skill in the art would look at DeSantis and go immediately to Betaxolol rather than Timolol, because Betaxolol doesn't have the negative side effects that Timolol does.

You're not able to tell us that one way or another; is that correct sir?

A. No. As I understand the question that you asked, no.

Q. You -- the answer is, no, you're not able to tell us that? Is that correct, sir?

A. That's correct.

Q. But even in DeSantis, we're warned away from Timolol, aren't we?

A. Again, I don't have the text of that patent in front of me at the moment to be able to -- and I can assure you I have not memorized any of the

patents-in-suit nor DeSantis.

MS. BROOKS: Well, then let's pull up DeSantis, DTX123, and specifically, Mr. Exline, at the bottom of Column 1.

Q. (By Ms. Brooks) DeSantis teaches one of -- one of skill in the art at the very bottom of Column 1, at least one beta-blocker, Timolol, has increasingly become associated with serious pulmonary side effects attributable to its effect on beta-2 receptors in pulmonary tissue.

Is that correct, Dr. Laskar?

A. Yes, I'm reading that. Thank you.

Q. And that is the only negative comment about any beta-blocker that you can find in DeSantis; is that correct?

A. In the absence of reading to the next column, I'll trust that -- you have reviewed it more carefully, more recently than I.

Q. Thank you, sir.

MS. BROOKS: Pass the witness, Your Honor.

THE COURT: Redirect?

MR. RUZICH: Thank you, Your Honor.

Can we pull up DTX145 and 6. Again, DTX145 to Figure 1.

REDIRECT EXAMINATION

BY MR. RUZICH:

Q. Do you see Brimonidine and Apraclonidine in this figure, Dr. Laskar?

A. Yes, I do.

Q. And can you locate the secondary amine that counsel suggested would be attacked by Timolol?

A. I see that there are what can be considered secondary amine in the five-member hexacycle.

Q. Okay. Does Apraclonidine have this exact same secondary amine?

A. Absolutely. That entire -- that substructure is common in Clonidine, Apraclonidine as well as Brimonidine.

Q. Does DeSantis claim Apraclonidine with Timolol?

A. It does.

Q. What would a person expect about the ability to combine Brimonidine and Timolol in light of DeSantis?

A. In light of DeSantis, those are identified. I would mention that as a formulator, it is part of the normal routine, normal testing in evaluating a formulation to place those two materials together, and to experimentally verify any predispositions or -- or suggested interactions that other literature might --

might propose could happen, might happen, may happen. And it is uncertain about the certainty -- redundant. One is not certain that that reaction will, in fact, occur until one puts those materials together.

Q. Great. Does that complete your answer?

A. But you have to start somewhere.

Q. Thank you, Dr. Laskar.

MR. RUZICH: No further questions, Your Honor.

MS. BROOKS: No further questions, Your Honor.

THE COURT: All right. You may step down.

THE WITNESS: Thank you.

THE COURT: Any other witness?

MR. BENSON: Defendants call Dr. Tanna.

THE COURT: Dr. Tanna, you understand you're still under oath.

Okay. Let's proceed.

MR. LEE: May I approach, Your Honor?

MR. BENSON: May I approach the witness, Your Honor?

THE COURT: Yes. The Court has a commitment. We're going to quit today precisely at 5:00 o'clock.

MR. BENSON: The binder looks worse than it is.

THE COURT: I don't know what it means. I'm just telling you.

MR. BENSON: Okay. Thank you.

May I proceed?

THE COURT: Please do.

ANGELO P. TANNA, M.D., DEFENDANTS' WITNESS, PREVIOUSLY SWORN

DIRECT EXAMINATION

BY MR. BENSON:

Q. Welcome back, Dr. Tanna.

A. Thank you, Mr. Benson.

Q. Dr. Tanna, do you understand as part of an obviousness analysis, you are required to consider secondary considerations that may have been raised by Plaintiff?

A. Yes, I'm aware of that.

Q. Okay. And do you understand -- first, were you present in the courtroom when Dr. Noecker testified earlier today?

A. Yes, for all but two minutes.

Q. Okay. And do you understand Dr. Noecker testified about unexpected results and long-felt needs, which are secondary considerations?

A. Yes.
Q. Now, in view of Dr. Noecker's testimony, has your opinion about the validity of the claims of the '149 and '976 patent changed?
A. No, it has not.
Q. Okay. I'd like to start with the unexpected results.
Could you give me the legal standard you applied in analyzing unexpected results?
A. I compared the claimed inventions with the closest prior art.
Q. Okay. Did Dr. Noecker, in your opinion, provide a definition of the closest prior art?
A. No.
Q. Did -- in your opinion, did Dr. Noecker provide any analysis about the closest prior art?
A. No.
Q. Now, in your opinion, did Dr. Noecker compare the fixed combination products, which is an embodiment of the patents, to the closest prior art?
A. No.
Q. All right. What is your opinion as to what is the closest prior art with respect to these claims?
A. I believe DeSantis discloses the closest prior art, and I believe the closest prior art is effectively

the claimed invention itself.

Q. So in the event the Court finds that the DeSantis reference does not anticipate the claims at issue, do you have an opinion as to what the closest prior art would then be?

A. Yes. In that case, my opinion would be that the closest prior art is the concomitant serial administration of Brimonidine twice a day at 0.2% and Timolol twice a day at a concentration of 0.5%.

Q. Why do you believe that that is the closest prior art with respect to the claims of this invention?

A. Because the number of differences between the claimed invention and what I just described as the closest prior art is the smallest. That comparator, what I just described as the closest prior art, BID/BID concomitant administration, possesses the smallest number of differences compared to the claimed invention.

Q. And why is it important that it possesses the smallest number of difference, if one is interested in examining certain properties of the composition?

A. Because as you add more and more differences between the claimed invention and your comparator, it becomes increasingly likely the differences that might be observed could be attributable to those additional changes in your comparator.

Q. Okay. Now, what did Dr. Noecker compare the fixed combination to in his analysis?

A. I heard three comparisons. I heard a comparison of the fixed combination twice a day to Brimonidine administered serially with Timolol concomitantly with the Brimonidine being administered three times a day, and Timolol being administered two times a day. That was one.

Another comparator was Brimonidine monotherapy three times a day at the 0.2% concentration.

And the third comparison I heard was only with respect to one side effect, which was ocular allergy. And that was with Brimonidine dosed twice-per-day monotherapy.

Q. Now, were any of those comparisons to the closest prior art as you've identified it?

A. No.

Q. And just for clarity for the remainder of your direct, if I'm referring to the closest prior art, I'm referring to the BID/BID concomitant administration you described, okay?

A. Yes.

Q. All right. Now, Dr. Tanna, did you compare the fixed combination to the closest prior art as you have defined it?

A. Yes, I have.
Q. I'll direct you to DTX217, please. Please let me know when you get there.
MR. BENSON: Savi, if I could have Page -- I believe it's Page 5, which is a little more clear to see what -- what this particular reference is.
THE WITNESS: Well, I'm afraid I don't have 217.
MR. BENSON: You know, it might be hiding under your 216 tab.
THE WITNESS: Yes, I found it.
MR. BENSON: I had the same problem.
Q. (By Mr. Benson) Could you please identify this document for me?
A. Yes. This is the clinical study report of the 507T study conducted by Allergan.
Q. And what is being compared in the -- in this particular study?
A. It's a clinical trial that compares the BID administration of the fixed combination with what we've just defined as the closest prior art, the BID/BID administration concomitantly.
Q. Okay. Let's go to Page 14 and, again, as we did yesterday, I'm using the numbers on the bottom left-hand corner.

A. Yes.

MR. BENSON: And if I could get the table blown up.

Q. (By Mr. Benson) Can you describe for me what we're looking at?

A. Yes. We're looking at a table that describes the incidents of the side effects that were observed in the clinical trial. These weren't absolutely all of the side effects, but these were the ones that occurred with an incidence of greater than 1%.

Q. Okay.

A. And it's broken into two groups. The incidents in the combination group, the fixed combination, that is, and the incidents in the BID/BID concomitant therapy group.

Q. So the combination is the fixed combination and the adjunctive, is that the closest prior art as you've defined it?

A. Yes, BID/BID concomitant administration.

Q. Okay. I'm going to identify those second -- or those side effects Dr. Noecker suggests are relevant to unexpected results.

And those would be oral dryness, somnolence -- or somnolence, allergic conjunctivitis, conjunctival folliculosis, and foreign body sensation.

Now, with respect to these side effects, could you please describe for me the differences between the fixed combination and the closest prior art?

A. Yes. There are some numerical differences, but there are no statistically significant differences. And in most cases, when there is a numerical difference, the incidence of side effects was actually a little bit higher with the fixed combination.

Q. Okay. Now, with respect to allergic conjunctivitis, what specifically does the 19T study show us?

A. The 19T study shows us -- and that was a comparison between the fixed combination and Brimonidine administered three times a day and Timolol administered twice a day.

Q. I'm sorry. I think I made a mistake. I meant this study which is --

THE COURT: 19T, I promise you.

Q. (By Mr. Benson) The 507T study, the study that's in front of you in this particular study --

A. Yes.

Q. -- could you please tell me specifically with respect to allergic conjunctivitis?

A. Could you just repeat the question in its entirety, please?

Q. I don't know if I even remember the question, but I will try.

I just wanted to identify allergic conjunctivitis. And could you just let me know what the differences were between the fixed combination and the closest prior art?

A. There is no statistically significant difference, which is what really counts in a study like this.

Q. Thank you.

With respect to these other side effects that haven't been identified, are there any other -- relevant differences between the two treatment groups?

A. There is no statistically significant difference in any of these side effects in this table.

Q. Okay. Now, Dr. Noecker showed us a number of -- of clinical research reports during his unexpected results analysis.

Did he identify this particular study?

A. No, I don't believe so.

Q. Now, Dr. Noecker testified about systemic side effects.

How do systemic side effects come about with a topical eyedrop?

A. When you apply an eyedrop on the surface of

the eye, some proportion of that medicine gets into the tear drainage system. And the tear drainage system carries the medicine into the nose and into the mouth. And along the way, those structures are surrounded by capillaries so the molecules of the medication can enter the bloodstream. And, in fact, the levels can get pretty high, because the medicine doesn't go through the liver first as it would if you were to take it as a pill, for example.

Q. Now, have you seen any evidence about the -- well, let me ask you a different question first.

What would a person of ordinary skill in the art expect the blood plasma concentration of Brimonidine to be in a TID-dose monotherapy as compared to a BID-dose monotherapy?

A. With Brimonidine monotherapy, BID versus TID, one would just naturally expect that the blood concentration of the serum or the plasma concentration would be higher with the three-times-a-day dosing. Because you're applying more drug to the surface of the eye, there is more opportunity for the medicine to get into the bloodstream. So you'd expect a higher concentration in the blood.

Q. Have you seen any evidence in Allergan's clinical research studies to support this idea that the

blood plasma concentration is higher in the TID-dose than the BID-dose Brimonidine?

A. I have. In the 12T and 13T clinical trials, pharmacokinetic studies were done in which the blood plasma levels were actually measured. And in those studies, there were three groups.

One group of patients received the fixed combination twice a day, and another group received the monotherapy of Brimonidine three times a day. So in comparing those two, as expected, there was a higher concentration in the subjects who were getting the Brimonidine three times a day. And it was about 25 percent higher.

MR. BENSON: Savi, if you could pull up DTX211 at 8.

Q. (By Mr. Benson) And rather than having you thumb through the expensive document --

A. Thank you.

Q. -- we'll just go there.

MR. BENSON: And if you could, please, blow up the pharmacokinetics portion.

Q. (By Mr. Benson) Is this the information you were referring to?

A. Yes, it is.

In the second paragraph, it specifically says

Brimonidine concentrations were 24 percent lower in the combination group than in the monotherapy group at week 2.

And here they're referring specifically to the Brimonidine three-times-a-day monotherapy group. And that difference is statistically significant.

And then it goes on to say that at some other timepoint, it wasn't statistically significant, and at one other, it was. So it kind of goes back and forth.

Q. And is the disclosure in the 13T study similar?

A. It is very similar.

Q. And just for the record, that would be DTX212 at 8.

Have you confirmed that?

A. I have. I have looked at that.

Q. Okay. Would a person of ordinary skill in the art expect the incidents -- the incidents of systemic side effects to be greater with the TID Brimonidine monotherapy as compared to the BID monotherapy in view of the higher blood plasma concentrations?

A. Yes, but, again, now you just mentioned the BID monotherapy. So that would be a logical step away from 12T and 13T, which looked at BID fixed combination therapy.

Q. I'm sorry. I must have misspoke. I meant -- I meant the fixed combination product.

So same question, but would a person of ordinary skill in the art, in view of the blood plasma concentration information you reviewed, expect higher incidences of side effects with the TID monotherapy as compared to the fixed combination BID treatment?

A. Yes. That would naturally follow, given what we know about the dosing all by itself. And it would also naturally follow, given now what we know about the blood plasma concentrations.

Q. So did you ever see -- did Dr. Noecker ever compare the fixed combination to a Brimonidine treatment regime, either monotherapy or concomitant, wherein the Brimonidine was dosed twice a day?

A. Not with respect to systemic side effects, but, yes, with respect to local allergic conjunctivitis.

Q. Okay. So just with respect to that one side effect, correct?

A. That's correct.

Q. Okay. Now, would a person of ordinary skill in the art also expect the concentration of the drug to affect ocular side effects?

A. Yes. The more drug you deliver to the surface of the eye, the more likely you would observe ocular

local side effects.

Q. Now, with respect to all ocular side effects Dr. Noecker testified about, with the exception of allergic conjunctivitis, did he ever compare the fixed combination to a Brimonidine treatment regime wherein the Brimonidine was being administered twice a day?

A. No, he did not.

Q. Do you have an opinion as to whether or not the ocular side effects -- and, again, we'll put aside for the allergic conjunctivitis for a moment -- but the other ocular side effects Dr. Noecker testified about, do you think the results, comparing the fixed combination to the -- to the various treatment regimes he compared, were surprising?

A. No, they were not surprising.

Q. Okay. So let's return to the -- the allergy.

And can I direct you to PTX91 in your binder, please.

I hope it's in your binder. Actually, it is not in your binder. I have it here, though.

MR. BENSON: Your Honor, may I approach the witness?

THE COURT: Yes.

Q. (By Mr. Benson) Dr. Tanna, do you recall Dr. Noecker testifying about this -- this publication?

A. Yes, I do.
Q. Can you tell me a little bit about this publication?
A. It is a -- the result was a retrospective chart review that was conducted that compared the allergy rates among patients who were receiving twice-a-day Brimonidine 0.2% monotherapy versus patients who were receiving twice-a-day Combigan.
Q. Now, yesterday when you were testifying, you testified about DTX144, which was a retrospective chart review done by first author, Stewart.
Do you recall that?
A. Yes, I do.
Q. And do you recall Dr. Noecker testifying about that document today?
A. Yes, I do.
Q. And what did Dr. Noecker say about the retrospective study conducted in DTX144?
A. He correctly stated that the results of the study like that are less reliable, because the methodology is not as strong as, for example, a prospectively conducted clinical trial.
Q. And was that your opinion as well?
A. Yes, it was.
Q. Were you using DTX144 for the purpose of

examining the results of that study?
A. No.
Q. And what were you using it for?
A. Just to demonstrate that in that chart review, BID -- excuse me -- BID Brimonidine use was being done in the real world in combination with beta-blockers.
Q. Okay. So with respect to PTX91 that you have in front of you, do you -- do you agree with Dr. Noecker that the type of study done in this -- in this reference is also unreliable?
A. I agree it's weaker evidence.
Q. Okay. Well, be that as it may, why don't we go to Page -- third page, so Page 3. And at this time, the PTX numbers are on the lower right.
MR. BENSON: And I'd like to highlight the chart at the very top.
Q. (By Mr. Benson) And do you recall Dr. Noecker testifying about this?
A. Yes, I do.
Q. Now, if a person of ordinary skill in the art or any skilled practitioner were to compare two different treatment regimes, wherein each regime contained Brimonidine, approximately how long would it take before a difference in allergic side effects could be detected between those two drugs?

A. My opinion is that about three months the difference would be apparent, and if you had a large enough study, which I considered the 507T to be a large clinical trial, by the way, that you would be able to detect the difference at that point.

That doesn't mean that everybody who is going to develop an allergy will have declared themselves by then, but at that point, I would expect enough of a difference that someone would be able to make such a determination.

Q. So what does the reference Dr. Noecker was relying on indicate with respect to the two treatment regimes here at the three-month time period?

A. It indicates that the incidence of allergy is significantly higher by 18 months in the Brimonidine BID monotherapy group compared to Combigan BID.

Q. Now, again, with respect to the 507T study you told us earlier that when you compared Brimonidine or the fixed combination to the closest prior art, at three months, there was no statistically significant difference in allergic conjunctivitis, correct?

A. That's correct.

Q. Do you have an opinion as to whether or not any masking ability of Timolol to kind of improve the allergic conjunctivitis rate was already present in the

prior art BID/BID concomitant therapy regime?

A. Yes, I think it was already present in the closest prior art, BID/BID concomitant therapy. And I think that you know that, because, first of all, in the 507T study, the allergy incidence was similar.

And not only that, but when you compare 507T with other studies, you see that the allergy incidents in both groups was lower than had been seen in other well-done studies.

Q. Let's -- all right. Let's -- let's talk about the IOP-lowering ability of the fixed combination as compared to the closest prior art.

Was the IOP-lowering ability of the fixed combination in comparison to the -- made in the 507T study with respect to the closest prior art?

A. Yes, it was.

Q. And what was the result?

A. The result was that there was no significant difference in pressure-lowering efficacy between fixed combination BID and concomitant BID/BID therapy.

Q. Now, were the results of those studies ever published?

A. Yes, they were published in 2005 in an article that was written by Goni, G-O-N-I.

Q. And I'll direct you to DTX023.

And, Dr. Tanna, just to be clear, because you're not representing that this reference is prior art, correct?

A. This is not prior art.

Q. Okay. And is -- this is the study that -- that compares the fixed combination to the closest prior art, correct?

A. Right. It's the peer-reviewed publication that arises from the 507T Allergan clinical trial.

Q. Now, did Dr. Noecker refer to this -- this -- well, let me set up some foundation.

Did you review Dr. Noecker's expert report that was submitted in this litigation?

A. I did.

Q. And that -- was that report of Dr. Noecker submitted in response to your own invalidity opinions?

A. Yes, it was.

Q. And did Dr. Noecker cite the Goni article?

A. I don't believe so.

Q. Did Dr. -- or did Dr. Noecker cite the 507T study --

A. No, he did not.

Q. -- in that report?

And did Dr. Noecker talk about either the 507T study or the Goni reference in giving his testimony

today?
A. I don't believe he did.
Q. Do you believe that Dr. Noecker was aware of the Goni reference when he submitted his expert report?
A. He must have been. I know he has cited this in some of his own papers.
Q. I'll direct you to DTX282.
All right. If I could -- is this the reference that you are referring to?
A. I'm still getting to it.
It is, yes.
Q. Now, can I direct you to Page 8, and there is a paragraph on the right-hand column called Brimonidine/Timolol fixed combination. And I'll take you to the very last sentence in this -- in this reference.
And what does Dr. Noecker say here about the fixed combination as compared to the closest prior art?
A. Both treatments were well-tolerated with no difference in adverse events between groups.
Q. Do you recall Dr. Noecker talking about the afternoon trough associated with BID Brimonidine monotherapy?
A. Yes, I do.
Q. I'd like to direct you to -- do you recall

testifying about the 19T study yesterday?

A. I do.

Q. Okay. I'll direct you to that, which is DTX213, and in particular Page 6.

MR. BENSON: And I want the very last paragraph on the bottom of this inserted table.

Q. (By Mr. Benson) And you can -- can you tell me what's being described here?

A. It's basically a disclosure that at the 28-day mark, there was no statistically significant difference in mean IOP value between the combination and the concurrent groups at all timepoints, except hour 8 where the concurrent group had a lower mean IOP than the combination group.

And what they mean there is that concomitant therapy, TID/BID, resulted in better pressure lowering than the fixed combination at the hour 8 afternoon timepoint. That's the key timepoint where you see a difference between Brimonidine monotherapy TID and Brimonidine monotherapy TID.

So this is where you would go to, to look for a difference, if you were going to compare the fixed combination to TID/BID monotherapy. It's the key comparator.

Q. Okay. And is this the basis of your opinion

that the fixed combination is not as effective as TID/BID concomitant therapy?

A. Yes, it is.

Q. And is this the very same trough coming up again that Dr. Noecker was talking about?

A. It's the same timepoint, same trough, yes.

Q. Okay. And this is with respect to the fixed combination, correct?

A. That's correct.

Q. And is this what a person of ordinary skill in the art in early 2002 could have reasonably expected?

A. I think one could reasonably expect this, yes.

Q. Now, do you recall Dr. Noecker testifying about PTX77?

MR. BENSON: I'm going to have to put this on the ELMO, because I don't have a copy, unless we can get Mr. Exline to put that up.

That's fine. We can do it this way.

Q. (By Mr. Benson) This is PTX77, and Dr. Noecker testified about this today.

MR. BENSON: And I can't seem to figure out what I'm doing here. Sooner or later, I will figure it out or not.

All right. I just can't get it on there.

Q. (By Mr. Benson) Okay. Now, can you describe

for me what we're seeing here?

A. I would -- I think this is the Sherwood paper; is that correct?

Q. That's correct.

A. Okay. So the Sherwood paper compares the fixed combination -- you'll have to remind me of the comparison here.

It's the fixed combination twice a day versus Brimonidine monotherapy three times a day and Timolol monotherapy twice per day.

Q. Now, do you recall Dr. Noecker testifying about the unexpected nature of these results?

A. I do.

Q. Do you agree with that?

A. I don't think it's unexpected. I think it's pretty much exactly what you would expect, based on previous experience with BID/TID comparisons of Brimonidine monotherapy, based on what one of ordinary skill would know about Timolol.

Q. When you say -- when you say reasonably expect, do you mean that the person would expect those exact numbers?

A. No, that's not at all what I mean.

Whenever you make any kind of a comparison to -- to anticipate or to determine what you would

expect the results to be -- for example, the claimed invention -- basically, the previous experience just gets you into the ballpark. You don't expect to nail it.

For example, I heard some use of the Cosopt experience to try to make a determination of what would happen with the fixed combination Combigan. And I think that you're doing an apples-to-oranges comparison, so you'd expect to get into the right ballpark, but that's about it.

Q. Okay. Dr. Noecker also testified about long-felt need. Do you feel Combigan satisfied a long-felt need?

A. I don't think so, no.

Q. Why not?

A. Well, I think there is a place for fixed combination agents. There's no question about that.

But when you have the possibility of serial administration of the fixed combinations, that, I think, eliminates the strong phrase, long-felt need.

I think that also, since we have other fixed combination agents available and we had them prior to the claimed invention, that also diminished the need for another fixed combination.

So, for example, if at the time of the claimed

invention, a patient was on, let's say, Cosopt, which was readily available in the United States and elsewhere, or Xalacom, which was available in Europe and elsewhere, those patients would not be able to potentially benefit from Combigan, because they're already on Timolol in their fixed combination agent that they're on.

So there's no room for helping that patient with this new claimed invention.

Q. Now, considering your own opinions that you've expressed in Court and all of the evidence that you've heard throughout this proceeding and also all the evidence that you've read and in particular Dr. Noecker's testimony about unexpected results and long-felt need, what is your opinion regarding the obviousness of claims of the '149 and the '976 patent?

A. My opinion stands, that they are obvious in view of the prior art.

MR. BENSON: I'll pass the witness, Your Honor.

THE COURT: Court's in recess until 9:00 a.m.

COURT SECURITY OFFICER: All rise.

(Court adjourned.)

CERTIFICATION

I HEREBY CERTIFY that the foregoing is a true and correct transcript from the stenographic notes of the proceedings in the above-entitled matter to the best of my ability.

/s/_____ _____
SUSAN SIMMONS, CSR Date
Official Court Reporter
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Expiration Date: 12/31/12

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SHELLY HOLMES Date
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