- VOLUME E -

IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE DISTRICT OF DELAWARE

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ALLERGAN, INC.,	:	CIVIL ACTION
Plaintiff,	:	
vs.	:	
BARR LABORATORIES, INC., TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., and SANDOZ, INC.,	:	
Defendants.	:	NO. 09-333-SLR-MPT

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Wilmington, Delaware
Friday, February 4, 2011
8:30 o'clock, a.m.

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BEFORE: HONORABLE SUE L. ROBINSON, U.S.D.C.J.

- - -

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-and-

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Official Court Reporter

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P R O C E E D I N G S

(Proceedings commenced in the courtroom, beginning at 8:30.)

THE COURT: Mr. Lombardi, you may continue.

MR. LOMBARDI: Thank you, your Honor.

... TIMOTHY L. MACDONALD, having been duly sworn as a witness, was examined and testified further as follows ...

CROSS EXAMINATION

BY MR. LOMBARDI:

Q. Good morning, Doctor.

A. Good morning.

Q. Doctor, you talked a little bit yesterday about your long-term relationship with Allergan; is that right?

A. I did.

Q. It goes back to the late 1980's; is that right?

A. That's correct.

Q. And you've worked with them on this trial?

A. Pardon me?

Q. You've worked with them on this trial?

A. Correct.

Q. And you've worked with them on a previous trial?

A. Correct.

Q. And that was a trial concerning the same basic drugs; is that right?
A. That's correct.
Q. At that time, they were accused of infringement; is that right?
A. Correct.
Q. Did they assert that the patents were obvious in that case?
A. Excuse me? Which patents are we talking about?
Q. The patents in the prior case where you worked with Allergan.
A. Can you lay those out for me? Do you mean Stjernschantz?
Q. Whatever patents were involved, was a Stjernschantz patent involved?
A. That was.
Q. Was there any allegation that any of the patents, including the Stjernschantz patents, was obvious in that case by Allergan?
A. Not to my knowledge.
Q. Okay. Now, your work goes back to, you said at least 1989; is that right?
A. Correct.
Q. And you've worked under contract, consulting contacts with them since then?

A. Correct.
Q. Two years consulting contract?
A. Generally, yes.
Q. All right. And you worked for other companies for a period of time in addition to Allergan; is that right?
A. That's correct.
Q. And then about ten years ago, you agree that you wouldn't work with anyone else at least on ophthalmic type of drugs; is that right?
A. About five years ago, but that's correct, yes.
Q. And so now you exclusively work with Allergan?
A. Correct, with one exception.
Q. Okay. And you agreed to do this because you liked working with Allergan?
A. Correct.
Q. You have a good relationship with them?
A. Correct.
Q. And with the people there?
A. That's correct.
Q. In fact, back in the 1980s, you told us you were actually, you were somewhat a witness to the invention story here; is that right?
A. Yes.
Q. Okay. So you were there and you told us you were just blown away by what you saw when you were there; is that

right?
A. That's correct.
Q. Now, are you proud of the role that you played in the development of this drug?
A. I'm proud of the role I played in the development or discovery of these drugs, yes.
Q. All right. And are you proud of the role you've played in the discovery of what is called, what you call the prostamide receptor?
A. I was not involved with the discovery of the prostamide receptor, but its exploration, yes.
Q. And you're proud of your work in its exploration?
A. Yes.
Q. You're so proud, sometimes you refer to it as "our receptor"; isn't that right?
A. You may find that somewhere. I don't recall it. I certainly wouldn't acknowledge that it's our receptor.
Q. Well, did you call it "our receptor" yesterday during your testimony?
A. You're going to -- presumably, yes.
Q. All right. Well, we'll look at the record.
But you're proud to be associated with Allergan and all the work that went on with this drug; is that right?
A. Yes, I am.
Q. All right. Not exactly neutral in the proceedings,

are you, Doctor?

A. Well, I would hope that a consultant is neutral. That's my role.

Q. Okay. That's just fine.

So now what role did your involvement with Allergan, and specifically on the prostamide receptor and bimatoprost, play in your obviousness analysis?

A. What role?

Q. Yes.

A. None.

Q. Okay. Your understanding is that for purposes of your obviousness analysis, at least, whatever you observed at Allergan is not the relevant inquiry; is that right?

A. That's correct.

Q. What's relevant is what was known in the prior art; is that right?

A. That's correct.

Q. So to the extent you're influenced at all in your decisions or your opinions by what you saw when you were at Allergan, that would be wrong; isn't that right?

A. I would -- my opinions are independently arrived at as a neutral observer of the data as of 1992, that's correct.

Q. Of what data?

A. Well, of all the materials supplied to me, all the materials that I've seen. That information as of 1992 is

what I took into consideration in analyzing the obviousness considerations.

Q. All right. So I'm not talking about secondary considerations.

A. That's correct. Secondary or subsequent.

Q. I'm talking about obviousness. When you say all the materials were all the materials that you considered, what were all the materials you were talking about? I don't need you to list every one, but, generally, what were they?

A. They were materials provided both by you, or your counsel, and my counsel, and materials that I independently investigated.

Q. Okay. Were any of those materials from Allergan?

A. Supplied to me by our patent --

Q. So --

A. Supplied by our attorneys. Yes.

Q. Did you consider internal documents of Allergan?

A. Nothing that was not supplied to me.

Q. All right. Well, no. But in terms of what was supplied to you, in arriving at your expert opinion on obviousness, did you consider internal Allergan documents?

A. They were supplied to me, yes.

Q. And you considered that on the part of your obviousness opinion; is that right?

A. Sure. I considered all the materials presented to me.

Absolutely.

Q. Okay.

MR. LOMBARDI: Could I have the Elmo, please?

BY MR. LOMBARDI:

Q. Okay, Doctor. You recognize this demonstrative from yesterday; is that right?

A. That's correct.

Q. And that is a demonstrative that shows compounds that you talked about during your testimony; is that right?

A. That's correct.

Q. And on the right is bimatoprost. That's what is at issue in this case; correct?

A. Correct.

Q. And what is on the left are various compounds from the Stjernschantz patent; is that right?

A. That's correct.

Q. Okay. Now, there's a lot of talk about what you didn't understand yesterday and a lot of things were discussed. I want to just talk and see what we can agree on for a minute. Is that okay?

A. Okay.

Q. All right. So the compounds, all of these compounds have alpha and omega chains; is that right?

A. They do.

Q. Every one of these compounds has a phenyl ring?

A. Every one has a 17-phenyl. Correct.
Q. And the 17-phenyl is something that you agree was very well-known in the art; is that right?
A. It had been established, yes.
Q. All right. You know of many, many compounds that have a 17-phenyl ring; is that right?
A. Correct.
Q. Okay. Now, compound 17 and compound 2 also have a double bond at the -- what's that, 13, 14 position?
A. They do.
Q. And bimatoprost has that double bond; is that right?
A. That's correct.
Q. So at least as far as compounds 2 and 17 and bimatoprost are concerned, the only difference is over here (indicating); is that right?
A. That is correct.
Q. And bimatoprost -- I've marked the amide group for bimatoprost; is that right?
A. You have.
Q. Okay. And then for compound 2, instead of an amide group, it has an ester; is that right?
A. That's correct.
Q. And for compound 17, instead of an amide group, it has a carboxylic acid; is that correct?
A. That's correct.

Q. Now, so the difference -- would you agree, just to see if we can agree on this, the difference between compounds 2, 17 and bimatoprost lies at the C-1 position; is that right?
A. We agree.
Q. Okay. And there are just different groups at that C-1 position; is that correct?
A. That is correct.
Q. All right. Now, let me just ask you, just so we make sure there's no dispute about this, if I wanted to, back in 1992, a person of ordinary skill in the art would have had no difficulty making the change from, say, the carboxylic acid of compound 17 to the amide group of bimatoprost; is that right?
A. You're talking about synthetically?
Q. Yes, just making the change.
A. Yes.
Q. Okay.
A. I mean making the compound, yes.
Q. No problem with that?
A. Correct.
Q. Routine?
A. Yes.
Q. Okay. And, similarly, a personal of ordinary skill in the art back in 1992 would have had no problem making the change from the ester group to the amide group of

bimatoprost; is that right?

A. That's correct.

Q. Routine?

A. Right. It required an intellectual understanding, not a synthetic understanding, at that time.

Q. And we're going to talk about the intellectual understanding.

A. That's correct.

Q. I'm just trying to see what we can agree on first.

A. Mm-hmm.

Q. And compound 9, that's what became known as latanoprost; is that right?

A. That's correct.

Q. The only changes between compound 9, latanoprost and bimatoprost, are at the same place here, the C-1 position; right?

A. That's correct.

Q. That's one. And then the other one, there's no double bond for compound 9; is that right?

A. That's correct.

Q. And a person of ordinary skill in the art would have known how to make -- how to execute those changes?

A. One wouldn't have understood really how to make the 13, 14 double bond from the single bond. That's a difficult transformation. But I grant you that you could make

bimatoprost in 1992.

Q. All right. Now, you knew, or one would know as of 1992 -- well, strike the question.

Compound 17 is the bimatoprost-free acid; is that right?

A. 17-phenyl PGF2 alpha. Correct.

Q. It's bimatoprost-free acid?

A. Well, known as bimatoprost-free acid in retrospect.

Q. Well, sir, I heard you say that yesterday, so I went back and looked.

Did you look at footnote 191 of your expert report?

A. No, I probably -- I'm sure I did, yes.

Q. At some point? Did you know at footnote 191 of your expert report, you said, bimatoprost-free acid and bimatoprost acid refer to 17-phenyl PGF2 alpha?

A. In retrospect.

Q. Well, you didn't say in retrospect in your expert report, did you?

A. I should have.

Q. Do you remember? Did you?

A. Apparently not.

Q. Do you want to take a look at it?

A. No. No.

Q. Okay. Will you take my word on that?

A. Yes.
Q. So, yesterday, was that the first time in this case that you said that compound 17 in retrospect is bimatoprost-free acid?
A. Is that the first time?
Q. Yes.
A. In this case?
Q. I'm putting aside conversations with your attorneys.
A. I think I was only on the stand that one time, and we didn't talk about bimatoprost-free acid or 17-phenyl PGF2 alpha.
Q. How about in your deposition?
A. I don't recall.
Q. Well, do you recall in your deposition that you were shown exactly this structure and that you identified it? You said, we are calling this bimatoprost-free acid. That was your testimony under oath.

Do you recall that?

A. I don't, but you're going to show me, I'm sure.
Q. Well, do you deny that you said that at your deposition?
A. No, I do not.
Q. All right. So at your deposition, you don't deny that you called that bimatoprost-free acid. And so in your trial testimony, when your counsel was asking you questions, was

the first time you insisted that that need to be referred to as bimatoprost-free acid; is that correct?

A. I think yesterday when we were discussing it, we were talking about 1992. When I was considering my deposition, I was considering it as of 2010.

Q. Okay. Can we call it bimatoprost-free acid?

A. Yes. Let's get past this.

Q. Okay. Thank you.

Now, you knew, or let's say the person of ordinary skill in the art as of 1992 knew that bimatoprost-free acid would reduce IOP in the eye; is that right?

A. That's correct. Knew, again, that 17-phenyl PGF2 alpha or bimatoprost-free acid.

Q. I thought we had gotten past that.

A. Okay. Let's get past that.

Q. All right. So bimatoprost-free acid, as of 1992, the person of ordinary skill in the art knew that it would lower intraocular pressure in the eye; isn't that correct?

A. That's correct.

Q. And the person of ordinary skill in the art in 1992 knew that that carboxylic acid at C-1 would not be good to administer to the eye; is that right?

A. It would be irritating, but it would lower IOP.

Q. Right. But in terms of the side effects, beyond the

IOP --

A. That's correct.

Q. -- it would not be desirable --

A. That's correct.

Q. -- to administer it directly to the eye?

A. Correct.

Q. And that is one thing, I mean that was known; is that right?

A. Yes.

Q. We don't dispute that, do we?

A. I hope not.

Q. Okay. Good.

And one of the places you know that from is from the Bito reference; isn't that right?

A. That's correct.

Q. Because Bito, you put up some things about Bito yesterday, didn't you?

A. Yes.

Q. But you didn't put up the part about Bito that talks about, you can make a change in that carboxylic acid that will make it so that the drug penetrates the cornea better?

A. You can make an ester is what Bito taught.

Q. Exactly. Keep an ester at the C-1 position; is that right?

A. Correct.

Q. And the point of putting the ester at the C-1 position based on the teachings of Bito is that when you put it at the C-1 position, you take the carboxylic acid out of play, at least when it's first administered to the eye; is that right?

A. It promotes penetration through the cornea.

Q. Right.

A. That's what Bito taught.

Q. Right. By replacing the carboxylic acid?

A. Correct.

Q. And Bito taught you could put something else in. In this case, an ester group; correct?

A. Right.

Q. And that ester would convert to the carboxylic acid once you penetrated the cornea; is that right?

A. That's called a prodrug.

Q. Right. And that's what Bito taught?

A. That's correct.

Q. And so Bito taught that you've got this compound, and we you'll all agree that everybody knew bimatoprost-free acid back in 1992 would lower IOP; is that right? We've talked about that?

A. That's correct.

Q. But we all knew that you wouldn't want the carboxylic acid of compound 17 to go directly into the eye; is that

right?
A. Correct.
Q. Okay. And Bito teaches you that you can replace that carboxylic acid with something that will convert into it.
A. Bito teaches that you can replace a carboxylic acid with an ester. Let's not get past that.
Q. No. You know what, I guarantee you, we're going to talk about that. But just for general purposes, Bito tells you that you can substitute something for the carboxylic acid that will convert to the carboxylic acid; is that right?
A. He teaches esters.
Q. Which is something you can convert that will convert to the carboxylic acid; right?
A. That's correct.
Q. All right. Now, let me ask you, then, another question.

You talked about the esters from Bito; is that right?
A. Correct.
Q. So there's no doubt in your mind that Bito would have taught to replace the C-1 carboxylic acid of bimatoprost-free acid to an ester, at least; is that right?
A. That was Stjernschantz. But, correct.
Q. Okay. And Bito said something about that

Stjernschantz actually incorporated that; correct?
A. That's correct.
Q. And Stjernschantz, you can see that in compound 2, because the ester is there at the C-1 position in compound 2; right?
A. Correct.
Q. All right. Now, let me ask you this, sir. Suppose an ester was not available to you in 1992. Okay?
A. Okay.
Q. All right. For whatever reason, because it's patented, whatever reason, it's not available to you.
A. Mm-hmm.
Q. What would you have used to change into that carboxylic acid? You needed something, didn't you?
A. So we're talking about converting into compound 17?
Q. Bimatoprost-free acid.
A. Correct. As Allergan initiated their study, they would have taught you that to make esters of the 9, 11, or 15 positions would have been the approach taken. That was their prodrug approach. That's exactly what one would have expected, or tried to do to make compound 17 if you did not have available the C-1 ester.
Q. You talked about Allergan internal work there, didn't you?
A. Those were documents provided to me.

Q. Okay. I'm talking about your obviousness analysis right now.

A. That's exactly what was obvious to me at the time.

Q. Okay.

A. Not obvious, but I mean that's what -- that's the approach I would have taken.

Q. All right. So is it your testimony that you wouldn't have considered any other change at the C-1 position?

A. So you're asking me, or what you want me to say is, I would have considered an amide at this position to replace. That, I presume is what you're saying, and amides were not prodrugs.

This entire analysis is based on a prodrug approach. That is, that C-1 converts -- excuse me. That C-1 converts to the carboxylic acid. Amides were not known to officially convert to the C-1 acid in 1992. They were not considered prodrugs or suitable candidates as prodrugs in 1992.

So you would have not approached that kind of substitution at C-1. You would have approached other sites on the molecule to make prodrugs suitable for conversion into bimatoprost-free acid as we've now gotten past.

Q. Sir, I didn't ask you about amides.

A. No.

Q. Let me ask my question and see if you can answer my

question, sir.
A. Okay.
Q. Okay? Is it your testimony that if you knew that you couldn't use an ester at the C-1 position, you would not have considered any other substitution at the C-1 position?
A. That's correct.
Q. Okay. Now, as a matter of basic chemistry, Doctor, you know that amides hydrolyze; is that right?
A. I do.
Q. Okay. So as a matter of basic chemistry, when we say it hydrolyzes, we know that an amide converts into a carboxylic acid; is that right?
A. An amide converts into a carboxylic acid on the time frame of a thousand or greater relative to its ester.
Q. I didn't ask you about the rate, sir. I just asked you if it converted.

Does it convert to a carboxylic acid?

A. These things are relative. And so it does convert.

MR. LOMBARDI: Your Honor, I just need --

THE COURT: All right. Try a yes or no to the question asked, and then you can give your explanation, sir.

THE WITNESS: Yes, it does convert to an acid.

BY MR. LOMBARDI:
Q. And it -- go ahead.
A. But the difference is significant, so substantially

significant, that one doesn't consider it as a candidate.
Q. You don't consider it?
A. One doesn't.
Q. All right. Okay. But so the carboxylic acid here, just so that we're clear, literally, the carboxylic acid that's in compound 17, bimatoprost-free acid, at the C-1 position --
A. Yes?
Q. -- that is the carboxylic acid that amides, as a matter of basic chemistry, hydrolyze into; is that right?
A. If you have an amide at C-1, eventually, it would hydrolyze into a C-1 carboxylic acid.
Q. All right. Thank you.

Now, prior to 1992, Doctor, a person of ordinary skill in the art would have reasonably expected that if you amidyzed that carboxylic acid group at the C-1 position of bimatoprost-free acid, at least some of the amide would convert back to carboxylic acid in the body.
A. The half life of an amide in water is approximately 500 years.
Q. Sir, can you answer yes or no first and then explain your answer, please?
A. State the question again please.
Q. Prior to September of 1992, a person of ordinary skill in the art would have reasonably expected that if you

amidize the carboxyl group at the C-1 position of bimatoprost-free acid, at least some of the amide would convert back to carboxylic acid in the body.

A. Yes, that -- that is, I think, something one would expect. But one, again, needs to consider that one is interested in a drug here, and a prodrug approach relies on efficient conversion of the prodrug into the drug. 500-year half life is not an efficient conversion.

Q. All right. Now, Doctor, I take it, then -- well, I'm just going to ask you the question. I think I know the answer, but I'm just going to ask you the question so we have it for the record.

So what we know is, we have bimatoprost-free acid which we know will lower IOP as of 1992; is that correct?

A. Correct.

Q. And we know that you don't want to have that carboxylic acid in the drug that you deliver to the eye; is that correct?

A. That's correct.

Q. And I've told you to assume that you can't use an ester at the C-1 position.

A. Correct.

Q. But we know as a matter of basic chemistry that an amide hydrolyzes into carboxylic acid.

A. That's correct.
Q. And we know -- well --
A. On a time frame that's inefficient.
Q. And we know, and we know that you would expect in September of 1992, you'd reasonably expect that if you amidize that carboxylic acid, that you would get at least some conversion back to the carboxylic acid in the body?
A. That's correct.
Q. And given all of that, I take it your testimony is, you never would have thought to use an amide; is that right? That's your testimony?
A. Because I was interested in a drug if I were Allergan's staff. So if I was interested in a drug, no, that would not be something one would consider.
Q. And one of the reasons is, you have said, I think, there were a lot of things said yesterday, and I just -- you don't think anybody would ever propose or consider an amide as a prodrug back in this time frame; is that right?
A. I think in that time frame, a simple amide was not considered. Let me change that.

In 1992, a simple amide was not considered a prodrug, that's correct. Yes.
Q. All right. Had anybody proposed it or considered it?
A. I've seen tables in which the amide was included without description and, yes, I've seen material provided by

your counsel that might have suggested that these are, again, as we talked about earlier, needles in haystacks.

Q. All right. Okay. So let me just go back to where we were before.

So we are talking about this bimatoprost-free acid that we know in 1992 is going to lower IOP and we're talking about possibly changing at the C-1 position if the ester was for some reason not available.

Let me ask one more question about that. It's the case, isn't it, Doctor, that as of 1992, there was no literature in the art that taught that an amide would not hydrolyze sufficiently to create a biological effect in the eye?

A. There's a lot of evidence to that effect.

Q. Sir, is it the case that there was no particular literature that existed in the art prior to September of 1992 that taught that a PGF2 alpha C-1 amide would hydrolyze insufficiently to create any biological effect in the eye?

A. That had never been administered to the eye. C-1 amide of a PGF2 alpha was never administered to the eye in 1992.

Q. Sir --

A. Well, outside of Allergan's staff.

Q. Can you answer my question yes or no?

A. Can you -- can you ask it again? I'm sorry.

Q. All right. Okay. And will you try to answer yes or no first and then move to explanations?
A. Right.
Q. Sir, as of September of 1992, there was no particular literature that existed in the prior art that taught that a PGF2 alpha C-1 amide would hydrolyze insufficiently to create any biological effect in the eye? Yes or no?
A. There's an -- there's an inversion in there that I don't understand. So you're saying there's no literature that showed it was insufficient?
Q. Correct.
A. There was no literature at all.
Q. So there's no literature that showed that it was insufficient?
A. That's correct.
Q. Okay.
A. Or sufficient.
Q. All right. So let's step back just a second, sir.

So what we have here is we have bimatoprost-free acid, compound 17 there in the middle with that carboxylic acid. We know that that is going to lower IOP in 1992; is that correct?
A. That's correct.
Q. And we know that you don't want to put it into the eye with the carboxylic acid at the C-1 position; is that

correct?

A. What we know is that we don't want PGF2 alpha active agent to be put in the eye. The -- the prodrugs at other sites could well have had no effect.

Q. Sir, if you -- we're short on time. If you could just please address the questions I'm putting to you.

We know, based on Bito, that you don't want the carboxylic acid to be at the C-1 position when you administer this drug to the eye; is that right?

A. That's what Bito taught.

Q. Thank you.

A. Let me just make a comment here. What one knows is that one doesn't want activity, prostanoid activity. You do not generate prostanoid activity by derivatizing 9, 11 or 15 either, and even maintaining the free acid.

Q. So you are going back to what you know about what happened inside Allergan?

A. I'm just --

Q. Whenever you refer to 9, 11 and 15; is that right?

A. I'm just saying that --

Q. Sir, is that what was done at Allergan?

A. Yes, it was.

Q. That wasn't prior art, wasn't published before 1992?

A. That's correct.

Q. All right. Let's talk about what was published, sir,

and what you knew --

A. Okay.

Q. -- before '92.

You didn't want that carboxylic acid there based on Bito; correct?

A. Correct.

Q. And I have told you, we can't have the ester group. And so we know that an amide will hydrolyze into carboxylic acid.

A. In an insufficient rate, yes.

Q. And we know that an amide will hydrolyze in the body, to some extent, if it's at that C-1 position; is that right?

A. That's correct.

Q. And now we know that there's no art out there that specifically tells you that an amide wouldn't work in the eye, wouldn't hydrolyze in the eye; is that correct?

A. There's a lot of literature, I just said, to indicate that amides were not suitable prodrugs.

Q. Well, let me ask you again, sir. Was there any particular literature that existed in the art prior to September of 1992 that taught that a PGF2 alpha C-1 amide would hydrolyze insufficiently to create any biological effect in the eye?

A. There was no literature at all.

Q. So there was no literature; correct?

A. Period.
Q. Thank you.
And based on all of that, I take it your testimony is still, you wouldn't -- you wouldn't have ever thought of an amide?
A. Not if I was interested in making a drug.
Q. Yes. Because you would have done it the way the folks you were consulting with at the time did it, with other esters in other positions; right?
A. I was charged with responsibility of -- of providing ideas or options or directions for modifying prostaglandins, or even new compounds for the eye.
Q. Okay.
A. So the answer is no.
Q. Now, let me talk about amides a little bit, sir.
I'm a little -- I'm not sure, and so I just want to make sure I understand what your position is.
As of 1992, you say nobody knew about amides being used as prodrugs? Is that right, or do I have that wrong?
A. There were articles on prodrugs that taught away from the use of amides as prodrugs, that's correct.
Q. All right. So there were no articles that suggested or proposed the use of amides as prodrugs?
A. I would imagine that there were indications. In fact,

there is a table with an amide in it as a suggested prodrug with no followup in that conversation, or that article.

Q. So at least -- you're referring to Lee and Bundgaard, I take it?

A. That's correct.

Q. And so you're at least acknowledging that there was a suggestion that an amide could be used as a prodrug in that instance; is that right?

A. There was a table entry with no followup discussion. That's correct.

Q. You said that before. But my question was, are you saying or not, one way or the other, that Lee and Bundgaard contains a suggestion based on that table that an amide be used as a prodrug?

A. What I'm saying is, is the conventional wisdom in 1992 was that you could not use an amide as a prodrug for carboxylic acid unless it was modified in such a way as to be either an activated amide or a peptide amide. Could not be a simple amide.

Q. I'm just asking about the Lee and Bundgaard article, sir.

A. That's what I tried to answer.

Q. Okay.

A. I'm thinking the totality of the evidence in 1992.

Q. No.

THE COURT: And, Mr. Lombardi, could you give me an exhibit number?

MR. LOMBARDI: Yes, I could. Lee and Bundgaard is Exhibit DTX-1006.

THE COURT: Thank you.

BY MR. LOMBARDI:

Q. And I'm going to put it up in a minute. All I want to do is just get a yes or no to this one question.

A. Okay.

Q. Okay?

A. Certainly.

Q. So let's see if we can do that.

Lee and Bundgaard has a table in it that you've referred to; is that right?

A. That's correct.

Q. Is that, in your view, a suggestion that an amide can be used as a prodrug?

A. When I see something in a table --

Q. Can you answer yes or no?

A. Not really, no.

Q. All right. You can't answer the question yes or no?

A. I cannot answer the question yes or no.

Q. All right. Now, were you here when Dr. Wheeler testified by deposition?

A. I was.

Q. Did you listen to his testimony?
A. I did.
Q. Did you understand that you disagree with Dr. Wheeler on this point?
A. I do.
Q. And Dr. Wheeler, you know -- was Dr. Wheeler -- he's right back there?
A. Correct.
Q. Was he one of the fellows you worked with for these 20 years?
A. That's correct.
Q. Was he there back in '89 when you were blown away?
A. He was.
Q. Okay. Now, Dr. Wheeler, you know, testified that amides had been proposed as prodrugs before 1992.
A. He did.
Q. All right. And you disagree with him?
A. That's -- Dr. Wheeler is a biologist. He had -- his training was not in chemistry. My training was in chemistry. At that time, I had a number of years in medicinal chemistry, actively pursuing drug discovery and development. So I would suggest that perhaps my opinion in this is -- is a little more relevant.
Q. Superior to his?
A. In that case, yes.

Q. Okay. And he was -- okay. Well, let me ask you this. Now, are you suggesting -- well, let's look at the Lee and Bundgaard document.

I think this is the -- one of the two demonstratives you put up.

And Lee and Bundgaard is DTX-1006; is that right?

A. I believe so, yes.

Q. Okay. And this is what you called out to talk about; is that right?

A. That's correct.

Q. All right. So let's look at the table, first of all, sir. Okay? Okay?

A. Yes.

Q. All right. So, first of all, you know that -- what was this whole book about? What was the title of this whole book that this article was in?

A. I've forgotten. It's Prodrugs, is it?

Q. That's part of it. Did it have a subtitle?

A. I've forgotten.

Q. All right. Was it "Topical and Ocular Drug Delivery"?

A. There you go.

Q. Ocular would mean what?

A. Eye.

Q. Okay. That would be relevant to this case; is that

right?
A. That's correct.
Q. All right. So topical and ocular drug delivery. And what was the title of this chapter in which the table that you looked at appears?
A. Improved ocular drug delivery with prodrugs.
Q. Okay. So we're talking specifically about delivering drugs for ocular uses; is that right?
A. That's correct.
Q. Okay. Let's look at Table 2. Okay? Are you there?
A. I am.
Q. Table 2 says prodrugs forms of various functions in drug substance?
A. Right.
Q. So, there's no confusion, right, Doctor, this is specifically talking about a prodrug for ocular delivery purposes?
A. That is correct.
Q. And it specifically lists amides, is that right?
A. It does.
Q. So, when they list an amide there, you thought they were at least suggesting the possibility of a amide, didn't you, doctor?
A. The very first thing I would do.
Q. Can you answer my question yes or no and tell me what

you would do?

A. It suggested, yes. Then I want to look at the chapter to try to find out what exact examples they have provided, that is, the substrate on R would make a significant difference with regard, is it a simple amide, is it an activate amide, is it a peptide amide? What sort activity is involved?

If one looks in that chapter, there is no discussion of amides whatsoever.

Q. Sir, that R, is little ambiguous for you there, too?

A. It is.

Q. Because it's ambiguous in the patent as well, right?

A. That R group in the patent as I said at the time -- we're not discussing the patent application at this point.

Q. We don't have to.

Here we are, the functional group here.

What this tells you, is it lists an amide. Do you see that?

A. I do.

Q. When else does it say, that the amide will convert into?

A. It's a prodrug for the carboxylic acid.

Q. So the amide will convert into it carboxylic acid is what it is saying, right?

A. We have ascertained that. We don't disagree with

that.

Q. Okay.

Now, if you highlight up here that the majority ophthalmic prodrugs developed up to now are esters derived from hydrolysis or carboxylic acid groups present in the parent molecules, do you see that.

A. I do.

Q. Do you remember what the rest of paragraph goes on to say?

A. No, I do not. Please show me.

Q. It goes on to say, that yes, the majority of ophthalmic drugs, esters. There are times when esters don't work?

A. I would have to see it. But I'm not disagreeing with you.

Q. This is DTX-1006. I'll go to Bates page 0008.

Is that big enough for you to read, doctor?

A. Yes.

Q. Where you quoted from was right up here, right, where my pen is pointing, the majority of ophthalmic prodrugs. That is where you quoted from in your chart?

A. Yes.

Q. The majority of ophthalmic prodrugs up to now are esters derived from hydroxyl or carboxylic acid groups.

Do you see that, Doctor?

A. Yes, I do.
Q. Then it goes on, in a number of cases, however, other strategies are required, since the drug to be modified does not contain such groups readily amenable to esterification.
Did I read that correctly?
A. Yes, you did.
Q. Even when esterification is feasible, ester prodrugs may create problems owing to chemical instability in aqueous eye drops formulations. Do you see that?
A. I do.
Q. Such cases will be discussed below along with an account of the chemistry of some newly developed nonester prodrug types that have been or may be applied to ophthalmic drugs.
Do you see that?
A. I do.
Q. So, then they go on to the next page. That's where the table is, right?
A. Yes.
Q. They say esters are number one on the list, right?
A. For carboxylic acid, yes.
Q. Then they go to the table number three on the list. It's number 2, is another kind of ester, right?
A. Correct.
Q. Next thing after that is the amide, right?

A. Correct.
Q. If an ester doesn't work, this piece of art tells you the next thing in line is an amide, if you want to make that carboxylic acid, doesn't it?
A. No, it does not.
Q. Let's look at it.
Why to you suppose they listed it here, sir?
A. I certainly tried it figure that out. That's the first thing I tried to figure out when I saw that on the table. There is no discussion of amides in the text.
Q. Except right here where it says it converts into a carboxylic acid?
A. That's the only place it is.
There are no examples.
Q. Do you think they put it there because they didn't think you should use an amide?
A. I think they put it in there for the same reason that there is a possible conversion at that point.
Nobody used an amide as an ocular prodrug.
Q. Okay.
That's not my question. It's clear that they are suggesting that amides are possible when you have a functional group of a carboxylic acid if esters aren't available for some reason?
A. That's not what they are suggest.

I don't see how you get that out of that table. You're reading much more into the table than a person of ordinary skill in the art would.

Q. Tell me, Doctor, you as a person of ordinary skill in the art, what does it mean to you, prodrug form of various functional groups and drug substances.

Do you see that?

A. I do.

Q. They say functional groups, carboxylic acid, do you see that?

A. Yes I do.

Q. Prodrug formed, an amide is listed there.

Put aside the rest of article. What does that mean?

A. What that means to me -- and the very first thing I would do yet again is refer to the article to really he'll determine what that himself. I would not intuitively, instantly make an amide from a ester because it's in a table.

That makes no sense.

Q. That's not all you know about it. We went through this.

A. What else do I know?

Q. You know that bimatoprost free acid?

THE COURT: You are talking over each other.

THE WITNESS: My apologies.

BY MR. LOMBARDI:

Q. You know that bimatoprost-free acid was known from esters and was effective lowering intraocular pressure?

A. Yes.

Q. You know that amides hydrolyzed in free acid carboxylic acid?

A. Slowly.

Q. Yes?

A. Yes, slowly.

Q. Okay. Thank you.

You know that amides were will hydrolyze into carboxylic acid in the human body?

A. Yes.

Q. There is no art that says they won't do that in the eye?

A. That's correct.

Q. And then you have a book come out that says in a table if you want the carboxylic acid function group once the prodrug formed is an amide, right?

A. When it is in a vacuum and looking back in time at something like this, there was a body of literature. You're taking a single example out of context. There was a body of literature that suggested, or it taught against the use of amides as prodrugs.

If there were more than one example, I'm sure you're

going to pull it up and show me because there isn't.

Q. Do you know what the date of this reference was?

A. About 1990, was it not?

Q. Was it 1992?

A. It could have been.

Q. You cited a reference called Lee and Lee?

A. I did.

Q. Do you know what the date on that one was?

A. Approximately the same?

Q. It was earlier, wasn't it?

A. '89.

Q. Right.

So this was as of September of 1992, the most updated version -- most updated art, is that right?

A. I also cited Silverman which came out, I believe, as well.

Q. I'm going to get to Silverman if I have time. I'm not sure I'm going to have much the way we're going.

Lee and Lee, the one you cited, sir?

A. Yes.

Q. That's the same Lee that wrote this article, right?

A. The same Bundgaard, especially Lee?

Q. The Lee that you pointed to from 1989 is the same Lee that I'm pointing to in the 1992 article?

A. That's correct.

Actually, if you read the articles, you'll see that there are substantial portions of the text that overlap.

Q. Okay.

The Lee that wrote your 1989 reference, wrote this one which specifically lists an amide as a prodrug that you would use in ocular use to convert to the carboxylic acid, is that right?

A. That's correct.

Q. Okay.

Now, let's go back to Stjernschantz quickly?

A. Yes.

Q. We have no debate, I think, that Stjernschantz taught that the bimatoprost-free acid would have the effect of lowering IOP, is that right?

A. That's correct.

Q. You accept that as a teaching of Stjernschantz?

A. I do.

Q. Do you also accept as a teaching of Stjernschantz -- let me go back to the chart.

I just put back on the board our chart of compounds.

Do you also accept as a teaching that Stjernschantz -- that compound 2 which has the ester at the C1 group, right?

A. Yes.

Q. Compound 2 will have an effect of lowering intraocular pressure in the eye?

A. That's correct.

Q. Okay.

And compound 2 acts by the conversion of the ester at the C1 position to the carboxylic acid that you see in Compound 17, correct?

A. That's correct.

Q. But there was a problem that Stjernschantz recognized with compound 2, is that right?

A. That's correct.

Q. The problem was hyperemia?

A. Correct.

Q. And when you have a problem with hyperemia, that's a problem on the surface of the eye, is that correct?

A. That's correct.

Q. So that means that you're getting too much acid on the surface of the eye, is that correct?

A. I'm not sure what the interpretation of that is.

There are certainly several. It could well be there is too much PGF2 alpha, 17 phenyl or bimatoprost-free acid, if you want to call it that.

In other words, there is too much activation most likely of the prostanoid receptor.

One doesn't know what the magnitude of the hyperemia is.

Q. You would agree if you would put the bimatoprost-free

acid directly into the eye it would lower IOP?

A. It would.

Q. And you would agree if you put the bimatoprost-free acid directly into the eye it would cause severe hyperemia, is that right?

A. That would be expected, yes.

Q. And that would have been expected in 1992?

A. Yes.

Q. I think in 1992 the thinking would have been that bimatoprost-free acid was a prostaglandin analog and prostaglandins caused IOP lowering and hyperemia, and, therefore bimatoprost-free acid might act the same way, right?

A. That's correct.

Q. Now, hyperemia is a surface effect as you said?

A. Yes.

Q. And hyperemia occurs due to a fact of lack of penetration of the corneal epithelium, is that right?

A. Not my field of expertise.

Q. Okay.

All right. Let me ask you to assume that it does, okay. I understand that you don't know yourself. Let me ask you to assume it does.

Let me just put the eye up so we have something to look at. This is a basic structure. Doctor, do you see

that?
A. Yes.
Q. The corneal epithelium. Can you show us where it is with your pointer?
A. That's this outer layer on the cornea here.
Q. So IOP, intraocular pressure lowering requires getting through that corneal membrane into the aqueous humor, is that correct?
A. That's correct.
Q. One logical approach before 1992, if you had a drug that caused hyperemia but also lowered intraocular pressure, IOP, is that all right with you?
A. That works.
Q. But lowers IOP -- one strategy to use would be to try to make sure that the drug doesn't metabolize until it gets inside the corneal epithelium, is that right?
A. That's correct, if it's a prodrug strategy. That's exactly what a prodrug strategy attempts to utilize?
Q. Okay. So that would be a logical, reasonable approach for somebody in 1992 to pursue?
A. That's what Bito taught, Stjernschantz followed.
Q. If you knew that with the ester group at the C1 position you were causing hyperemia, if you knew that, you might want to make a change there, right?
A. Or somewhere else in the molecule, yes.

Q. It might have been that hyperemia was caused by it fast metabolism of the ester group, right?
A. Could have been.
Q. A logical approach could be to go to something that metabolized slower than the ester group?
A. Or another derivative at other sites.
Q. You're saying, yes, a logical approach would be to go with something other than the ester group that metabolized slower than ester group?
A. We don't know what causes hyperemia. We're not sure if it's free acid. We're not sure what the mechanism is.

To make that extension would be again an assumption. It would have been perhaps a direction to pursue. It certainly wouldn't have been obvious in any necessary way. That's an outcome that one would pursue.

Q. Maybe a research direction?

All I'm asking you is it would have been a logical approach, a logical research direction?

A. It would have been a research direction. It would have been a research enterprise. You couldn't have predicted the outcome of a study of that type, correct.
Q. So, just to be clear, we've got compound 2 which has that ester at C1, right?
A. Correct.
Q. We know there's hyperemia with that, right?

A. We do.
Q. We also know compound 2 is a good drug in terms of lowering IOP, correct?
A. We do.
Q. So a good strategy, a probable research direction as you put it would be to replace that ester with something that had a slower metabolism, correct?
A. You could have done that with --
Q. Could you answer my question, please?
A. Change the isopropyl ester. Let's be specific. You could have changed to a number of different ester derivatives.
Q. That wasn't my question.
A. Okay.
Q. My question was, it was logical -- it was a normal, reasonable research direction in 1992 to change -- to pursue the idea of changing the C1 ester that had a slower metabolism?
A. A different ester perhaps.
Q. I said something, right?
A. Correct.
Q. That's a logical approach, isn't it?
A. That's certainly something one would pursue.
Again, there was no necessary understanding that would be a successful outcome. That was a research direction.

Q. But you just said it is certainly something someone would pursue?
A. Someone might pursue?
Q. I think you said something someone would pursue?
A. If I did, let me correct myself.
Q. Correct yourself.
A. They might pursue it. It's a research direction. There were options that one could examine.
Q. Okay.
A. And the reason is that the logic -- the metabolism of the ester is fast, that might be creating more acid on the front of the eye -- on the surface of the eye rather than inside the eye, right? That would be the logic of this research plan? That would be the logic of the research plan.

But, as I said, we don't know what causes hyperemia.

We don't do back to fusion. We don't really have a clue as to what causes hyperemia.

Q. Now, one way to reduce the metabolism of that ester group is to put an ester group there?
A. Virtually block the hydrolysis, correct.
Q. And that ester group would slow the metabolism, is that right?
A. Profoundly.
Q. You believed it was extraordinarily well established

in 1992 that an amide group would have a slower metabolism than an amide group, isn't that right?

A. Profoundly slower, correct.

Q. Sir, you're not here saying that it would be illogical to try an amide at that C1 position, are you?

A. I'm saying it wouldn't have been a logical choice for a prodrug, no, it would not.

Q. Whether it's a prodrugs or not, we have a lot of information about prodrugs that came out between '92 and the present, right?

A. Of course. Hindsight is 20-20.

But the book you're talking about isn't titled prodrugs. We're actually after a prodrug strategy. We want something to be able to hydrolyze in a reasonable time frame. Ones expectation of an amide would have been that it would have been a very unreasonable time frame.

Q. Okay. Just to make sure we're together on the one point, though, sir.

A. Correct.

Q. You wouldn't say it was illogical to a pursue an amide if you were trying to show the metabolism of the compounds by replacing the ester?

A. I would have said it would not have been obvious. It wouldn't have been a natural pathway that one would have pursued.

Q. You see the logic in doing it?
A. In hindsight.
Q. Let's talk for a minute about what happened inside Allergan.
Let me show you what's in evidence as PTX 95, please.
Here's PTX 95, sir.
Do you see that, sir?
A. I do.
Q. You've seen that before, is that right?
A. I do. I have.
Q. This is an internal document at Allergan, from Allergan, is that right?
A. Yes.
Q. If you look at the very top, it's talking about synthesis of PGF2 alpha prodrug. It's got a series of people, and one of which testified here, Dr. Garst. Do you see that?
A. Yes.
Q. This was possibly pre-invention at Allergan, is that right?
A. Yes, it is. Do we know the time of this?
Q. Doesn't it have a date on it?
Let's go here. There's an underlined portion that is not underlined that I put on there. It says under prodrug, the ideal situation selective metabolism of the prodrug in the

anterior segment ciliary muscle with metabolism in the conjunctiva or cornea.

Do you see that?

A. I do.

Q. That's essentially the logic you and I were just talking about; is that right?

A. That's correct.

Q. So you can at least agree that the logic that your friends at Allergan endorse here has some merit to it; is that right?

A. As I said, there was an entire prodrug program ongoing when I -- became a consultant at Allergan.

Q. Well, let's go to the next page. Actually, it's the third page with Bates numbers ending 316.

And you see in that bottom left-hand column, it says -- what is the heading?

A. Antagonist Prodrugs.

Q. So still part of the prodrug work; is that correct?

A. That's correct.

Q. All right. And so it says, although the authentic prodrug approach is a very elegant concept, its success cannot be guaranteed due to the high metabolic rate of the cornea.

Do you see that?

A. I do.

Q. So the problem they're talking about there is with the ester groups; right? They metabolize too quickly; right?

A. I'm not quite sure what they're saying there actually, but other than what it says. I'm not sure what they're referring to. Excuse me.

Q. Okay. Then they say, back diffusion of nascent PGF2 alpha from the cornea is a definite possibility, and this would cause hyperemia.

Do you see that?

A. Yes, I do.

Q. That's what we were talking about.

A. That's what I just alluded to correct.

Q. PGF2 is the carboxylic acid we know; right?

A. Mm-hmm.

Q. Yes?

A. Yes. I'm sorry.

Q. And it says, the synthesis of prodrugs that possess antagonistic properties is an important, concurrent strategy.

Do you see that?

A. I do.

Q. It goes on to say, this concept simply makes use of excess prodrug accumulated in the conjunctival sac to counteract the adverse effect of back diffused PGF2 alpha.

Do you see that?

A. I do.
Q. So when they talk about back diffused PGF2 alpha, you're worrying about the PGF2 alpha, the carboxylic acid, coming back from the back to the front of the eye and causing hyperemia?
A. That's correct.
Q. They're saying with this concept of their antagonist prodrug program, they're assuming there's going to be carboxylic acid made; right?
A. For a prodrug, you need carboxylic acid to be generated, yes.
Q. Right. So by definition, this antagonist prodrug program is converted to a carboxylic acid; is that right?
A. For activity at the PGF2 receptor, FP receptor, or the classical receptor.
Q. Let's keep going.
A. Depending on the year, this memo may also have nonclassical receptor.
Q. Okay. All right. And so then it says initially at the bottom, the amides of PGF2 alpha and their esters were selected to test the -- I can't read that.
A. Antagonist prodrug.
Q. Prodrug hypothesis. Thank you.
A. Mm-hmm.
Q. Then we'll go to the next column. And do you know

what's coming here? What the prodrug is that they talk about?

A. I do.

Q. Okay. Let's blow it up.

What is the prodrug that they list as number one in their program?

A. I'm not sure. Is the -- oh, the dimethyl amide of PGF2 alpha has been reported by Corey to be an antagonist of PGF2 alpha in the classical gerbil colon assay.

Q. So what the scientists are saying, the Allergan scientists are saying there, they're using PGF2 alpha amides as prodrugs; is that correct?

A. What they are trying to do in that particular case --

Q. Can you just answer my question? This is in the prodrug program, isn't it, sir? And the first one they talk about is PGF2 alpha amides?

A. The prodrug program also had a separate program.

Q. Can you answer my question, sir?

A. I'm not quite sure that that is -- yes. The answer is that is in the prodrug analysis, correct.

Q. All right. It's amides; right?

A. Mm-hmm.

Q. Okay. So -- was that a yes?

A. Yes. I'm sorry.

Q. All right. Then let's go back to that, where we were

before, that paragraph there.

And what they are saying is that the concept of using the amides is to make use of excess prodrug accumulated in the conjunctival sac to counteract the adverse effect of back diffused PGF2 alpha.

And we've already said, that indicates that they expect there to be conversion to PGF2 alpha with these amides; is that right?

A. The reason I asked --

Q. Sir, can you answer my question?

A. Yes. Can I --

Q. Thank you.

A. -- proceed?

Q. Yes. Go ahead.

A. The reason I asked for the year is because when I reviewed this program, I said it was a fantasy of the medicinal chemists involved to consider this as an approach. And the reason is, is because if the amide truly is an antagonist, when it gains access to internal ocular tissues, it will also be an antagonist.

And so it's going to be a function of the rate of metabolism which was expected and anticipated to be slow. As you can see, it's certainly not expected to occur on the surface of the eye.

And when it gained access inside, it was also

going to be an antagonist and block the activity of any released acid, because one presumed the acid to be released very slowly.

And if you will look at my memo of September 1989, you'll see that I called this approach a fantasy, which it is.

Q. Okay. Well, whatever you thought, sir.

A. Okay.

Q. That -- whatever you thought?

A. I thought you were asking for my opinion. I'm sorry.

Q. No. I asked a question. You wanted to explain yourself.

A. Okay.

Q. And I let you explain yourself. But this says antagonist prodrugs.

So they are talking about prodrugs, and that means they expect that the -- that the amide that's laid out here is going to convert to the carboxylic acid; isn't that right?

A. They can expect what they like. I mean --

Q. Is that what they are saying, sir?

A. That's what they're saying.

Q. So they --

A. That's not what one would expect given an ordinary skill in the art.

Q. That's not what you would expect?
A. That's correct.
Q. They evidently had a different expectation than you did about their prodrug approach; isn't that right?
A. There is no expectation here. There is no -- there is a hope, it's a whisper. There's absolutely no indication that this is going to be a successful approach.
MR. LOMBARDI: Thank you very much, Doctor.
THE WITNESS: Thank you.
THE COURT: All right. Redirect.
MS. BROOKS: Thank you, your Honor. Just a few brief questions.

REDIRECT EXAMINATION

BY MS. BROOKS:
Q. So, Dr. Macdonald, let's clear up just a couple of things.
PTX-95 Mr. Lombardi showed you. That was the document you were just discussing. And he showed you this one line that was underlined that said, the ideal situation would be selective metabolism of the prodrug in the anterior segment, e.g., ciliary muscle, with no metabolism in the conjunctiva or cornea.
Do you recall him showing you that sentence?
A. I do.
Q. What he didn't do was read the next sentence to you,

which was, what did the inventors at Allergan propose they would do in order to deal with the previous sentence?

A. A number of PGF2 alpha esters at the 9, 11 and 15 hydroxyl groups have been prepared to test the feasibility of this approach and they are listed below.

Q. So it wasn't an amide approach, it was an ester approach?

A. In that particular discussion, that's correct.

Q. Now let's go to that fact, the 9, 11 and 15.

Now, you said that at Allergan internally, assuming that the C-1 wasn't available to you to turn that into an ester, where would you go and where the inventors internally at Allergan had gone was the 9, 11 and 15 locations to make ester -- esters there; right?

A. That's correct.

Q. Now, putting aside what you learned at Allergan, just based on your chemistry experience in 1992 as a chemist, if you were told, you can't use the C-1 for an ester, what are the other obvious sites on this molecule where you would go?

A. They're the 9, 11 and 15 hydroxyl sites, which you would esterify.

Q. Why?

A. Because you knew that they would release the prodrug in a reasonable time frame at a reasonable level.

Q. And would that have been the obvious choice to make

back in 1992?

A. That was the obvious choice.

Q. And did, in fact, the inventors try that?

A. That's the direction they initially took, that's correct.

Q. But did they end up going down a completely different direction?

A. They did, because they discovered a novel receptor, yes.

Q. Now, Mr. Lombardi showed you this chart, which is the three compounds in Stjernschantz, and then on the right side is the compound bimatoprost. And he asked you whether it would be easy to essentially take the ester of compound 2 or the acid of compound 17 or the ester of compound 9 and replace it with an amide. And you said, yes, it would be fairly routine to be able to do that; is that right?

A. That's correct.

Q. Based on all of the prior art that was out there back in 1992, would it have been obvious to do that?

A. As a prodrug?

Q. Yes.

A. No, it would not.

Q. Why not?

A. Because amides were not designed or thought to be suitable prodrugs for carboxylic acids.

Q. And you mention that amides -- Mr. Lombardi tried to get you to say now amides do metabolize. They hydrolyze.
A. That's correct.
Q. You kept saying, "Yes, very slowly." What is the significance of the fact that they were known to hydrolyze very slowly?
A. Because they were known to hydrolyze very slowly -- or let me start again.

Prodrugs need to be released at an adequate rate in sufficient amounts to produce the active agent. If it's too slow, it will not do that. And that's exactly what the anticipated, or the expected result of an amide compound would be. In fact, amides are usually designated as stable molecular substructures in drugs.

Q. And what's the significance of that as far as using an amide as a prodrug?
A. That you would not teach or not use an amide as a prodrug.
Q. Now, Mr. Lombardi also went through DTX-1006, the Lee and Bundgaard article, and showed you Table 2, and there listed on Table 2 for various possible prodrugs was -- let me get my reading glasses on here since I can't see the page -- was an amide.

Do you recall that?

A. I do.

Q. And so I'm looking for Table 2 here. There we go.

So here is Table 2, and it's actually -- there were only a couple of items put on that chart that Mr. Lombardi showed you, starting with esters, and then going to another kind of esters and then amides was third.

A. Correct.

Q. Now, that snippet actually came off of a slide that Dr. Mitra showed.

How many other suggested prodrugs are listed on Table 2 beside amides?

A. Well, maybe two dozen, perhaps.

Q. And how many of them -- we don't need to count actually, but let's just look.

The first one is esters. Second one is esters. Fifth one down, esters. Esters, esters, esters.

There are a lot of esters listed on here; is that right?

A. There are.

Q. And only one amide?

A. That's correct.

Q. Now, you've mentioned that after listing an amide on Table 2 along with all these esters and other things that's possible, a suggestion of a possible prodrug.

Did Table 1 contain all of the examples where they had actually used these various molecules?

A. It did.
Q. And did Table 1, I believe goes over two pages. There are so many on them. But on this page, do we see in the examples in Table 1 of Lee and Bundgaard anything about an amide?
A. We do not.
Q. And if we go to the second page, which continues on with Table 2, do we see anything about an amide?
A. We do not.
Q. But to be fair to Mr. Lombardi, the rest of the chapter then goes on and starts discussing all of these different possibilities; is that right? That's what's in the rest of the chapter?
A. That's correct.
Q. So let's see what Lee and Bundgaard teach in the rest of the chapter about the use of amides as prodrugs.

What does Lee and Bundgaard teach one of skill in the art as to -- let me put it this way. If one took the suggestion, the hint, of Table 2, to use an amide as a prodrug and then read the section of Lee and Bundgaard that discusses amides as prodrugs, what kind of expectation of success would one have?
A. Amide prodrugs has been used only to a limited extent only to the relative stability of amides in vivo. There's a Reference 100 that refers back to an earlier Lee paper, I

believe, or perhaps it's a Bundgaard article, which refers to one example, which is -- it goes on to say, this problem can be circumvented by introducing an enzymatically hydrolyzable -- oh, excuse me. The only example turns out to be a peptide amide in the entire literature that I could identify.

Q. So we still don't have any literature, including Lee and Bundgaard, that suggest to anyone as of 1992 to use a simple amide at the C-1 position in order to make a drug that will lower intraocular pressure or treat glaucoma?

A. That's correct.

Q. To this day, have you found anything?

A. In retrospect?

Q. Let's say in 1992, up to 1992.

A. 1992, no. To this date, I really can't identify amide prodrug particularly for ocular use.

Q. And I take it you've looked?

A. I have.

Q. Now, this is just a minor little point, but I just wanted to clear it up so that it would be fair.

Mr. Lombardi said, now, Dr. MacDonald, yesterday you said that you shouldn't call Compound 17 of Stjernschantz bimatoprost-free acid, but you, yourself, have called it that.

Do you remember that discussion?

A. I do.
Q. And he pointed you to footnote 11 of your -- I'm sorry -- footnote 191 of your expert report.
Do you recall that?
A. I do.
Q. Now, do you recall in your expert report discussing a paper that had been cited by Dr. Mitra called Camras, which was published in 2004?
A. I do.
Q. And in discussing that paper, did you say that the problem with Camras, which was published in 2004, is that it was a study in which a patient's aqueous humor was removed during cataract surgery after seven-day treatment with bimatoprost, suggesting it is a definitive study that finally analyzed bimatoprost's hydrolysis and activity in human eyes.
Do you recall you talking about Camras, the 2002 paper, in that way?
A. I do.
Q. And that's where your footnote appears, where you are referring to bimatoprost-free acid, and bimatoprost acid referred to 17-phenyl PGF2 alpha.
Do you recall that?
A. I do.
Q. So why is it that in 2004 does it become appropriate

to refer to 17-phenyl PGF2 alpha as bimatoprost-free acid?
A. Because bimatoprost had been on the market at that -- at that point, and it was a named compound.
Q. Is there any way to call Compound 17 in Stjernschantz bimatoprost-free acid without using hindsight?
A. No.
Q. Had the term bimatoprost even been coined back in that time frame?
A. No.
Q. Had the term bimatoprost-free acid even been coined during that time frame?
A. No.
Q. Now, just one more question so we can be sure we're on the same page.

When we were talking about this, the Lee and Bundgaard article, you said that it was talking about a peptide amide; is that right?
A. That's correct.
Q. And that that is not a simple amide?
A. That's correct.
Q. And could you explain to the Court the difference between a simple amide and an activated amide or a peptide amide?
A. A peptide amide contains an amino acid and is a substrate for a specific class of enzymes, which we had

discussed earlier, which are the peptidases. And so peptidases are a lot more prevalent than the nonspecific, if you will, amidases. Relatively small family of enzymes.

There are three classes of amides which we term simple activated and peptide or amino acid amides.

Q. And what is the difference as far as how one might expect a simple amide to behave if you put it at the C-1 position versus an activated amide?

A. They all need enzymatic hydrolysis or enzymatic mediation of hydrolysis, and there's a very small number of enzymes that catalyze the conversion of simple amides as compared to, for example, peptide amides, or even activated amides.

MS. BROOKS: Thank you, Dr. MacDonald.

No further questions, your Honor.

THE COURT: All right. You may step down. Thank you, sir.

(Witness excused.)

MR. WARNER: Your Honor, the defendants call Dr. David Sherman.

MR. LOMBARDI: Make sure they're done first.

MS. BROOKS: I think we need to rest, your Honor.

THE COURT: All right.

MS. BROOKS: We are moving along.

Your Honor, we rest at this point and we would ask an opportunity to reargue our JMOL motion at a subsequent time.

THE COURT: All right. It's going to be reserved. I'm not going to rule from the bench. But, yes, you may do that before we close the record.

MR. WARNER: Thank you, your Honor. The defendants call Dr. David Sherman.

DEFENDANTS' REBUTTAL TESTIMONY

... DAVID HOWARD SHERMAN, having been duly sworn as a witness, was examined and testified as follows ...

MR. WARNER: Thank you.

Your Honor, Dr. Sherman will be offering opinions on unexpected results, particularly in connection with pharmacology of bimatoprost and receptor pharmacology.

THE COURT: All right. Thank you.

MR. WARNER: May I approach to hand him a binder?

THE COURT: Yes, you may.

(Mr. Warner handed a binder to the witness.)

DIRECT EXAMINATION

BY MR. WARNER:

Q. Good morning, Dr. Sherman.

A. Good morning.

Q. Can you briefly tell the Court what you're here to testify about?

A. Yes. I'm here to testify about whether or not there are any unexpected results relating to bimatoprost in this case.

Q. And what are your opinions, just briefly, on that matter?

A. My opinions are that there is no new prostamide receptor that could even be considered unexpected.

Two, even if there was, it wouldn't be anything new or surprising.

And, third, that bimatoprost acts in its free acid form and not as its ethylamide form.

Q. Dr. Sherman, what do you consider to be your areas of expertise as they relate to the issues in this case?

A. As it relates to this case, I'm a protein biochemist, medicinal chemist, and also I have an expertise in receptor pharmacology.

Q. So before we get into the substance of your testimony, I want to talk a little bit about your background.

Can you take a look in your binder at Defendants' Exhibit 861, please?

A. 861?

Q. Do you have that? It should be a copy of your C.V.?

A. Right. There it is. Okay.

Q. Do you have that there?
A. Yes, I do.
Q. And that's your current curriculum vitae?
A. Yes, it is.
MR. WARNER: Your Honor, at this time, we move Defendants' Exhibit 861 into evidence.
MR. McCANN: No objection, your Honor.
(DTX No. 861 was admitted into evidence.)
THE COURT: Thank you.
BY MR. WARNER:
Q. Dr. Sherman, can you tell us a little bit about your college and post-graduate experience, please?
A. Yes. I received my Bachelor's degree with honors from the University of California, Santa Cruz, and then I received two Master's degrees and my Ph.D. at Columbia University in New York City.
Q. Did you then do any -- what was the subject matter of your Ph.D.?
A. I worked on the total synthesis of biologically active hormones. Specifically, 11 keto progesterone.
Q. Did you do any post-doctoral fellowships, anything like that?
A. Yes. I did two. One in the Department of Pharmacology, Yale Medical School, and a second one in the Biology Department, the Center For Cancer Research at MIT.

Q. Following your post-graduate work, were you ever involved in industry?

A. Yes. I worked for about three or four years at Biogen Research Corporation in Cambridge, Massachusetts, and then I went on to the United Kingdom to work for three years at the John Innes Institute.

Q. Just generally speaking, what type of work were you doing?

A. This was all related to molecular immunology, molecular pharmacology, and -- and drug discovery.

Q. And do you have a -- currently, are you in academia?

A. Yes. I am a Professor at the University of Michigan.

Q. And what are your current academic -- current academic appointments at the University of Michigan?

A. I have academic appointments as the Vahlteich Professor of Medicinal Chemistry in the College of Pharmacy. I'm also a Professor of Chemistry. I am a Professor of Microbiology and Immunology at Michigan Medical School.

Q. Are you also affiliated with the Center For Chemical Genomics at Michigan?

A. Yes. I'm the Director of this center, which is the University of Michigan Drug Discovery Center, known as the Center for Chemical Genomics.

Q. And, just generally, can you tell us what is the purpose and what are the goals for the Center for Chemical

Genomics?

A. At the center, we work with collaborators mainly within the medical school, but also outside institutions on drug discovery and development projects.

Q. In your work at Michigan, do you teach about G protein coupled receptors or GPCRs?

A. Yes, I do. I teach a big course in the College of Pharmacy to doctor of pharmacy students, and this is a course in medicinal chemistry and molecular pharmacology where we discuss small molecule drugs. And, in particular, GPCRs, because they're such an important drug target for many pharmaceuticals on the market.

Q. Dr. Sherman, do you also have experience in biological enzymes and hydrolases?

A. Yes. My -- my research group works with many types of enzymes, multi-functional proteins, and also hydrolases that are involved in converting prodrugs and other molecules to hydrolyzed forms.

Q. So I take it you also do work with prodrugs?

A. Yes, I do.

Q. Can you talk about that experience briefly?

A. Right. I work with a number of compounds that are prodrugs. Mutamycin C, for example, is a well-known prodrug. Some of the macrolide molecules, macrolide antibiotic-type molecules are prodrugs, and other cancer-

related therapeutics that are prodrugs.

Q. Do you have any experience in the area of prostaglandins and prostaglandin research?

A. Yes. Actually starting as an undergraduate, where I began working with prostaglandins that were derived from natural sources. As a graduate student, I worked on synthetic schemes for prostaglandins because they were such an important molecule at that time, the late seventies, early eighties. And now also working with prostaglandin-related molecules, especially in my teaching at the College of Pharmacy.

Q. And are you a published scientist?

A. Yes, I am.

Q. It's in your C.V., but roughly how many journal references?

A. About 175 publications.

Q. Has your work in all these areas you've just been discussing been recognized by your peers or other professional groups?

A. Yes.

Q. Are there any particular recognitions that you are very proud of?

A. I have a number of awards, starting in the early nineties from Eli Lilly, when I received a life sciences award. More recently, the American Chemical Society A.C.

Cope Scholar Award, the Charles Thom Award for the for the Center of Industrial Biology, and I was elected a Fellow of AAA as the American Association For the Advancement of Science.

Q. And you mentioned the A.C. Cope Scholar Award, I believe?

A. Yes.

Q. Could you tell us a little bit about what that is and why it's awarded?

A. So that's a prestigious award given by the American Chemical Society, which is the major society for chemists in the United States, and recognizes scholars at various stages in their career. I was -- I was awarded as a senior investigator. And it relates to my work on biologically active molecules, many of which are pharmaceutical.

Q. So can you explain, Doctor, how all of these areas of expertise, it sounds very multi-disciplinary, how that all coalesces in this case, in terms of the opinions you're going to offer?

A. Right. Especially, you know, when I moved to Michigan, I was asked to lead the Drug Discovery Center. And it's because of my multi-disciplinary training in chemistry and protein biochemistry, molecular pharmacology, which is essential for drug discovery and development. And this is how I'm viewing the issues in this case.

MR. WARNER: Your Honor, I offer Dr. Sherman as an expert in the field of medicinal chemistry, receptor pharmacology and protein biochemistry.

MR. McCANN: No objection, your Honor.

THE COURT: Thank you.

BY MR. WARNER:

Q. Your opinions today, we mentioned f.

GPCR, and your opinions relate in large part to that; is that right?

A. Right.

Q. Before we get into that, were you in court when Dr. Mitra testified? He gave an opinion about his view of a person of ordinary skill in the art is relevant to this case?

A. Yes.

Q. And do you share the same opinion?

A. Yes, I agree.

Q. You were also here yesterday when Dr. Regan testified; is that right?

A. Yes.

Q. And did you hear him discuss his view of a person of ordinary skill in the art?

A. Yes.

Q. Would any of your opinions change in this matter if the Court adopts Dr. Regan's view of a person of ordinary

skill in the art?

A. No, they wouldn't.

MR. WARNER: Can we look at Defendants' Demonstrative 4-1, please?

BY MR. WARNER:

Q. Dr. Sherman, can you tell us what is depicted here?

A. Right. So we've heard a little bit about -- about receptors previously.

This is a depiction of a protein coupled, a G protein coupled receptor, and it has a number of parts. But the key issue about receptors is that they can detect some sort of signal from outside the cell, capture that in the form of a ligand or a drug or another type of small molecule, and then transfer an important signal through the protein molecule to elicit gathering of something called a G protein. And that G protein then results in further signalling. That ultimately leads to a biological response.

There are three basic parts. One is this N-terminal segment, which is on the outside of the membrane of the cell, and then within the membrane are these seven transmembrane domains. These, of course, are all made up of polypeptide sequence.

And then there are intracellular loops, such as this loop, as well as this important tail, called the carboxy terminal tail, which often along with this -- this

final loop here (indicating) play a role in recruiting the G proteins that are then critical for eliciting a biological response.

Q. And is this a representation of what the FP receptor that we're talking about in this case might look like?

A. Yes. This is an accurate representation.

Q. You talked a little bit about the intracellular C-terminus, which is that longer tail?

A. Yes.

Q. Can you please tell the Court what that is for?

A. Right. So this is a very important part of the G protein coupled receptor.

Number one, as I mentioned, it's critical for recruiting the G proteins that in turn will elicit a secondary signal leading to a physiological response.

That also plays a role in many instances in forming dimers, whereby two identical chains of a GPCR will actually come together to form a pair. And often that intracellular carboxy terminal tail plays a role in that dimerization process.

Q. You also mentioned that to the left of the intracellular C-terminus is another loop inside the cell. What is that called?

A. Right. So this is the third loop (indicating), and you can see that it's intracellular.

Q. Does that also -- sometimes is it possible that has a role in G protein recruitment?

A. Yes, it does, indeed. It can play that role.

Q. It doesn't always, but it's possible?

A. Right. It doesn't always, but it can play a role, and it often will play that role in the context of this longer carboxy terminus.

Q. You've discussed a little about dimers. So is this single unit how most GPCRs exist in nature?

A. Well, the weight of evidence shows that in many, if not most instances, GPCRs will come together to form some sort of a dimer.

Q. And what portions of the receptor are involved in the dimerization process?

A. Well, there can be different components of the receptor, but very often, it is this carboxy terminus that plays an important role, not only in dimerization, but also making sure that the receptor gets from its point of synthesis, where it's actually made in the cytoplasm, to the membrane.

Specifically, the GPCR must be located in the membrane in order to do its work, and if it can't get there, then it can't work properly.

Q. Dr. Sherman, yesterday, there was some discussion of splice variants and a splice variant heterodimer.

Do you recall that testimony?

A. I do.

Q. And Dr. Regan posited that there is a splice variant heterodimer of the FP receptor that is a prostamide receptor.

Do you remember that?

A. Yes, I do.

Q. Do you agree with that opinion?

A. I do not agree that there is a prostamide receptor or a heterodimeric form of that receptor, no.

Q. All right. So to understand your opinions in this matter, let's start with, what's your understanding of splice variant, just generally speaking?

A. So a splice variant, it's a slightly altered form of what we see as this normal receptor protein. And in the splice variant, something has changed, and that change can result in a variation of the protein structure. Often, it will result in amino acid changes or truncations to the protein relative to the normal protein of polypeptide sequence.

Q. And do those truncations occur in what's alleged to be the splice variants at issue in this case?

A. Yes.

Q. And can you tell us a little bit about using that diagram?

A. Yes.
Q. What the purported splice variant would look like?
A. So in this case, specifically, the alt 4 FP splice variant (indicating) is missing this 17th transmembrane domain. And it's missing the entire carboxy terminal region of the molecule.
Q. So what effect would that have on a GPCR that's missing its entire intracellular C-terminus?
A. Well, it would have very significant effects, negative effects, because, number one, it's missing the entire intracellular carboxy terminus. And as I mentioned, that's essential for signal transduction, for recruiting G proteins. It's also essential for moving the receptor from the cytoplasm to the appropriate position in the membrane. And it's also playing a role in dimer formation, which is often the form that these receptors take to be active.
Q. And in your opinion, would a splice variant be efficacious if it had activity in terms of the intracellular C-terminus?
A. No, it's wouldn't.
Q. Have you seen any data in this case about whether that's -- your opinion is correct in that regard?
A. I have seen data that supports my opinion.
MR. WARNER: So let's take a look, please, Jeremy, please at Plaintiff's Exhibit 221A.

BY MR. WARNER:

Q. This is a color version of the Liang article, Doctor. It might be in your binder as Defendants' Trial Exhibit 167.

And I want to go to page 6. If you could highlight the third set of graphs.

BY MR. WARNER:

Q. Now, Doctor, can you explain what the authors are suggesting is shown here?

A. Yes. So in these graphs, the authors of the Liang paper have taken a CDNA, which is a copy of DNA representing this alt FP4 form of the receptor gene, and they've expressed it in human embryonic kidney cells.

And you can see in this graph that there's absolutely no activity. This receptor is dead, nonfunctional. And the flat line denotes that there's absolutely no response in the biological assay system.

Q. Now, there was also discussion of the splice variant forming a heterodimer. Can you explain what that is?

A. Right. So in the assay in this experimental system, this artificial system that they've developed, they've expressed both the wild-type FP receptor, the normal receptor, CDNA, along with the alt FP4 form. And they're alleging to generate a heterodimeric form of this receptor.

Q. And is the heterodimer, the hetero portion just refers to one-half is slightly different from the other?

A. Right. So using my hands, if this is the normal FP receptor chain, and this is the -- the alt FP4 form, they're alleging that they come together this in this way to form a heterodimer.

Q. Do you think that's happening in this case?

A. I do not think it's happening.

Q. Why is that?

A. Because all of the data that I have observed fails to provide convincing evidence that it's coming together and functioning as a receptor.

Q. Now, I want to ask you to assume just for a minute, Doctor, that the heterodimer that Allergan and Dr. Regan have discussed actually did -- does form naturally occurring cells.

A. Yes.

Q. Do you have any evidence as to whether or not the function of that heterodimer would be any different from the natural FP receptor?

A. There's absolutely no evidence that it would function any differently. The only component that would function is the -- the normal chain of that heterodimer, the normal FP chain.

Q. And is that because of the splice variant itself has zero activity?

A. That's correct, as we see in this assay here.

MR. WARNER: And if you could come out to the page, Jeremy, and look at the top two left graphs.

BY MR. WARNER:

Q. And, Dr. Sherman, is the information reported in these graphs consistent with your opinion that if there is a heterodimer, its activity is the same as the FP receptor?

A. Yes. So what we see here is the normal FP receptor that has presumably formed a homodimer, and the natural ligand, which is PGF2 alpha. And we see a very nice calcium response here. Very rapid response with a slow decay.

Now, what we see here is essentially the same thing with the FP alt FP4 alleged heterodimer.

Now, it's important to realize that in the cell, both a CDNA for the FP gene, which would presumably express the normal receptor, and the CDNA for the alt FP4 are co-expressed together. That means that in the very least, a homodimer for the normal FP receptor will also be expressed in that cell. It will also express the, presumably express the alt FP4, but we've seen that's not functional at all.

Now, we see an identical -- not response with a slow decay. In my opinion, that's PGF2 alpha against the homodimeric form of the normal FP receptor.

Q. We've been talking about the splice variant in the heterodimer as hypothetical or purported.

Now, this paper suggests that they do exist; is

that right?
A. In this paper, they allege that it exists, yes.
Q. All right. And this is a paper by Dr. Woodward and some others at Allergan?
A. Exactly.
Q. In your opinion, is there any evidence in this paper that the splice variant or a splice variant heterodimer of the FP receptor has ever been expressed, or expressed or found in any naturally occurring human cells or tissues?
A. No. This paper provides no evidence, no indication that heterodimer is expressed in normal human tissue, particularly eye tissue.
Q. Okay. And so what actually is being expressed in this paper?
A. What's being expressed here, the investigator generated copy DNA's and inserted those into a retroviral vector, and then transferred essentially infected the HEK cells. And those HEK cells then acquired the ability to artificially express those genes.
Q. So does this paper in your mind establish that there actually is a prostamide receptor?
A. No, not at all.
Q. And have you seen any physical evidence that a prostamide receptor actually does exist in any human tissues?

A. I have not seen evidence of that.
Q. Have you seen any physical evidence that any prostamide receptor, a splice variants or heterodimer of any kind, physically exists in any tissues?
A. No, I have not seen that.
Q. Now, there was also a discussion yesterday of various types of pharmacological evidence that were discussed as supporting a prostamide theory, so outside the context of molecular cloning.

Were you here for that as well?

A. Yes.
Q. Do you agree that the pharmacological evidence available leads to the conclusion that there's a prostamide receptor?
A. I do not agree with that opinion.
Q. And what is your opinion on the matter about, explain the pharmacological profile of bimatoprost.
A. In my opinion, the profile can be entirely explained by the action of the free acid form of bimatoprost on the normal FP receptor.
Q. So let's start out kind of at the beginning. I want to look at JTX-5, which is the '708 patent, please.

MR. WARNER: And, Jeremy, if you could go to page 4 we are looking at Figure 3 of the '708 patent.

BY MR. WARNER:

Q. Do you recall this graph, an experiment being discussed during testimony, Dr. Sherman?

A. Yes, I do.

Q. Can you explain essentially what's going on here?

A. Right. So this is the radioactive ligand binding assay, and what you have here is a molecule that has a radioactive tag on it bound to its presumed receptor, and then a competition assay is being conducted to compete away the radioactive label.

And what we see here with the 16 meta chlorophenoxy PGF2 alpha, which is the C-1 acid form, in, and this dose response will compete away that label.

And in the amide form, the amide derivative or the carboxy group has been converted into the amide, we see a -- a corresponding dose response. But the end point is about a twofold difference, so it's less effective, as we'd expect, in this assay.

Q. In order to explain the conclusions drawn from this assay, do you have to invoke a prostamide receptor theory in order to explain differences between the activity of the amide derivative and the other compound tested?

A. No, not at all. In fact, you can see that there is competition. I mean, there's a dose response competition where this derivative essentially washes out the label. And this can be readily explained by hydrolysis of the amide to

the corresponding carboxylic acid form, and in that way out-competing the radio labeled form of the drug.

Q. Let's turn to Table 4 now, which is at page 5 of the '708 patent.

And we've actually put this together. The Table 4 splits two columns, two pages, so this is the full table put together.

Can you just generally explain what's shown in this table, Doctor?

A. Yes. This is a smooth muscle stimulant assay and we're looking at EC 50s, and we've heard the definition of that before.

Now, what we're doing is comparing PGF2 alpha and its potency in the cat iris assay versus the guinea pig ilium against a variety of other ligands.

Q. And is one of them, one of the ligands tested there the compound bimatoprost?

A. Yes. Bimatoprost is shown right here (indicating). This is the ethylamide. And we see that potency, a very nice potency in the cat iris and virtually no activity in the guinea pig ilium.

Q. So there's activity of bimatoprost in the cat iris and no activity in the pig ileum?

A. That's correct.

Q. And in order to explain that activity, Doctor, do you

need to invoke a new receptor other than the classical FP receptor?

A. No, not at all.

Q. So how would you explain the differential pharmacology shown there?

A. Well, it's well-known and it was well-known at the time this assay was run that amides can be converted by amidases and tissues to the carboxylic acid, and in that way, one would expect the activity of this to correspond to a C-1 acid form of the drug.

Q. And is the C-1 acid form, that is the bimatoprost-free acids, or 17-phenyl PGF2 alpha?

A. That is correct.

Q. And it's also shown in that table that that acid, when directly put into the assay, has potent activity in the cat iris?

A. Yes. It's right here. You see the same magnitude of activity. About 11 as opposed to 34, but the same magnitude of activity.

Q. Is it unreasonable, Doctor, as of 1992 for a person of ordinary skill in the art to have thought that the difference in enzyme levels between the cat iris and the guinea pig could account for the different potencies in these two assays?

A. No. It wouldn't have been unreasonable. There was a

lot known about -- about these types of hydrolases, their ubiquity in tissues and the differences between various animals and tissues and their presence of particular types of these hydrolase enzymes.

Q. Now, you've reviewed all the data in the '708 patent; is that right?

A. I have.

Q. And is there anything in your mind that would have been surprising to a person of ordinary skill in the art in 1992 about the pharmacological data compiled and reported in that patent?

A. No, I don't believe so.

Q. Is there anything in there that requires the existence of a prostamide receptor different from the FP receptor in order to explain?

A. No. One of skill in the art would have immediately been drawn to the hydrolase theory.

Q. Now, can you turn in your binder to Defendants' Exhibit 985, please?

A. Did you say 95?

Q. 985. I'm sorry.

A. 985. Okay.

Q. And that's a paper by David Woodward and others entitled "Pharmacological Characterization of Novel Anti-Glaucoma Agents."

Do you see that?

A. Yes, I do.

MR. WARNER: Your Honor, at this time, defendants move Exhibit 985 into evidence.

MR. McCANN: No objection.

THE COURT: Thank you.

(DTX No. 985 was admitted into evidence.)

MR. WARNER: Jeremy, can we take a look at that at page 986, please?

BY MR. WARNER:

Q. We're not going to go in detail through all the data, but do these graphs report potential activity of bimatoprost and its free acid in other compounds and different assays?

A. Yes.

Q. Okay. And now can you turn in your binder to Defendants' Exhibit 186?

A. Okay.

MR. WARNER: I have a different copy in my binder. This has already been admitted as Plaintiff's Exhibit 495, so why don't you put that one up.

MR. WARNER: So we're looking at Plaintiff's Exhibit 495. And if you could turn to page 5 in that.

And, Jeremy, if you could blow up the Figure 4 right there with the explanation, too.

BY MR. WARNER:

Q. And, Dr. Sherman, this is just some more differential pharmacological data that Dr. Woodward was shown over the years ensuing the patent, ?

A. That's right.

Q. With all the data that you've reviewed showing bimatoprost in activity or activity in different assays, is there anything that requires you to invoke the existence of a prostamide receptor to explain that data?

A. No, not at all.

Q. Let's just take one more example. Can you explain what's shown in this graph?

A. Yes. What we see here is an assay, the cat iris sphincter assay system, where a number of drug molecules are being submitted for a biological response. Among them are PGF2 alpha, bimatoprost, prostamide F2 alpha, latanoprost free acid and latanoprost isopropyl ester.

And I'd like to point out, what is interesting about this is the lowest response comes from latanoprost isopropyl ester itself. The reason that's interesting is because we all agree that latanoprost, which is an isopropyl ester, is hydrolyzed to its free acid form.

Well, in this particular assay, in this cat iris sphincter assay system, that one actually has the -- the poorest activity, suggesting that the esterase is required to hydrolyze that isopropyl ester are not as effective.

In contrast, bimatoprost is being effectively converted to its free acid form, and in that way we see a very nice, rapid response at a high potency.

Q. Now, in this assay that in order for the bimatoprost to be hydrolyzed to its free acid and show that function, there would have to be an appropriate hydrolase to hydrolyze the bimatoprost; is that right?

A. That's correct.

Q. And you suggested that the esterases maybe weren't appropriate to hydrolyze latanoprost?

A. Well, they weren't as effective. We see that there's definitely a response. You know, it's one to two orders of magnitude lower than the best, but, nevertheless, it is substantial, and you can see the dose response here.

But those esterases apparently are not doing their job as well in this preparation as the hydrolases are on bimatoprost converting it to its free acid.

Q. And wouldn't it have been surprising at all that there were different types of enzymes that had different levels of activity on, for example, bimatoprost versus latanoprost in a single assay like this?

A. This wouldn't have been surprising. This class of enzymes is one of the best characterized classes of enzymes. The hydrolases, it's well-known.

Q. And we also talked about prostamide antagonists

yesterday. That was discussed.

Do you recall that?

A. Yes.

Q. And it was suggested that the existence of certain prostamide antagonists support the view that there's a new prostamide receptor.

Do you remember that?

A. Yes, I do remember.

Q. Can you explain how you understand that theory?

A. Well, basically, in terms of agonists and antagonists, there's a spectrum of activity in these molecules. In other words, in many cases, that when there's a claim of an antagonist, which is an inhibitor of an agonist, it's actually operating as a partial agonist. So there's a spectrum of activity from full agonist to partial agonist to partial antagonist to full antagonist.

So it requires great care in evaluating these assays what exactly is going on.

Q. Now, can you take a look, then, in your binder at Plaintiff's Exhibit 468, please?

A. Sorry. 468?

Q. Plaintiff's Exhibit 468.

A. 468. Okay.

Q. And is this one of the articles that you reviewed purportedly discussing prostamide antagonists?

A. Yes, it is.

MR. WARNER: Your Honor, at this time, defendants move Plaintiff's Exhibit 468 into evidence.

MR. McCANN: No objection, your Honor.

THE COURT: Thank you.

(PTX No. 468 was admitted into evidence.)

MR. WARNER: Jeremy, if you would blow up the abstract, there's a mention of the AGN 211334 compound.

BY MR. WARNER:

Q. Do you see that?

A. Yes.

Q. You reviewed data about that, Doctor?

A. Yes.

Q. If you could also turn in your binder to Plaintiff's Exhibit 470.

A. 470? Mm-hmm. Okay.

Q. And this is another article discussing prostamide antagonist activity; is that right?

A. That's right.

MR. WARNER: All right. Can we have that up on the screen, Jeremy? This has been admitted.

And if we could turn, please, to page 5.

BY MR. WARNER:

Q. And, Dr. Sherman, is it your understanding that this graph purports to show the inhibitory effect of a prostamide

antagonist?

A. Yes, that's what it purports to show.

Q. All right. And how is that explained in the top graphs?

A. Okay. This is a pretty straightforward explanation.

What we have in the bottom two panels is bimatoprost-free acid, 17-phenyl PGF2 alpha in an assay system showing its activity with two concentrations of the purported antagonist, 204396.

And you can see at these curves, these dose response curves are essentially the same, meaning there's -- there's no effect of that purported antagonist whereas above here (indicating), showing the alleged antagonistic activity of that same molecule at two concentrations, using bimatoprost as -- as the drug.

Now, what is occurring here in my opinion is very straightforward. In this assay system, the antagonist, which is an ethylamide --

Q. And let me pause just a second so we can put up Defendants' Demonstrative Exhibit 4-2, which I think will help illustrate this concept.

Go ahead, Doctor.

A. Right. What's occurring here is very straightforward. We can see the structure of bimatoprost, the ethylamide here (indicating), and you can see that these molecules being

called antagonists, the top two have ethyl amides. This is the one that's actually used in the paper (indicating).

The ethylamide in that molecule is simply competing with the hydrolase that's normally converting bimatoprost to its free acid form. And because of that competition, less drug is being hydrolyzed. There's a lower concentration, lower effective concentration of the drug, and that's why we see a shift in that curve to the right.

Q. So in your opinion, is that shift in the curve explained by the existence of prostamide receptors distinct from the FP receptors?

A. It is not due to the prostamide receptor, it's due to the hydrolase activity.

Q. And I just want to make something clear. Those are three of the various antagonists that have been reported; is that correct?

A. Yes.

Q. Are all of those antagonists ethyl amides?

A. So two of them are ethyl amides. This one has an ether functional (indicating). And the bottom one is a propyl amide. You can see three carbons instead of two. That makes it a propyl amide.

Q. And those were different molecules?

A. Yes, they are.

Q. Can the differences in their structure affect their

potency as antagonists?

A. Yes. Very much so. I will point out that this one is an ether as well (indicating).

Q. Then there was another category of evidence that has been discussed, and this is the concept of what have been called latanoprost poor responders?

A. Yes.

Q. And these are patients, as you recall, who are alleged to respond to bimatoprost when latanoprost has not worked effectively.

Do you remember that?

A. Yes, I do.

Q. In your mind, would the existence of those patients require the, also the existence of a prostamide receptor different from the FP receptor to explain?

A. Not at all.

Q. All right. And based on your understanding of the case, would it make logical sense that those patients would -- that a prostamide receptor would explain those patients?

A. No. In fact, interestingly, it's totally inconsistent with this heterodimer prostamide receptor theory.

MR. WARNER: So, Jeremy, if we could have Defendants' Demonstrative 4-3, please, and you can go all the way to the end of it.

BY MR. WARNER:

Q. And so, Doctor, I just want to make sure that your opinion in this matter comes out clear.

So what happens with the functional FP receptor in patients who do respond to latanoprost?

A. Yes. So we all agree that latanoprost operates as its free acid on the normal FP receptor.

Now, in non-responders, the contention is, Allergan contends that that FP receptor must not be functional, and there must be a heterodimer, their alleged hetero dimers that's operating to result in the function of bimatoprost. The problem is, as we've, in that heterodimer form, as we saw in Liang, there must be a functional form of that FP receptor. Now, that's inconsistent with the idea that there would be latanoprost non-responders.

Q. And so if the FP receptor exists in these responders, why might it be that latanoprost doesn't work in those patients?

A. I mean the most straightforward explanation is there is a lack of the required esterases that would convert the isopropyl ester of latanoprost to its free acid. And if that can't happen, latanoprost cannot work at the normal FP receptor.

Q. Now, Doctor, if that was the case in 1992, would it have been surprising that bimatoprost amide would work in those patients?

A. Would it have been surprising that latanoprost free acid would work?

Q. I'm sorry. Would it have been surprising that if latanoprost wasn't working because of an esterase deficiency, would it have been surprising that bimatoprost would work?

A. No, not at all.

Q. Okay.

A. That wouldn't have been surprising because even in the absence of an esterase, you can still have the appropriate hydrolases. I mean, we've seen this in an appropriate exhibit. So it wouldn't have been surprising to one of skill in the art that you could have that situation.

Q. Doctor, have you also heard, there was a suggestion I think made earlier in testimony that using latanoprost and bimatoprost together can have an additive effect in just lowering IOP.

Do you recall that?

A. I do.

Q. And have you reviewed evidence with respect to that opinion?

A. Yes.

THE COURT: And before we go into that, it has been two hours. We'll take our 15-minute break.

(Short recess taken.)

- - -

(Proceedings resumed after the short recess.)

MR. WARNER: May I proceed?

THE COURT: You may.

BY MR. WARNER:

Q. Dr. Sherman, we're just wrapping up. I just have a couple more questions.

Before the break, we were talking about whether or not there's an additive effect when latanoprost and bimatoprost are used together.

Do you recall that?

A. Yes.

Q. And my question to you is, of all the literature that you've reviewed, is there any evidence that there is even such an additive effect in a human patient?

A. No, there is not.

MR. WARNER: Thank you very much, Doctor. No further questions.

THE COURT: Cross-examination.

MR. McCANN: May I approach the witness, your Honor?

THE COURT: Yes, you may.

(Mr. McCann handed an exhibit book to the witness.)

MR. McCANN: May I proceed, your Honor?

THE COURT: Yes, you may.

CROSS EXAMINATION

BY MR. McCANN:

Q. Good morning, Dr. Sherman.

A. Good morning.

Q. Nice to see you again.

A. Good to see you.

Q. To begin with, you're aware that the asserted claims in the case do not claim a new receptor?

A. I am aware of that.

Q. And you understand that the asserted claims, claim bimatoprost, the compound, correct?

A. Yes.

Q. And then methods of using bimatoprost to either reduce intraocular pressure or lower, I'm sorry, or treat glaucoma; is that correct?

A. I believe so.

Q. All right. Now, it's your opinion that bimatoprost is a prodrug?

A. That is my opinion.

Q. And it forms 17-phenyl PGF2 alpha, bimatoprost-free acid?

A. Yes.

Q. It acts on the wild-type FP receptor or the classical FP receptor?

A. That's correct.
Q. It's your opinion that in the human eye, bimatoprost is converted to the free acid form?
A. That's correct.
Q. Okay. Now, you understand from the testimony you've heard during the case and the record that you reviewed, that the Allergan scientists disagree with that?
A. I understand.
Q. And you heard some of them testify about the work they did leading up to the patents being applied for in 1992?
A. Yes.
Q. And I'm not sure if you were here, but did you hear Dr. Garst testify, he's one of the inventors, about the discovery being the scientific highlight and certainly the scientific surprise of his professional career?
A. I was not here on Monday.
Q. All right. So you did not hear him give that testimony?
A. Correct.
Q. Did you hear Dr. Woodward testify?
A. I did.
Q. Did you hear all of his testimony?
A. I believe so.
Q. Okay. And did you hear his testimony about the work that he put into this project that led to the

patents-in-suit?

A. Yes.

Q. Okay. Now, in that testimony, in some of the testimony you heard from Dr. Regan and Dr. MacDonald, there was discussion -- and you just covered this on direct a little bit -- there was discussion about functional assays that were performed?

A. Yes.

Q. Some animal studies?

A. Yes.

Q. And some antagonist studies?

A. Right.

Q. And then I think Dr. Noecker also testified about some clinical studies related to these, the non-responders, the low responders.

Do you recall that?

A. Right.

Q. All right. And Dr. Noecker, he's a glaucoma specialist?

A. Yes.

Q. And he also offered some testimony that he believed that bimatoprost was more efficacious than latanoprost.

Do you recall that?

A. I did hear him say that.

Q. Okay. I would like to talk for a little bit about

splice variations in dimers.

Now, you understand the pharmacology issues in this case concerned the use of GPCRs?

A. Yes.

Q. And a GPCR is a receptor encoded by a gene?

A. Yes.

Q. Genes can undergo alternative splicing?

A. Yes much.

Q. That alternative splicing can happen in the human body?

A. It can.

Q. Okay. A GPCR gene is capable of forming a spliced variation?

A. Yes. There are -- there's evidence of that in some cases, yes.

Q. And when that splice there may occurs, that would make a different version of the GPCR? A truncated version?

A. A variant, yes.

Q. All right. Now, dimers. We were talking about this a little bit. Dimerization is when you have one protein, another protein, they become associated in some way; is that correct?

A. Yes.

Q. And you agree that dimerization can occur in the human body?

A. The evidence supports that in most cases.
Q. And you agree that these GPCRs are capable of dimerizing?
A. The evidence suggests that.
Q. In fact, they typically dimerize it?
A. Yes. That's what the evidence shows.
Q. Okay. And the GPCRs are capable of forming heterodimers; is that correct?
A. There's evidence for that, yes.
Q. And that is, again, where you have two GPCRs that are not identical interacting or associating with each other?
A. Yes. They're variant forms of the two receptors.
Q. Now, if I understand you, though, your testimony correctly, you believe that it has never been shown in science that a GPCR and its spliced variant can heterodimerize; is that correct?
A. It has been indicated from some types of data that heterodimers can form with some splice variants and their wild-type partner.
Q. So it can happen?
A. There has been some types of evidence to show that. Not definitive biochemical evidence, but there has been some indication to show that in some -- in some papers that I've seen.
Q. So if it were to happen, would you find that

surprising?
A. If it were to happen, I would look at the data and evaluate what is actually being alleged, and then I would make my evaluation.
Q. So what I'm trying to understand, though, is assume for a second that it can happen, that it's definitively proved, as you put it. Would that surprise you or not surprise you?
A. It wouldn't surprise me, no.
Q. Now, you gave some testimony on direct concerning some of the functional assays; is that correct?
A. Yes.
Q. Cat iris, Swiss 3T3?
A. Right.
Q. Those studies?
A. Right.
Q. Okay. And you recall the testimony of Dr. Woodward and Dr. Regan, that one -- the early indications of what they believe to be the novel pharmacology here was the amide and some of the other compounds showed activity in the cat iris but not the 3T3 assay?
A. Correct.
Q. Okay. And you believe that what most likely is happening is not some kind of novel pharmacology with a new receptor, but, rather, the amide is being hydrolyzed; is

that right?
A. Correct.
Q. Okay. And you believe in the cat iris because it's tissue from a living animal. That tissue is more -- a formerly living animal, I guess. That tissue is more likely to contain amidases than you would see in a homogenous preparation such as the 3T3; is that right?
A. Well, there is the opportunity for different types of there class of enzyme to be -- to be produced, because you have different cell types in that preparation.
Q. All right. So to be clear, though, in the 3T3, where you see the weak or no activity --
A. Right.
Q. -- in your view, you would expect there are no enzymes, no amidases present; is that correct?
A. Well, we see from the data that the 3T3 cell uniformly doesn't offer hydrolysis of bimatoprost to its free acid. It's not the fact that it's a homogenous cell line. There may be homogenous cell lines like HEK that do generate amidases.
Q. In any event, though, in the 3T3, you believe the inactivity is because there are no amidases in that particular study?
A. That's my belief, yes.
Q. In the cat iris, you believe there are amidases there,

and that's what's causing hydrolysis, and therefore the inactivity of bimatoprost?

A. That's my opinion, yes. I believe that.

Q. And you believe that a scientist could design an assay to determine how much hydrolysis is actually occurring; is that correct?

A. Yes.

Q. And there are techniques such as HPLC and mass spec that could answer that question?

A. Yes.

Q. Okay. And you believe that a test like that would be straightforward?

A. Yes.

Q. Now let's talk about the antagonist studies.

You heard Dr. Regan testify about the antagonist studies?

A. Yes.

Q. And he testified that those studies show ethylamide antagonist blocking receptor activity at the prostamide receptor.

Do you recall that?

A. Yes.

Q. In your opinion, those results could be explained by amidase competition?

A. Yes.

Q. The antagonists, or at least some of them, were ethyl amides?

A. Yes.

Q. I think you said one was an isopropyl?

A. One is propyl.

Q. Propyl. I'm sorry.

And bimatoprost itself is an ethyl amide?

A. Correct.

Q. And if I understand the theory correctly, though, because both the antagonist and the alleged agonist, the bimatoprost, have amide groups, they would compete for those same amidases?

A. Correct.

Q. And that would affect the potency?

A. That's correct.

Q. Okay. And you also believe that a scientist could design an assay to test for that phenomenon occurring?

A. Yes.

Q. And HPLC and mass spec is again a straightforward technique to do such an experiment?

A. Yes.

MR. McCANN: Okay. Could we have, while we're talking about the assays, I think it's PTX-495A, figure 8. And this is already in evidence.

Yes. If you could enlarge figure 8, please.

BY MR. McCANN:

Q. Now, I believe on, if I understood correctly, on direct examination, you were looking at this figure, which Dr. Regan had also discussed; is that correct?

A. That's correct.

Q. And this assay is examining bimatoprost, which are the filled circles, and prostamide F2 alpha, the filled squares, latanoprost-free acid, the filled diamonds and the isopropyl ester, the open diamonds, in a cat iris?

A. Correct.

Q. And I think what you were indicating was the latanoprost isopropyl ester, sort of lower potency, that 1530 number, could be explained by that issue with the hydrolysis of the isopropyl ester; is that right?

A. Correct.

Q. And that would be either not enough esterases or some issue with the esterases that just prevented the proper hydrolysis?

A. Yes. That's -- that is a reasonable explanation for what's going on here. There's -- the other explanation that's possible is that the latanoprost-free acid is simply less effective against the FP receptor in the cat iris, so we have to consider that as well.

Q. All right. Now, with respect to bimatoprost, it's your belief in this assay, it's a cat iris that the

bimatoprost is hydrolyzed?

A. Correct.

Q. By an amidase?

A. By an amidase.

Q. Now, would you agree with this statement: Esters are cleaved by a variety of enzymes, including acetyl cholinesterases, butyl cholinesterases, amidases and peptidases. These enzymes are present in ocular tissues.

Would you agree with that statement?

A. Yes.

Q. The ability of these enzymes to cleave amides is inherently lower than their ability to cleave esters.

Would you agree with that statement?

A. In some instances, that's true.

Q. So in this assay where the amidases are cleaving the bimatoprost and hydrolyzing that to the free acid, those same amidases are capable of cleaving the isopropyl ester to make a latanoprost-free acid; isn't that correct?

A. Well, there are different enzymes that are involved here, so the esterases that are cleaving latanoprost to its free acid are different protein entities than the hydrolase that would be catalyzed in the hydrolysis of bimatoprost.

Q. And you do agree that an amidase can hydrolyze an ester?

A. I'm sure that's true.

Q. Yet in this case, it's your testimony that the amidase, for some reason, is not hydrolyzing the isopropyl ester, only bimatoprost?

A. Well, I need to be clear, because what you're suggesting is that it's one and the same enzyme. It is not. They are different enzymes. The esterase is hydrolyzing the isopropyl ester of latanoprost. A separate and distinct hydrolase would be converting bimatoprost to its free acid.

Q. Okay. So what we have, then, in figure 8 as a special kind of an amidase, that's not capable of hydrolyzing the ester?

A. Well, as you stated, that's correct, because they're separate and distinct enzymes. They're not one and the same enzyme. It's very important to understand that.

Q. You have never worked with a cat iris assay; isn't that correct?

A. That's correct.

Q. And so you wouldn't be aware that the cat iris assay is washed as part of the preparation of the assay?

A. I have seen the protocols for making these preparations.

Q. And the purpose of the washing is in part to remove enzymes that might be present in the tissue preparation; isn't that correct?

A. Well, it's typically to remove salt and other ions

that can disrupt the assay system. I mean, the proteins are sticky. They're going to largely remain behind. And even if they don't, they're going to be re-synthesized by a living cell very quickly.

Q. But, in any event, part of the purpose of washing is to remove enzymes as well; isn't that correct?

A. No, not necessarily. Ions and salt are really what the washing step is largely for.

Q. You're aware of -- you heard Dr. Noecker's testimony about some of the human data; isn't that correct?

A. I did hear some of that.

Q. And he described low responders to latanoprost?

A. Yes.

Q. And he described the efficacy of bimatoprost over latanoprost in those low responders?

A. Yes.

Q. And you believe those results can be explained by an esterase deficiency or polymorphism?

A. By an esterase deficiency.

Q. You don't think there's a different receptor; is that correct?

A. That's correct.

Q. All right. So you do believe, though, that there are assays that could be run to determine whether there is or there is not this new receptor present in human tissue;

isn't that correct?

A. I do believe that.

Q. And there would be techniques such as mass spectrometry that would help answer this question?

A. There are a series of -- of experiments and technologies available that could address that question directly.

Q. QPCR?

A. That -- QPCR is a way to actually determine, to quantify the level of messenger RNA.

Q. So it would be a useful technique in analyzing the question, though, whether the receptor is present in what amount?

A. No, it would not.

Q. What would it be useful for?

A. It would just be useful for showing the quantity of messenger RNA in the tissue.

Q. What about size exclusion chromatography?

A. Size exclusion chromatography is useful to show the size of proteins in a protein preparation when you want to determine the size of the various proteins.

Q. Analytical ultra centrifugation?

A. Same thing, but at higher resolution. And it also can give you information about dimerization.

Q. So these techniques in varying ways would be useful,

though, for determining whether the prostamide receptor as Allergan has postulated here is, in fact, present in ocular tissue?

A. The key approach is that that failed to be addressed over the last 21 years, are experiments that directly assess the presence, the physical presence of that receptor. So far, none of the data that has been presented by Allergan shows the physical existence of the receptor itself.

Q. But that technology exists that you are describing?

A. It does exist.

Q. And it could be implemented to determine whether the prostamide receptor actually exists in your opinion?

A. Yes.

Q. In fact, I think Dr. Mitra testified, these tests would take about a month; is that correct?

A. Well, it depends what you have at time zero for it to take a month. But if you -- I mean, it would take a longer discussion actually to determine how long it would take.

Q. All right. It can be done in a reasonable period of time?

A. It can.

Q. All right. Now, there were some efforts by Allergan to do molecular characterization of this prostamide receptor; isn't that correct?

A. There were very limited efforts.

Q. And you discussed some of that on your direct, the Liang/Woodward experiment?
A. Yes.
Q. And that was in PTX-221A?
A. Correct.
Q. And if you could turn to that in your notebook.
MR. McCANN: And if I could have the Elmo, please.
BY MR. McCANN:
Q. I just want to look at this graph that we had on the screen earlier.
Now, this is from figure 4 of PTX-221A?
A. Right.
Q. And when Mr. Warner was asking you some questions, he first asked you about the C panels; isn't that correct?
A. Correct.
Q. And if I understand correctly, in the C panels, what you are seeing is the alt F 4 protein in both panels; is that correct?
A. That's correct.
Q. And in the left panel, PGF2 alpha is introduced?
A. Yes.
Q. And you see, I think you described it as no activity?
A. That's a flat line. There's no activity.
Q. And then in the alt -- sorry -- in the right panel,

you see again that same protein, the splice variant protein, the alt 4 with bimatoprost, and you see about the same activity?

A. No activity.

Q. Okay. And then in the next panel up, what you see is what the paper calls the wild-type FP receptor; is that correct?

A. Correct.

Q. And that's the naturally occurring, or what some of the people in the case called the classical FP receptor?

A. Right.

Q. All right. And there you see PGF2 alpha demonstrating one level of response; correct?

A. Yes.

Q. And bimatoprost, a lower level of response; is that correct?

A. Yes.

Q. And then, finally, what you see in the top panels is the dimerized wild-type and the alt F 4 protein on the left; correct?

A. The alleged dimerization.

Q. The alleged dimerization.

And then on the right the same. And in each case, again, PGF2 alpha and bimatoprost are applied; correct?

A. That's correct.
Q. Okay. Now, earlier, when you were giving your testimony, you only focused on the top left panels; isn't that right?
A. That's correct.
Q. And you did not look at the bimatoprost responses on the right side?
A. That's correct.
Q. All right. And what we see is on the right side, again, lower activity of bimatoprost against that compared to the PGF2 alpha against the wild wild-type receptor; is that correct?
A. I want to make clear that that is what the authors are alleging. I do not agree with their interpretation.
Q. In any event, looking at the graph, the peak on the right in figure 4, Panel B2, is lower than that of figure 4, Panel B1?
A. It is lower.
Q. And in the top figure, figure 4, Panel A2, there is a response from bimatoprost when it's introduced into the assay with this dimerized protein; is that?
A. Based on the interpretation of that authors that I do not agree with.
Q. But there is a response depicted in the graph?
A. There is a response, but it's not according to the

interpretation of the authors.

Q. Right. So you agree there is a responses. You just don't agree with the interpretation of what that response is showing?

A. I disagree vehemently with the interpretation.

Q. All right. Now, you also displayed a demonstrative of the prostamide receptor; isn't that correct?

A. Yes.

Q. And you reviewed the demonstrative before it was presented to the Court?

A. Right.

Q. And you tried to be accurate?

A. Right.

Q. And you were discussing this demonstrative in connection with the non-responder issue; isn't that correct?

A. Right.

Q. I just want to make sure the record is clear. We're looking at DDX-4.

In the hypothetical prostamide receptor -- well, first of all, would you agree with me that each of the receptors, the seven trans member domains, they're all the same, aren't they?

A. I don't understand what you mean, they're all the same.

Q. Well, look where it says functional FP receptor.

A. Yes.
Q. Do we have seven trans member domains?
A. Right here?
Q. Yes.
A. Yes.
Q. And that diagram is the same. You see the same picture with hypothetical prostamide receptors?
A. Okay.
Q. Do you agree?
A. I'm not sure what you mean by they're the same. Like here to here, they're the same?
Q. This image --
A. Yes?
Q. -- under the prostamide receptor is the same under the functional PF receptor?
A. Yes. It was copied and placed in each of the panels, yes.
Q. So it's the same image in each of the three panels?
A. Right.
Q. Now, you understand in the prostamide receptor has postulated by Woodward and Liang, the hypothetical prostamide receptor should actually have more than just what was depicted there; isn't that correct?
A. Well, they allege that it's a heterodimer.
Q. Right.

A. But they have no evidence in 20 years for its existence.

Q. But what I'm trying to make clear is when you drew the hypothetical prostamide receptor, you did not depict as a heterodimer; isn't that correct?

A. I don't believe that it exists.

Q. That's what you indicate by saying it is hypothetical, but when you put the hypothetical prostamide receptor on the demonstrative, you did not show it as a heterodimer; isn't that correct?

A. What's shown here is not the alleged heterodimer.

Q. And so it's the hypothetical prostamide receptor, but not anything that looks like what Allergan says it looks like?

A. That's because I can't visualize that heterodimer. It makes no scientific sense to me.

Q. You can't visualize the heterodimer between the GPCR and its splice variant?

A. It's an entity based on no evidence that I can't visualize that would bear anything to reality.

Q. Thank you.

Now, during your testimony, we've discussed a number of different assays that could be run to shed further light on this question in your opinion; isn't that correct? For example, HPLC and mass spec to analyze the presence of a

metabolite in the cat iris assay or in the antagonist studies?

A. Yes. Depending upon what specifically you're -- you're referring to, there are ways to -- to design experiments.

Q. And, again, as we discussed before, in terms of characterizing the presence of this prostamide receptor protein that Allergan says exists, you believe there are assays that could be run -- we talked about this a moment ago -- that could be run to furtherance that question?

A. I do.

Q. All right. And you have a lab at the University of Michigan?

A. Yes.

Q. It's an academic research lab?

A. Yes.

Q. And your lab, I'm sure, has access to many of the instruments that you think would be useful in making these kind of inquiries?

A. Yes.

Q. And you are also consultant, correct?

A. I have consulted in the past, yes.

Q. When you perform expert witness consulting, it's through a company called PharmaForensics Laboratories LLC, correct?

A. That's not correct.
Q. You're not the founder and President of PharmaForensics LLC?
A. I am, but that's not the entity that actually performs the experiments. That's PharmaForensics Laboratories.
Q. You do have some affiliation with PharmaForensics Laboratory?
A. Yes.
Q. In connection with your expert work, if you're going to do test work that would be through PharmaForensics Laboratories?
A. That's correct.
Q. That company, PharmaForensics has a website, isn't that correct?
A. Yes.
Q. If you look in your binder, you should be fine.
PTX 1049, is that part of the website of PharmaForensics Laboratories? It should be at the very back?
A. Yes, it is.
Q. And the document, or the "about" us", ends with Jeffrey D. Kittendorf, PhD?
A. Yes, sir.
Q. He's one of your colleagues?
A. Yes, he is.

MR. MCCANN: At this time, we would offer PTX 1049 evidence.

MR. WARNER: No objection.

THE COURT: Thank you.

(At this time, PTX 1049 was entered into evidence.)

BY MR. MCCANN:

Q. In your volume there should another web page from the PharmaForensics Web page. If you would look at PTX 1048.

Do you have that, sir?

A. I do.

Q. Is that part of the web page for PharmaForensics lab?

A. Yes.

MR. MCCANN: At this time, we would offer PTX 1048 into evidence.

MR. WARNER: No objection.

THE COURT: Thank you.

(At this time, PTX 1048 was entered into evidence.)

BY MR. MCCANN:

Q. We have that on the screen now, but it's a little blurry.

Look at the top of the web page where it says partner, "partner with us to create and execute a scientific evaluation as a component of patent litigation strategy. --

let us take on the burden of scientific discovery so you can focus on your legal strategy."

Is that correct?

A. Yes.

Q. It then goes on and says, "PharmaForensics Laboratories can direct all aspects of scientific discovery, including review, design, execution, and analysis of experimental strategy".

Do you see that and is that correct?

A. Yes.

Q. Your consulting company, PharmaForensics Laboratory conducted some of the tests that we discussed in this case?

A. Yes.

Q. It's the case that you did not conduct any tests in this case yourself?

A. I did not.

Q. In fact, to be fair to you, you were not asked to conduct any tests, is that correct?

A. That is correct.

Q. In fact Teva and Sandoz are well enough off to pay for their own services?

A. There simply wasn't enough time?

Q. Wasn't enough time?

A. Yes.

Q. Do you know how long this case has been pending?

A. I was brought on to the case in October.

My expert report was due, I believe, in November.

Q. Now, you understand that Barr began the work on the ANDA in 2002?

A. I'm not aware of the timeline. All I know is when I get got started.

Q. When you were asked to do the test -- perform the test, there was plenty of time to conduct the test, isn't that correct?

A. I don't know the answer to that question.

Q. You don't know whether in seven years someone was able to conduct kinds of tests that you talked about today?

A. If someone had asked that this type of work be done, it could have been in a timely fashion.

Q. Exactly. If someone had asked?

A. I would have welcomed the opportunity.

Q. If asked, but you were not asked?

A. I was not asked.

Q. Now , you heard Dr. Mitra testify in court, correct?

A. I did.

Q. You heard him say he's not an expert in receptor pharmacology?

A. I don't recall that statement.

Q. You're an expert. You've been qualified by the court an expert in receptor pharmacology?

A. Yes.
Q. So you know about GPCR receptors?
A. Yes.
Q. Am I correct, before this litigation you had not heard of Dr. Regan?
A. I had not in all the teaching I've done, I had not focused on his name. I read a lot of papers, not everyone sticks in my memory.
Q. So you were unaware of his work in GPCR's?
A. I wasn't familiar with his name. That doesn't mean I wasn't familiar with his work.
Q. Are you aware now that he performed work on GPCR's?
A. Yes.
Q. He studied the article of Pharmacology?
A. That's been his focus for 30 years.
Q. He was one of the first people to clone a human alpha2 adrenergic receptor?
A. Yes.
Q. Which is GPCR?
A. Yes?
Q. He cloned a prostanoid GPCR receptor?
A. Yes.
Q. And they are also GPCRs?
A. Yes.
Q. You also know now that he has published many, many

papers on GPCRs?

A. Yes.

Q. He said there were 109 pages on his resume?

A. On GPCR pharmacology.

Q. Most of those were prostanoid GPCR receptors?

A. Pharmacology, yes.

Q. He also published a research article discussing splice variant of the FP receptor?

A. An alleged splice variant.

Q. Alleged, I suppose, correct?

A. It's alleged.

Q. We're talking about Veilhauer paper, correct?

A. Yes.

Q. He had six patents related to his work on prostanoid receptors?

A. Yes.

Q. And you know that Dr. Liang and Woodward, the first two authors on the Liang paper also have a patent on FP receptor splice variants, correct?

A. As I have said, this splice variant is an alleged splice variant of which there is no evidence for its existence.

Q. You understand that they have a patent on this receptor of which there is no evidence for its existence?

A. That's the fact.

Q. You understood that?
A. I do.
Q. If you look in your binder at PTX 961.
A. 961?
Q. Yes.
A. All right.
Q. That's the patent of the Lee and Woodward?
A. Yes.
Q. The title is, "Human Prostanoid FP Receptor, Method and Using the Same", correct?
A. Yes.
MR. MCCANN: We would offer PTX 961 into evidence.
MR. WARNER: No objection.
THE COURT: Thank you.
(At this time, PTX 961 was entered into evidence.)
BY MR. MCCANN:
Q. Now, you have eight patents listed on your CV, correct?
A. Yes.
Q. None of your patents discuss GPCR prostanoids, correct?
A. That's correct.
Q. To be fair, the patents are not the full extent of

someone's subject matter or expertise, is that correct?

A. That is definitely true.

Q. Your research has focused on microbial natural product biosynthesis?

A. The focus is on the biochemistry of complex modular photosyntheses and proteins that are of equal complexity to GPCRs.

Q. But are not GPCRs?

A. Not GPCRs.

Q. The research at the University of Michigan is focused on discovery of naturally occurring compounds for microorganisms, correct?

A. Yes.

Q. Like microorganisms like bacteria as well as direct discovery, correct?

A. All aspects.

Q. You've a lot of paper in it area?

A. I do.

Q. I found a 178 papers on your CV?

A. I was off by a couple.

Q. Unlike Dr. Regan, and although your credentialed, sir, you've never cloned a prostanoid receptor?

A. I have cloned a lot of genes.

Q. But not a prostanoid receptor?

A. No, I've done all my work on GPCRs in teaching.

Q. And your academic research program is not focused on GPCRs?
A. Not directly.
Q. In any of your publications, none of them specifically discuss GPCRs, correct?
A. That's correct.
Q. And you have two books listed on your CV?
A. Perhaps 22.
Q. None of those involved GPCRs, correct?
A. That's correct.
Q. You've never published a research article that specifically addresses prostaglandins, correct?
A. Again, that's, although I haven't published, it's been the subject of a significant amount of my teaching.
Q. I know. I was speaking as far as publications?
A. Yes, right.
Q. So unlike Dr. Regan, the research in your own academic lab has been focused on things other than specifically prostaglandins and prostaglandin receptors, correct?
A. It's been very focused on protein biochemistry of complex enzymes, transports and other receptors, yes.
Q. Now, you heard Dr. Mitra testify that a hundred of different laboratories were working on FP receptor?
A. Right.
Q. Your academic research lab is not one of those?

A. In my direct research lab, no. My teaching is very heavily involved in GPCR work.

Q. Not your research?

A. Not my research.

MR. MCCANN: I have no further questions.

Thank you. Sir.

THE COURT: Redirect.

REDIRECT EXAMINATION

MR. WARNER: Thank you, your Honor. I'll be very brief.

BY MR. WARNER:

Q. Dr. Sherman, Mr. McCann asked you a few questions about the ability of splice variant heterodimer wild-type genes, do you recall that?

A. Yes.

Q. Have you seen anything where a splice variant is lacking in terms of it being developed with a wild-type gene?

A. No. I have never seen an example.

Q. Did Mr. McCann show you one?

A. No.

Q. He also talked about an experiment that might be done HPLC, I think experiments that might be done using Mass spectroscopy and other tests that you had discussions on, right?

A. Yes.
Q. Do you know when the patent was filed in this case in 1992?
A. I'm not sure?
Q. I'll represent to you, 1992.
How long has Dr. Woodward and Allergan had to perform all those tests?
A. We're going on almost 20 years. Over 20 years based on the initial discovery of what they feel was a prostanoid receptor.
Q. You've never seen those tests performed to confirm from Allergan that prostanoid receptor?
A. I have never seen evidence of that, no.
MR. WARNER: I have nothing further. Thank you.
THE COURT: All right. You may step down. (At this time, the witness was excused.)
MR. FILARSKI: Defendant calls Dr. Kenneth Wright. He's here to discuss the opinions of Dr. Noecker.
... DR. KENNETH R. WRIGHT, having been called duly as a witness, was examined and testified as follows ...
DIRECT EXAMINATION
BY MR. FILARSKI:
Q. Doctor Wright, are you a certified ophthalmologist?
A. Yes, I'm a board certified ophthalmologist.

Q. Tell us a little bit about your education and how you got there.

A. I did my M.D. at Boston University, interned at Harbor General-UCLA. I did my residency at USC Medical Center at the Estelle Doheny Eye Institute, Los Angeles County.

I did a fellowship at Johns Hopkins in pediatric ophthalmology and comprehensive ophthalmology. And then a fellowship in pediatric ophthalmology at the Children's Hospital National Medical Center in Washington D.C.

Q. Tell us a little bit about your fellowship in glaucoma.

A. I did not have a fellowship specifically in glaucoma.

However, my fellowship was at the Wilmer Institute at Johns Hopkins did include comprehensive ophthalmology which included glaucoma.

I also had experience with pediatric glaucoma. In fact, publishing a paper during my fellowship, pediatric glaucoma.

Q. Are there any board certifications in glaucoma.

A. No, there are not.

Q. What do you do currently?

A. I'm practicing ophthalmology and pediatric ophthalmology in Los Angeles. I have private practice and institute for teaching research in Los Angeles.

Q. Are you attending staff at any medical school?

A. Yes, at the USC School of Medicine. I'm Clinical Professor of ophthalmology.

Q. In connection with that role, do you teach anything to do with glaucoma?

A. Yes, I do. I teach residents and fellows about glaucoma.

Q. How long have you been an ophthalmologist?

A. Very long. Over 25 years.

Q. Do you have any experience in treating or discussing glaucoma in the course of those 25 years?

A. Yes.

Q. Can you tell us a little about that? Have you conducted any clinical studies relating to glaucoma?

A. Yes, I was invited to be an investigator in three clinical studies on the efficacy and safety of glaucoma eye drops in children.

Q. What about articles? Have you published any articles in that area?

A. Yes, I have. To my recollection, I have three or four articles published on glaucoma.

Q. Textbooks?

A. I have several textbooks that I have written, specifically for the Academy of Pediatrics. I have a section on pediatric glaucoma that I wrote.

I also have a chapter on pediatric ophthalmology in

that book. I edited the chapter on glaucoma.

Q. I understand one of your textbooks is associated with a review course, a review book?

A. Yes, many years ago in late 1990's, I wrote, and was editor-in-chief on a book entitled Comprehensive Ophthalmology.

The publishers wanted a review book for residents to bone up for their boards, so they had a young resident write that book and they put my name on it. I did not write that book. It's a question and answer book.

Q. When was that book written?

A. I think it was written in the late 1990's, like 1997. And then there's been a subsequent addition to that book.

Q. Did you provide any input to the questions and answers in that review book?

A. I did not have input into the questions and answers.

The first edition, I might have had some input in pediatric ophthalmology. I did not in any way work on the glaucoma section.

Q. What year did you provide input?

A. These were all 1997.

Q. Let's talk about your current situation.

Do you now or have you treated patients with glaucoma?

A. Yes.

Q. What type of patients?

A. Adult patients, pediatric patients, patients that are referred to me for eye muscle problems.

Part of what I do that adults will present themselves, those patients who have glaucoma. I see family members of my pediatric patients and they will have glaucoma. I do treat glaucoma.

Q. I was surprised when I learned that children have glaucoma.

Can you tell us a little bit about that?

A. Glaucoma is devastating in children under the age of three. High pressure actually allows the eye to grow. So these poor children their eye is like a bulls eye. Their eye gets large. This enlarged eye, obviously, is damaging to the eye. And it's a very difficult type of glaucoma to treat, juvenile or congenital glaucoma.

Q. Are there similar characteristics between the two diseases, between children and adults where glaucoma is concerned?

A. The damage to optic nerve and the medications are similar.

Q. So, in the course of your work, have you had a chance to write prescriptions?

A. Yes.

Q. For glaucoma?

A. Yes.

Q. What drugs?
A. Right now our number one choice is the prostaglandin agonist. That's number one. Beta blockers and inhibitors are commonly used.
Q. Drugs that we've been discussing here in this trial?
A. Yes, sir.
Q. Are you familiar with latanoprost and bimatoprost?
A. Yes, I am.
Q. Would you take a look at Defendant's Trial Exhibit 867 that has been placed before you?
A. Yes.
MR. FILARSKI: Your Honor, may I approach?
THE COURT: Yes, you may.
(Mr. Filarski handed an exhibit binder to the witness.)
THE WITNESS: I've got it. Thank you. It didn't have a white tab.
Q. Sorry.
A. Just had a little sticky.
Q. Can you recognize that as your C.V.?
A. Yes.
MR. FILARSKI: Your Honor, we offer Defendants' Exhibit 867.
THE COURT: Any objection?
MR. THOMAS: No objection, your Honor.

THE COURT: Thank you.

(DTX No. 867 was admitted into evidence.)

MR. FILARSKI: Thank you.

At this time, your Honor, we'd like to offer Dr. Wright as an expert as a clinical ophthalmologist in the treatment of glaucoma.

MR. THOMAS: No objection.

THE COURT: Thank you.

BY MR. FILARSKI:

Q. Dr. Wright, do you understand why you're testifying here today?

A. Yes.

Q. What's your understanding?

A. My understanding is I'm testifying as a clinical ophthalmologist in regards to the long-felt need for a new alternative glaucoma medication.

Q. And do you have a summary of your opinions in this case?

A. Yes.

MR. FILARSKI: Would you show Exhibit 2, please?

BY MR. FILARSKI:

Q. Dr. Wright, does bimatoprost meet a long-felt need to treat glaucoma?

A. No.

Q. Why not?

A. Well, a long-felt need in regards to glaucoma treatment would be, we have a problem, we have a void in your treatment options, and that we're looking for an answer to that -- that need, an answer that would provide us an alternative treatment modality, and that would treat our patients better with better clinical outcomes, and with less or equal side effects. Bimatoprost doesn't do that.

Q. With respect to the points that you have put on this exhibit, you mention clinically equal IOP reduction. You also mention less compliance.

What do you mean by those?

A. Well, number one, it doesn't give us an alternative treatment. Bimatoprost, like Xalatan, or latanoprost, is a prostaglandin agonist. And they work by increasing outflow. Fluid gets out of the eye, reduces the pressure. Uveoscleral and trabecular meshwork. Both latanoprost and bimatoprost increase outflow through both -- both channels, and almost equally. And so it's not surprising to me that the clinical outcomes are equal. If you look at the literature on well controlled studies, the IOP lowering effect of both drugs is virtually identical.

The issue regarding compliance is important because if a patient doesn't use the drop, it's not going -- it's not going to stop optic nerve damage associated with glaucoma and it's -- the problem with bimatoprost, it has a

higher incidence of side effects, specifically hyperemia. And that has really been influencing the compliance.

And, finally, it's interesting to me that despite all the hoopla, all the advertising, latanoprost, Xalatan, is still the number one glaucoma medicine used by ophthalmologists and glaucoma specialists.

Q. So, Doctor, those are your reasons for why you believe bimatoprost does not improve upon the present prostaglandin treatment drugs.

Let's move to the bottom half of the slide here. Tell us why it does not improve upon the non-responder rate. Are you familiar with that term?

A. Yes, I am.

Q. Please explain why you believe that it does not improve upon the non-responder rate.

A. First of all, the term non-responder is vague, it's controversial, and it depends on the -- on the definition.

A true non-responder to me would be they have no response at all and that would be extremely rare. And Gandolfi, he estimates that it's approximately one percent of glaucoma patients. But to have no response at all, it would have to be like I don't have any prostaglandin receptors, or I have no esterase enzymes to convert it. I mean, how could that be? It would be very, very unlikely.

And, in fact, Gandolfi's clinical paper, in his

discussion, suggests it's probably one percent of glaucoma patients are latanoprost non-responders.

So first of all, it's a very muddy water in regards to what we really mean by non-responders. Then there's another term that's brought in called under-responder. There are a lot of patients that don't respond to where we want them to be. They don't make the target that we set for them. And really the target in glaucoma is stopping optic nerve damage.

So this whole issue about non-responders is complicated and actually somewhat confusing.

Q. You also note that there's no good controlled head-to-head bimatoprost trials.

Can you explain that, please?

A. Well, we have head-to-head studies, but what I'm saying here is that the other connotation of the non-responder is that it does not -- the patient does not respond to latanoprost, but somehow responds to bimatoprost. And those patients are so few, that there's not a good prospective head-to-head study looking at that patient group.

Q. Okay. I want to move to the term clinical significance. We've heard that term today and during the trial.

Can you explain that to us, what that means?

A. Well, clinical significance means that your treatment is doing its job in preventing progression of glaucoma, which translates to stopping optic nerve damage. Glaucoma really is defined as optic nerve damage. And the pressure is a risk factor.

MR. FILARSKI: Jeremy, slide 3, please.

BY MR. FILARSKI:

Q. Do you have a definition of clinical significance?

A. Well, here we see clinical significance of IOP reduction, and the American Academy of Ophthalmology expressed a guideline of approximately 25 percent.

If you look at studies throughout the literature, it's around 20 percent. And these are guidelines for what we find will, in most cases, retard optic nerve damage in patients with glaucoma. These are not absolutes, and in that AAO guideline, the first sentence is, the goal is to stop optic nerve damage.

Q. Would you take a look at Defendants' Trial Exhibit 1021 in your materials there before you?

Do you recognize that as the AAO guidelines you just mentioned?

A. Yes. This is the American Academy of Ophthalmology preferred practice pattern, which is basically a clinical guideline monograph.

MR. FILARSKI: Your Honor, we offer Exhibit 1021

into evidence.

MR. THOMAS: No objection, your Honor.

THE COURT: Thank you.

(DTX No. 1021 was admitted into evidence.)

MR. FILARSKI: Jeremy, page 16, please.

BY MR. FILARSKI:

Q. In the middle paragraph, starting with "when," just below there. Would you highlight in the middle there, where it says, an initial target pressure of at least 25-percent lower than pre-treatment levels.

Doctor, is this the section that you are relying upon in your opinion as to clinical significance?

A. Yes, but I want to point out that if you look at initiating therapy, right here it says optic nerve damage, and that is the first thing, and that is really the goal of glaucoma treatment.

Q. All right. Doctor, you also mentioned that the FDA has taken a position on clinical significance. Are you familiar with that?

A. Yes.

Q. And you're familiar with PTX-219, which is a letter from the FDA to Allergan?

A. Yes.

Q. Why is that letter significant to your opinion?

A. Well, first of all, it's a warning letter, and we

don't get warning letters from the FDA very often, and when we do as clinical ophthalmologists, we take heed, because it's a non-biased body which watchdogs for inappropriate advertising and helps us analyze clinical data. Because we get so many clinical papers, it's hard to know which ones we really want to hang our hat on.

So it's an important letter, and that letter specifically stated that when evaluating clinical studies, you need to see greater than two to three millimeters difference to be clinically significant.

So if you have a one or two-millimeter difference, one drug versus another, that's not clinically significant. So it helps us identify what is a significant difference in a drug.

Q. Doctor, are you familiar with a Goldmann tonometer?

A. Yes, sir.

Q. Did you prepare a slide relating to that device?

A. Yes, I did.

Q. What did you put in that slide?

A. I put a picture of my personal Goldmann tonometer. You can see my pediatric office in the background.

MR. FILARSKI: Exhibit 4, please.

BY MR. FILARSKI:

Q. Is this the slide you prepared?

A. Right.

Q. And --
A. This is the Goldmann tonometer.
Q. And what do you depict on the right?
A. This is the dial which is found down here, and the dial is moved by the examiner. As the examiner looks through the top piece. The examiner doesn't actually see this dial, and the dial is moved until fluid mires touch each other. These are -- these are half circles, or arches that move as you move the dial, and when they approach each other and they touch, you stop moving the dial. And that's your reading.
Q. And these arches are called mires, you said?
A. Yes, sir.
Q. Okay. Did you prepare an exhibit to explain what mires are?
A. I think we have a video.
Q. Would you explain how you did that?
A. I was on the Internet and I found a -- a clip, a video clip of actual human clinical setting, how we take the -- how we take the pressure.

MR. FILARSKI: Jeremy, Exhibit 5, please.

THE WITNESS: Here we can see the yellow mires. The bottom one is not complete. It should be a complete half arch. The top one, it fades out here.

And the idea is this part here from the top one

and this from the heart here from the bottom are going to come together and touch, and when they touch, you stop moving the dial. The problem is everything is dynamic and moving. And the other thing, the fluid is coming in and out so you can't really see distinctly when they touch each other. And it's very difficult even for an old guy like me, who has done thousands of these, to measure it.

What happens is, you take your measurement and then you repeat it on the same exact patient and you get a different measurement. And so there's a variability in measurement. And it's well-known, as I teach the residents, that we usually say two millimeters mercury.

BY MR. FILARSKI:

Q. Okay, Doctor. There's a lot of moving in that, motion in that video. Can you explain what that is?

A. Well, it's the patient looking though a high magnification through a microscope, and so any little movement is magnified. The patient is moving a little bit. You are focusing the device, and so that's movement. And then you're also turning the knob, so there's movement there.

So it's a -- it's our best way of measuring pressure, but it's by no means precise, and that's why we need to take multiple measurements. And we often see the patients back multiple times, so that we can get sort of an

average.

Q. Now, Dr. Noecker testified in this court that this machine had an error range of plus or minus 0.5 millimeters of mercury.

Do you recall that?

A. Yes, I do.

Q. Do you agree with that testimony?

A. No, I do not.

Q. Why not?

A. In fact, I'm surprised because, well, first of all, in Dr. Noecker's deposition, he said it was plus or minus one, which would mean a range of two, and that's what we do teach, is that, and that we know in the -- in clinical practice, that it's a not precise measurement and it's at least two millimeters mercury of variability.

Q. So just to be clear, what is, in your opinion, the appropriate error range that should be associated with the reading of this instrument?

A. Approximately two to three millimeters.

Q. Let's move to the IOP lowering opinions of Dr. Noecker.

He has indicated that latanoprost is less efficacious than bimatoprost when it comes to lowering IOP.

Do you agree with that?

A. No, I do not.

Q. Are you familiar with the Parrish study, which was previously admitted as DTX-304?

A. Yes, I am.

MR. FILARSKI: Would you put up Exhibit 6, please, Jeremy?

BY MR. FILARSKI:

Q. How does this study relate to your opinion?

A. Well, Rich Parrish is a professor at Bascom Palmer Eye Institute in Miami. And this was a very well-controlled prospective, randomized, masked evaluator study with a large cohort of patients. There was over 400 patients.

And it was one of the papers analyzed by the FDA, to see if this was a paper which warranted substantial evidence. And the FDA cites Parrish as a -- as a very-well done study, which is of significance.

And the study looked at latanoprost, bimatoprost and travoprost, and they found that the IOP lowering, when you compare latanoprost and bimatoprost, were almost identical, only one-tenth of a millimeter mercury difference. And when you put that into context, you can't even measure two. They're the same.

Q. In support of his opinion, Dr. Noecker relied upon a study that he performed, the Noecker study. Did you review that study?

A. Yes, I did.

Q. And do you have any criticisms concerning that study?
A. Well, I have criticisms, but I'm a clinician. A lot of what we rely on as clinicians are the evaluations of outside independent bodies. And there was a body of complaints that came in in regards to the Noecker study.
MR. FILARSKI: Could we go to Exhibit 8, please?
BY MR. FILARSKI:
Q. Is Exhibit 8 a list of your criticisms concerning the Noecker study?
A. Yes.
Q. Starting with the top one, clinically not significant, what do you mean by that?
A. The Noecker study, at the most, 2.2 millimeters difference between bimatoprost and latanoprost. And according to the FDA guidelines and my own clinical experience, that is not a clinically significant difference.
And number two, there was a letter to the editor of the American Journal of Ophthalmology, which is our prestigious journal --
Q. Let's stop there for a moment.
A. Sure.
Q. Exhibit PTX-229 is in your materials there?
A. Yes.
Q. Do you recognize that as the letter you were just referring to?

A. Yes. That is the letter I was referring to.

MR. FILARSKI: Your Honor, I offer PTX-229.

MR. THOMAS: No objection.

THE COURT: Thank you.

MR. FILARSKI: Okay. I'm sorry. It's Defendants' Trial Exhibit 229.

(DTX No. 229 was received into evidence.)

BY MR. FILARSKI:

Q. All right. I'm sorry. Please proceed with respect to your comments on the letter to the editor.

A. Well, this letter points out several problems with the Noecker study, and I just listed three here, but the unmasking of -- by hyperemia.

The hyperemia was much more prevalent in the bimatoprost group, and the evaluators who evaluated the degree of hyperemia were the same people taking the pressures. So they could interpolate that if they had a lot of hyperemia, that they were probably a bimatoprost patient. So that would possibly influence their pressure reading, and especially in this semi-subjective pressure reading of the applanation tonometry.

So this was the criticism of -- of the letter to the editor. There was also a question regarding how they performed their study, and it was also brought out in this paper, that it was very curious that Xalatan or latanoprost

showed very poor IOP reduction in this particular study, where in other studies, and in this author's experience, Xalatan should have brought the pressure down a lot more.

And so this was an outlier and another source of a red flag for questioning the -- the results in the Noecker study.

MR. FILARSKI: So can we go to Demonstrative 10, please?

BY MR. FILARSKI:

Q. Is this a slide relating to this letter that you had prepared?

A. Yes, it is.

Q. Why did you call out the top section? And I will just read it into the record.

Given this concern, it is curious that the data are not shown in a manner that controlled for hyperemia in the study subjects.

A. Well, this was that first point I brought out about unmasking about the study because of the increased incidence of hyperemia in the bimatoprost group.

Q. And in the lower half, you called out, in particular, it is curious that the hypotensive effect of latanoprost in this study is so significantly less than expected in either our clinical experience or than reported in other controlled trials.

Why is that important to you, Doctor?

A. Well, this is saying that we would expect latanoprost to lower IOP significantly a lot more than the Noecker group found, and that this was in contrast to this author's clinical experience and the reports of other controlled trials.

So this, again, is a red flag that this paper -- that there's something wrong with the conclusions and the results in this paper.

Q. Okay, Doctor. I want to turn to your comments about compliance of persistence studies. Time is short. So did you prepare a slide relating to that?

A. Yes, I did.

MR. FILARSKI: Could we have the next slide, please, No. 11?

BY MR. FILARSKI:

Q. Can you explain to us what this is?

A. We have here graphs of 2 compliance studies. They're actually called persistence studies in the literature.

And Arias looked at compliance over two years and found that the latanoprost-treated patients had 81 percent staying with the drug and staying with the treatment, where only 22.9 percent of the bimatoprost group followed through with the drug with a two-year followup.

Here's a second study by Reardon. It shows

almost identical, separate independent studies showing identical persistence or compliance success. 81 percent with latanoprost, much less with bimatoprost.

Q. Why is this important?

A. This is very significant because if a patient is not going to follow through with treatment, it's not going to work. And the question is, why the difference?

Well, in these papers, they cited the two most important reasons. One, efficacy. And, two, side effects, and with hyperemia being the most important side effect.

Q. You took this information from two exhibits, Arias DTX-1024, and Reardon, DTX-1025; is that correct?

A. Yes, I did.

Q. Doctor, I'd like to turn to the non-responder issue.

Are you familiar that Dr. Wright, or, I'm sorry, Dr. Noecker testified that bimatoprost had a better responder rate than latanoprost?

A. Yes.

Q. And do you agree with that opinion?

A. No.

Q. Why not?

A. Well, when I reviewed the literature and really looked at it, the responder rates are very similar for all three most popular prostaglandin agonists.

Q. Did you prepare an exhibit to help explain your

opinion?

A. Yes. Yes, I did.

MR. FILARSKI: Put up No. 12, please.

BY MR. FILARSKI:

Q. Would you explain to us what this is?

A. Here we have the target, our goal is to reduce pressure. And the first group of three bars is the percent of patients who achieve the goal of reducing the pressure by 20 percent or more. And the gray first bar is bimatoprost. And there's a Cantor study. And they found 77 percent with bimatoprost achieved that goal. Travoprost, only 64 percent. And latanoprost, 75 percent.

Now, these differences are clinically not that much, so achieving the 20-percent goal is about the same.

Let's look at achieving an even higher goal, a more difficult goal. Can we reduce the pressure to 30 percent or more? And here we can see bimatoprost, we can see travoprost and latanoprost, and they're all again about the same. In this case, from the Aung study, we almost had 50 percent in the latanoprost group versus almost 40 percent in the bimatoprost group.

But my point is that the responder rate, reaching that target, is similar across the board between the prostaglandin agonists.

Q. Now, Aung is a paper that we heard about yesterday and

you're familiar with that paper?

A. I'm familiar with the Aung paper.

Q. And the Cantor paper, are you familiar with that paper?

A. Yes.

Q. I would like to show you what has been previously marked as Defendants' Trial Exhibit 308.

MR. FILARSKI: Your Honor, may I approach?

THE COURT: Yes, you may.

(Mr. Filarski handed an exhibit to the witness.)

BY MR. FILARSKI:

Q. Is that the paper from which you prepared the slides we are discussing?

A. Yes, it is.

MR. FILARSKI: Your Honor, I'd like to offer Defendants' Trial Exhibit 308.

THE COURT: 308. Any objections? I take it no.

MR. THOMAS: No objection, your Honor.

THE COURT: Thank you.

(DTX No. 308 was admitted into evidence.)

BY MR. FILARSKI:

Q. Dr. Wright, did you also hear some testimony from Dr. Noecker concerning a number of studies, Gandolfi, Bournias, and Williams?

A. Yes.

Q. And did you review those studies?
A. Yes, I did.
Q. And Dr. Noecker relied upon those studies in support of his opinion that there were no -- that there was a population of non-or under-responders.
Do you recall that?
A. Yes.
Q. And do you agree with him?
A. No, I do not.
Q. Could you put up Exhibit 17, please? Would you explain to us, very briefly, why each of these three studies does not support Dr. Noecker's opinion?
A. Well, the Gandolfi study was a retrospective recruitment. Basically, Gandolfi, at a university in Italy, reviewed all the patients in the glaucoma clinic, and looked at those patients and then saw which patients were on Xalatan and did not respond.
What he meant by not responding, he says it didn't reduce pressure ten percent. But it's not well controlled, the protocol was not well lined out. We don't even know how many charts he reviewed.
So he found 15 patients out of the entire university that did not respond to Xalatan. 15 out of how many? We don't know. But in his conclusion, it's interesting that he states in there, he estimates

approximately one percent of the patients didn't respond. I mean, that's very low. 99 percent responded.

But he found these 15. There was no control group. And it was interesting that of the 15 patients, he states that 13 would respond to bimatoprost. However, we don't know if the reason is they weren't taking their meds in the beginning and now they're on this protocol and now they're going to take their meds. We dont know why. And so the numbers are incredibly small in terms of the non-responders.

Q. What about the Bournias paper?

A. It's open label, meaning that patients knew what was going on, so there's all sorts of inherent bias with this study, and it's out of control. There was 1,428 sites with no monitoring. So every site could do what they want.

Q. And what about --

A. There was no strict protocol. I mean, this paper is not good evidence.

Q. I'm sorry to cut you off.

What about the Williams paper?

A. Well, the Williams paper looked at a relatively small number of patients and it was open label. We knew what they were getting. And what's interesting, they found non-responder rate incredibly high, like 40 percent, which just does not make sense when you look at Gandolfi and the

rest of the literature.

So I don't look at this and I don't think the FDA would look at this as substantial evidence.

Q. Dr. Wright, if there are -- if there is a group of non-responders or under-responders, what are some of the explanations for the existence of that group?

A. Well, if there are a true non-responder -- true non-responder means he doesn't respond at all. How could it have no effect? It would be very unlikely, and that's what Gandolfi shows, it's very unlikely.

So what was your question?

Q. I asked, if there was a group of non-responders, what are the possible explanations for such a group?

A. Well, it could be that the patient has an esterase deficiency. Esterase deficiencies are autosomal recessive, which means that you wouldn't see it otherwise clinically. But they just have a decrease in the amount of enzymes, so they wouldn't metabolize to free acid as quickly or as well.

So that would be one reason, because bimatoprost is an amide and it would be metabolized by a different enzyme.

So it could be an esterase deficiency. And we know esterase deficiencies occur. Cholinesterase deficiency, for example, in anesthesia is very important.

Patients don't wake up because they don't have the enzymes to metabolize succinylcholine. So it could be the enzyme deficiency.

Q. Anything else?

A. It could be the concentration differences. Bimatoprost is six times the concentration of latanoprost, and it could be to do with the concentration.

And I want to quickly point out that in medicine, we never see a hundred-percent effect. And it's just like some patients respond good -- well, if they have a headache to aspirin versus Tylenol. Everybody is a little different and we don't always understand the intricacies of how different we are, and it's not unexpected that we would have some patients respond and some not.

MR. FILARSKI: Thank you, Doctor. I have no further questions.

THE COURT: All right. Cross-examination.

MR. THOMAS: Thank you, your Honor. May I approach, your Honor?

THE COURT: Yes, you may.

(Mr. Thomas handed a witness notebook to the witness.)

CROSS-EXAMINATION

BY MR. THOMAS:

Q. Good morning, Dr. Wright.

A. Good morning.
Q. Nice to see you again.
A. Nice to see you again.
Q. You explained to us that you are a specialist in pediatric ophthalmology; is that correct?
A. No.
Q. You're not a specialist in pediatric ophthalmology?
A. I am a specialist in pediatric ophthalmology. That's not a complete answer. I'm also a comprehensive ophthalmologist.
Q. I understand. But your specialty area is pediatric ophthalmology; correct?
A. I do pediatric ophthalmology and comprehensive ophthalmology. Many of my patients are adults. In fact, in surgery, half my patients are adults.
Q. And within the area of pediatric ophthalmology, you're aware that Lumigan and Xalatan are not approved by the FDA for use in children; correct?
A. Yes, with an explanation.
Q. Go ahead.
A. None of the medications that we use are approved by the FDA. When we go into surgery, all the anesthetics are not approved. So we put an intraocular lens in a child when I operate, it's not approved.
So we are very used to, as pediatric physicians,

used to using off-label, it's called off-label use of a drug.

Q. But you are aware that the labels for Lumigan and Xalatan specifically say they're not approved for use in children?

A. If you look at the labels, they do not warn against using. They just say they're not approved.

Q. That's why I asked, they're not approved.

A. Yes.

Q. And let's talk about your glaucoma experience. Were you here when Dr. Noecker testified?

A. Yes. Actually, the truth, I came in late. I got about half of it.

Q. Well, are you aware that Dr. Noecker testified that he sees about a hundred glaucoma patients per week?

A. I don't remember hearing that.

Q. That hundred, a little over a hundred was the best estimate that you could give us for the number of glaucoma patients you've seen in the last ten years; isn't that right?

A. No.

Q. All right. Would you turn, please, to your deposition, which is in the binder that I just gave you?

A. Can I clarify my answer?

Q. Well, let's look at your deposition first, sir.

A. Would you repeat the question, please?
Q. Yes. The best estimate that you have been able to give us for the number of glaucoma patients that you have seen in the last ten years is "over a hundred," but you weren't able to give us any other information on that.
A. You said "seen." I've seen a lot more than a hundred over the past ten years.
Q. How many have you treated?
A. That's a different question.
Q. Okay.
A. So you're asking me how many I've treated or how many I've seen?
Q. Is it true, sir, that the best estimate that you have given us for the number of glaucoma patients that you have treated in the last ten years is "over a hundred," but you couldn't give us a better number than that?
A. What I'm saying here -- you're asking me two different questions. One is seeing patients and one is treating. It's very different.

In my practice, I have a high percentage of patients with glaucoma because I treat adult strabismus, and those adult strabismus patients often come in with complex issues. I have seen thousands of patients with glaucoma.
Q. Okay.
A. I have treated -- let me finish.

Q. Okay.
A. I have treated one to 200 patients primarily myself as the primary glaucoma-treating doctor over the past eight years or so, and I put in my deposition that it's very hard to know. It's like how many times have I eaten potatoes in the last five years? It's very hard to know. This is a gross estimate.
Q. Okay. So you personally have treated between a hundred and 200 glaucoma patients over the past, since 2000; is that right?
A. Yes. And that's an ongoing process, let me add. When you have a glaucoma patient, they come in every three months, so a hundred patients is a heck of a lot of glaucoma patients.
Q. So Dr. Noecker sees as many glaucoma patients in two weeks as you've seen in the last ten years?
A. Now you're switching it.
Q. I'm sorry. I misspoke.
A. Are you trying to confuse me?
Q. No, sir, I'm not?
A. Okay.
Q. Let's just get it straight. Dr. Noecker treats in two weeks the total number of glaucoma patients that you have treated since 2000?
A. Probably not. He's seeing the same patients over and

over again. They're not different patients.

You know what's nice about glaucoma --

Q. Doctor, Doctor, we have very limited time.

A. I'm trying to give you an honest answer, but you're switching on me.

THE COURT: All right. Let's start over again. Play nice, because we are running out of time.

BY MR. THOMAS:

Q. Let me ask you a very straightforward question. The number of glaucoma patients that you have treated since the year 2000 is between 100 and 200; is that correct? Yes or no?

A. Are you asking me patient visits or number of individual patients?

Q. Patients.

A. 100 to 200.

Q. You are not a glaucoma specialist in that you see hundreds of patients every week, right, or every month?

A. I see probably 150 to 200 patients a week, and I am a glaucoma specialist in pediatric glaucoma. The three studies that I was involved with, I was invited because of my expertise in pediatric glaucoma.

Q. Okay. Let's talk about the drugs we're here to talk about, shall we?

You have a long list of publications in your

C.V., but none of them pertain to prostaglandin glaucoma drugs?

A. That is true.

Q. And you have a list of clinical trials in your C.V., but you have never participated in a clinical trial of prostaglandin drug, have you?

A. Not in terms of prostaglandin, but I have in terms of pharmacology and clinical trials on glaucoma medication.

Q. And you have participated -- and you received some research grants, but none of them pertain to glaucoma drugs? Prostaglandin glaucoma drugs, do they?

A. Some of them do pertain to glaucoma drugs.

Q. That is all right. I asked you about prostaglandin glaucoma drugs.

A. Specifically prostaglandin? No.

Q. All right. And you know the drug that we're here to talk about is Lumigan; is that right?

A. Yes.

Q. And you personally have very, very little experience with Lumigan; is that right?

A. Wrong.

Q. Isn't it true, sir, that the best estimate that you were able to give us for the total number of Lumigan prescriptions you have written in your entire life is between 10 and 20?

A. Yes, but my experience was your question.

I have been to more dinner seminars on Lumigan and bimatoprost than you could ever imagine. I teach it. I've been to conferences, CME. So that is not my limitation of experience.

The other thing I want to make out quickly is, I see lots of patients that are on Lumigan, hundreds, where I co-manage with another company, Hansen Ophthalmologists, or another glaucoma expert.

So those patients who come in on Lumigan, I'm taking their pressures. So I told you those specific patients that that are in my care, but that's different than the number of patients I actually manage and participate in the management of.

Q. Okay. So I just want to get a straightforward answer to a straightforward question.

In your entire life, the number of Lumigan prescriptions that you have personally written is between 10 and 20; right?

A. Well, that is true with an explanation. I have to explain.

I work with another physician who is a fellow, who has already done the residency, and they often write them for me. So those are the ones I actually handwrite. But in my senior position, often the fellow will write those

prescriptions. And I can't give you a very good estimate on how many they've written.

Q. Lumigan has been around for about ten years; is that right?

A. Yes, sir.

Q. So, on average, you personally have written one or two prescriptions per year?

A. Well, the other thing I want to say --

Q. Wait. Wait. Just answer my question, yes or no.

A. True, with a short explanation. True.

THE COURT: All right. Because your explanations are going to start counting against your counsel's remaining five minutes.

THE WITNESS: I want that to be -- but under my direction, many more.

BY MR. THOMAS:

Q. Now let's talk about the clinical significance of two millimeters of reduction, shall we?

You told us that the AAO, American Academy of Ophthalmology, has set 25 percent, generally -- varies from patient to patient, but 25 percent as a good target for reducing IOP; is that right?

A. Yes.

Q. And you, yourself, have never seen a study that shows a 15-percent reduction will slow the progression of the

disease?
A. I don't know if I remember that. I don't think there's a study showing 15 percent specifically stops optic nerve damage. It depends on the patient.
Q. All right. Thank you.
MR. THOMAS: Could we have PDX-705?
BY MR. THOMAS:
Q. And this is a patient with 20-millimeter baseline. So the difference between, with this patient starting at 20 millimeters, the difference between reducing this patient's IOP between 15 percent and 25 percent is 17 millimeters versus 15 millimeters; is that right?
A. Yes.
Q. And you would agree with me that 17 minus 15 equals two?
A. Yes.
Q. Okay. Now, let's talk about Xalatan non-responders.
MR. THOMAS: Could we have one of your slides? Actually, DDX-5-12, please, Mr. Exline.
BY MR. THOMAS:
Q. This is your slide; right?
A. Yes.
Q. And you believe it comes from a well-done study. You believe the Aung study is well done; correct?
A. Yes, I do.

Q. And what we're seeing here is we have 25 percent of the Xalatan or latanoprost patients are not getting at least a 20-percent reduction; is that right?

A. That is correct.

Q. And are you aware, sir, that 25 percent is about the same as the Lumigan market share within this group of Lumigan, Travatan and Xalatan drugs?

A. You're saying that Lumigan has 25-percent market share.

Q. Yes.

A. That sounds about right.

Q. Okay. So the non-responder rate, as measured by less than 20 percent, is about the same amount of the market share of Lumigan; is that right?

A. I think that's about right.

Q. Okay. But some patients need more; right? Some patients need more reduction --

A. Yes.

Q. -- than 20 percent?

A. Yes.

Q. If we could have DDX-5-15.

I'm sorry. Let's just stay on this one for a moment.

The Aung study itself shows that over 50 percent of the latanoprost patients don't get more than 30-percent

reduction; is that right?

A. That is correct.

Q. Now, while we're on Aung, would you turn, please, to DTX-229?

A. 229?

Q. 229. It's at DTX. I'm sorry, sir. It's in your counsel's binder.

A. I was looking at the wrong book. I don't see it here. Which -- do you want to help me? Here it is. Got it.

Q. This is the letter to the editor that your counsel showed you?

A. Right. Right.

Q. Now, he showed you the letter to the editor, but he did not show you Dr. Noecker's response to this letter, did he?

A. No, he did not.

Q. Would you turn to Dr. Noecker's response? The last page of the document, sir.

A. Yes, sir.

Q. And do you see that there's a response not only by Dr. Noecker, but several other doctors?

A. Yes.

Q. And would you read, please, into the record, the very last sentence of that letter?

A. "The conclusions of superiority of bimatoprost over

latanoprost are fully supported by every analysis performed on the findings of this study and are consistent with all previous direct comparison studies of bimatoprost and latanoprost."

Q. Thank you.

Now, in terms of Lumigan's efficacy for Xalatan non-responders, there are, in fact -- I know you don't agree with them, but there are, in fact, quite a number of studies that conclude that Lumigan is effective in Xalatan non-responders; is that right?

A. There are studies that show, and they're small, yes.

Q. Okay. For example, Gandolfi, Bournias, Williams, Sonty, all of these authors reached these conclusions that Lumigan is effective in treating patients who are not adequately treated with Xalatan; is that right?

A. That is correct.

Q. And you are not aware of any study that concludes that a majority of Xalatan non-responders do not respond to Lumigan?

A. I don't know either way. I don't know studies either way.

Q. And in terms of the efficacy, you said one is not more effective than the other.

A. That is correct.

Q. You're aware, though, that the party that you're here

to testify for has informed the FDA to the contrary?

A. I'm -- I'm sorry. Will you explain that?

Q. Yes. You're here to testify on behalf of the defendants; right?

A. No. I'm here to say the truth.

Q. Okay. Well, do you know that Barr, one of the defendants here, has informed the FDA that you're wrong?

A. No, I don't know what Barr said to the FDA.

MR. THOMAS: Could we have PTX-570, please?

THE WITNESS: This is the first time I've seen this.

BY MR. THOMAS:

Q. This is in PTX-570, which is in evidence. It's Barr's ANDA for bimatoprost.

And it states, "Bimatoprost is clinically the most efficacious ocular hypotensive agent and its activity exceeding that of both timolol and latanoprost."

Do you see that?

A. Yes.

Q. And you're saying that's not true; right?

A. I'm saying it's true with regard to timolol, but it's not true with regard to latanoprost. They didn't read the Parrish study.

Q. And this isn't in the Lumigan label; right? The FDA won't let Allergan put this on the label; right?

A. Yes. The FDA prohibits that. Yes.
Q. So it wasn't like Barr has to put this in their ANDA because it's in the Lumigan label; right?
A. I don't know if they have to or not. I don't even know what this letter is. I've never seen this before.
Q. You've never seen this?
A. I've never seen this letter before.
Q. So counsel didn't show you this before you came in here to testify?
A. Sir, I have about two feet of paperwork. I don't remember -- I don't remember seeing that.
Q. All right. And then, finally, let's talk about the FDA.

You think we ought to listen very carefully to what the DDMAC division of the FDA says; is that right?
A. Absolutely.
Q. Okay. You believe, you just said that you believe that Lumigan and Xalatan are superior to timolol in a clinically significant way; right?
A. Yes.
Q. But you're aware that the FDA does not allow either Pfizer or Allergan to say that in its marketing materials?
A. I may be aware of that. I specifically didn't study that.
Q. Are you aware that DDMAC has never allowed a company

that makes a glaucoma drug to say its drug is superior to any drug? Are you aware of that?

A. I'm not aware of that.

Q. Okay. And then, finally, on the FDA, you do think we should listen to what the FDA says; right?

A. Absolutely.

Q. Okay. So let's look at the labels.

MR. THOMAS: Could we have PTX-342?

BY MR. THOMAS:

Q. And this is a Lumigan label. You're familiar with that; right?

A. Yes.

MR. THOMAS: Let's have the pullout, please.

BY MR. THOMAS:

Q. You're aware that the Lumigan label says that Lumigan is a prostamide; right?

A. Yes.

Q. And you're aware that nowhere in the Lumigan label does it say it's a prodrug?

A. I did not specifically look for that, but I take your word for it.

Q. But you're aware that the Xalatan label does say it's a prodrug?

A. Yes.

Q. And you are aware that the Lumigan label says that it

causes outflow by both uveoscleral and trabecular meshwork outflow patterns; right?

A. Yes.

Q. But you are aware that the Xalatan label says that it only increases uveoscleral outflow?

A. Yes.

Q. And we should consider that to be important because it's in the FDA labels; right?

A. I think it should be important with an explanation.

Q. Would you like to explain?

A. Yes. It's clear that the literature that latanoprost also increases trabecular meshwork outflow. In fact, it was quoted in Noecker's own report at 30-percent increase of trabecular meshwork outflow versus 35-percent for bimatoprost. They're almost the same.

Q. But the FDA does not allow that to be in the Xalatan label, does it?

A. No, but it's not a warning.

Q. All right. This isn't a warning either. This is mechanism of action.

So what you are saying is there's good science in support of a factor that the FDA is not allowing to be put into the label itself?

A. I don't know if they didn't allow it or it was omission just by mistake.

MR. THOMAS: Nothing further, your Honor.

THE COURT: All right. Redirect.

REDIRECT EXAMINATION

BY MR. FILARSKI:

Q. Dr. Wright, with respect to the discussion about the Barr statements, you're not an ANDA expert, are you?

A. No.

Q. Do you -- you don't fill and file regulatory forms with the FDA with respect to ANDAs, do you?

A. No.

Q. With respect to the answer, or the letter to the editor concerning the Noecker article, did you read the reply by the authors?

A. Yes, I did.

Q. Did they answer the criticisms that both you have and the criticizer had?

A. They tried to, but I think those criticisms stand.

Q. And with respect to the Exhibit 5-12 --

MR. FILARSKI: Can we put that up, Jeremy?

BY MR. FILARSKI:

Q. Could you explain what you intend to show here?

A. Yes. The response rate, achieving target for the three most commonly used prostaglandin agonists, are very similar, and, if anything, at the 30-percent level, we see that latanoprost is actually better.

Q. What is the point of this slide?
A. The point of this slide is that the response rate is similar for all three agonists, and it makes sense because they work in the same way and they give the same results.
Q. Did you intend for this slide to have anything to do with marketing studies or positions on the market of the two drugs?
A. No.
MR. FILARSKI: Thank you. No further questions.
THE COURT: All right. You may step down. Thank you.
(Witness excused.)
MS. ADDY: Your Honor, our final witness will be Mr. Harry Boghigian, and he'll testify on the issues of lack of commercial success and unfelt need. I believe we can get through this in about ten minutes.
THE COURT: You don't have ten minutes left. I'm not sure plaintiff --
MR. SINGER: Your Honor, I would only ask if they are given extra time, that we be given extra time.
THE COURT: All right.
MR. SINGER: I can be as efficient as the Court likes.
THE COURT: All right. We'll give the defendant ten minutes and we'll give the plaintiff an additional --

how many minutes -- they have six left. All right. So an additional four minutes per side.

MR. SINGER: Thank you, your Honor.

MS. ADDY: So just to clarify, how many minutes do we have?

THE COURT: Ten minutes from the time we get this witness sworn in.

MS. ADDY: Thank you, your Honor.

... HARRY BOGHIGIAN, having been duly sworn as a witness, was examined and testified as follows ...

DIRECT EXAMINATION

BY MS. ADDY:

Q. Good morning, Mr. Boghigian.

A. Good morning.

Q. Have you been retained as an expert in this case?

A. Yes, I have. I've been retained by Barr, Teva and Sandoz in this case.

Q. And are you a consultant to the pharmaceutical industry?

A. Yes, I am.

Q. And when did you start working in this industry?

A. I started in this industry in 1971 with Hoff-LaRoche, which is one of the top ten pharma companies in the world.

Q. And while at Hoff-LaRoche, some of your positions were

Vice President of Business Operations, Vice President of U.S. Marketing, Global Business Director, VP and General Manager of the Canadian Division of Hoff-LaRoche; is that correct?

A. That is correct.

Q. And in these positions, were you involved with all phases of pharmaceutical product commercialization?

A. Yes, I was.

Q. How many drug products have you been involved with?

A. In the course of my career, probably over 40 drugs.

Q. And how many years did you work for Hoff-LaRoche?

A. I worked for Hoff-LaRoche for a total of 30 years.

Q. And after leaving Hoff-LaRoche, have you continued to work in this industry?

A. Yes, I have.

Q. And what are some of your current responsibilities?

A. After I left Hoff-LaRoche in 2001, I started a consulting company in late 2001, called Pharma Consultants, which services startups, small to medium-sized pharma companies.

Q. And you also have a research and development company?

A. In 2003, with two colleagues, I formed PBN Pharma, which is a very small research and development company, with 12 patents. We're about to launch our first product in another week or two, and that's headquartered in Chicago.

Q. And would you turn in your binder to Volume 2 to DTX-863?

MR. SINGER: May I have a copy, please?

MS. ADDY: I believe it's on your table.

BY MS. ADDY:

Q. Do you have it? Do you have it?

A. Yes, I do.

Q. And what is this document?

A. This is my C.V.

MS. ADDY: Your Honor, we move Defendants' Trial Exhibit 863 into evidence.

MR. SINGER: No objection, your Honor.

THE COURT: Thank you.

(DTX No. 863 was admitted into evidence.)

BY MS. ADDY:

Q. Mr. Boghigian, do you consider yourself an expert in pharmaceutical commercialization?

A. Yes.

Q. Do you consider yourself an expert in sales and marketing of prescription healthcare products?

A. Yes, I do.

MS. ADDY: Your Honor, I proffer Mr. Boghigian as an expert in the field of pharmaceutical commercialization, sales and marketing.

MR. SINGER: No objection, your Honor.

MR. McCANN: Thank you.

BY MS. ADDY:

Q. Mr. Boghigian, what is your general opinion of the commercial success of Lumigan?

A. My opinion is that the commercial success within the legal construct, that it's a failure. And that almost all of the sales are due directly to marketing, advertising and promotion.

Q. Why do you believe that Lumigan is not a commercial success?

A. Well, when you look at the market and all the parameters I looked at, it's very clear that the market sees this and the documents reveal that this is really a me, too product. It's really following in the footsteps of Xalatan, which it demonstrated that it's a new class of drugs, that it's a prostaglandin, it's effective in the treatment of open-angle glaucoma.

And if, indeed, it was truly innovative and had demonstrable unique features, you would have seen this product probably have a good opportunity to displace Xalatan as a product, but, on the other hand, you see just the opposite taking place.

Q. And do you plan to testify about anything else?

A. Yes, I do. I also plan to testify that based on all the evidence that I reviewed, I didn't see any unmet medical

need, either prior to the introduction of Lumigan or even after the introduction of Lumigan that it would address or has addressed.

Q. When Lumigan was first commercially launched in 1991, there were five classes of IOP-lowering drugs, but how many other drugs were available in the prostaglandin class?

A. At the time that Lumigan launched, there was only one prostaglandin on the market, and that was Xalatan.

Q. And when Xalatan was -- I'm sorry. When Xalatan was launched in 2001, it successfully displaced timolol. And why is that important?

A. Well, Xalatan launched in 1996, actually.

Q. I'm sorry.

A. And when it did, was introduced, within a short period of time, it displaced timolol, which is a beta-blocker and which was used primarily for the treatment of open-angle glaucoma.

Q. And why is it significant that Xalatan displaced timolol?

A. Well, I think what you're seeing is that with Xalatan's introduction, the market really saw a product that offered unique attributes, was a new class of drugs. It was a product that brought value to physicians, at least in addressing needs for their patients, and also addressing needs that they may have had in the treatment of open-angle

glaucoma. But it was very clear that the product offered some advantages versus what was currently on the market.

Q. If you could turn in your volume two of your binder to DTX-405.

A. Yes.

Q. Do you recognize this document?

A. Yes. This is an e-mail with attachments, and it appears to have attachments which are labeled HPF monthly updates.

MS. ADDY: Your Honor, we move Defendants' Trial Exhibit 405 into evidence.

MR. SINGER: No objection, your Honor.

THE COURT: Thank you.

(DTX No. 405 was admitted into evidence.)

MS. ADDY: And can we put up DDX 3-2, Jeremy?

BY MS. ADDY:

Q. What does this demonstrative show?

A. This is an Allergan document that was part of the documents I reviewed. And you can see that this is a -- this is a calibration of new product shares, new prescription shares as well as total prescription shares.

And what you are seeing here is they calibrated this over a period of 65 weeks. And they looked at Xalatan, Lumigan and Travatan. And you can see a very, very rapid uptake when Xalatan was launched.

And you can see the continued growth of Xalatan in terms of new prescriptions. First if Lumigan and Travatan, which were, by the way, both launched in March of 2001. They were launched simultaneously. And you can see that the uptake was very shallow and the growth curve leveled off very, very quickly over that 65-week period of time, whereas if you look at total prescriptions, and now this includes refills, you can see that, again, Xalatan continued to grow and had a very -- a much steeper uptake and is a strong indication of physician adoption.

This is a strong indication a physician saw this product was offering unique, demonstrable advantages in treating patients in their practice.

Q. Let's move to Defendants' Exhibit Demonstrative 3-4, and we're going to move really fast now.

What does this show?

A. This is the prostaglandin sales. It shows three products in the period 2001 to 2010. It's in millions of dollars.

You can see Xalatan, which is the dominant product in terms of sales, continuing to grow. You can see Travatan, and you can also see Lumigan with sales over that same period of time. And you can see that in 2007, or 2008, that Travatan actually has eclipsed Lumigan in terms of sales, and Lumigan is relatively flat in terms of sales.

Q. And what can you tell from that?
A. What you are seeing is the market reaction. What you are seeing is based on all the promotion that took place with these three products, that really Travatan is competing with Lumigan. The market kind of sees these two products as interchangeable. They're really not competing with peer, from looking at this, with Xalatan and that they're really competing amongst each other.
Q. And let's look at Defendants' Exhibit Demonstrative 3-8. Yes.
A. This is the --
MS. ADDY: Actually, let's move straight to 3-11, Jeremy. Thank you.
BY MS. ADDY:
Q. Can you tell us what this is?
A. Yes. I took prescription data, basically. I took prescription data, and I also looked at all of the marketing expenditures that Allergan provided.
And on an annualized basis, I correlated the prescriptions to the market expenditures, and it was very clear to see that there's a relatively close correlation between total prescriptions and marketing expenditures, which says to me that this product was primarily being driven by marketing expenditures, because you can see, as marketing expenditures level off in 2007/2008, so the

prescriptions, and as -- as marketing expenditures begin to decline, you can see again the continuation level off.

Q. And let's look also at DDX-322. And does this reflect what you see in your research, or in looking at Allergan's materials?

A. Well, this, again, confirms and correlates and really supports what you saw in the earlier graph. This was a review of a marketing campaign, and the marketing campaign had additional sales force focus -- that's the SF -- and investment in programs.

And what you can -- what you can see is that there was some change in terms of new and total prescriptions. But over that 16-month period of time, it would be my opinion that if you had this additional incremental increase, that this is relatively minimal, and I wouldn't say that this necessarily was driving any incremental sales with Lumigan.

Q. So how does all the --

THE COURT: Technically out of time, but if you have your final question.

MS. ADDY: Wrap up.

BY MS. ADDY:

Q. How does all this data we just examined impact your opinion on whether Lumigan was a commercial success, and did you see any evidence in the market that Lumigan met any

unmet needs?

A. No. This just confirms for me that Lumigan sales are almost all directed -- all a result of marketing promotion and advertising, and I didn't see Lumigan addressing any unmet needs in the marketplace whatsoever.

MS. ADDY: Thank you, Mr. Boghigian.

THE WITNESS: You're welcome.

THE COURT: All right. Cross-examination.

MR. SINGER: May I approach, your Honor?

THE COURT: Yes, you may.

(Mr. Singer handed an exhibit notebook to the witness.)

MR. SINGER: And may I proceed?

THE COURT: Yes, you may.

CROSS-EXAMINATION

BY MR. SINGER:

Q. Good afternoon, Mr. Boghigian. It's nice to meet you.

A. Good afternoon.

Q. You've done this before, haven't you, sir?

A. I'm sorry?

Q. You've done this before?

A. I have testified on several occasions.

Q. And you've testified, if I think I looked, you actually provided us a list of your testimony; isn't that correct?

A. That's correct.
Q. If you look in your binder, you should have DTX-865. Can you go to that, sir?
A. Yes.
Q. And is that the list of testimony you've given and that you provided us?
A. Yes. This appears to be the case.
Q. Okay.
MR. SINGER: Plaintiffs move into evidence DTX-865.
MS. ADDY: No objection.
THE COURT: Thank you.
(DTX No. 865 was admitted into evidence.)
MR. SINGER: Mr. Exline, if we could have that up on the screen.
BY MR. SINGER:
Q. This actually goes on for quite a number of pages, doesn't it, sir?
A. I'm sorry?
Q. This actually goes on for quite a number of pages?
A. Several pages. You know, it's not tight-spaced. It's double, triple, quadruple-spaced.
Q. It's six pages, isn't it, sir?
A. Well, if it's six pages, it's six pages.
Q. And you have actually testified in federal court, I

think it was seven times, and then once in Canada as well; is that correct?

A. I believe you're correct. I have not counted them recently.

Q. Okay. Fair enough.

And that's since 2003; is that right?

A. 2004, I believe, was the first one. Federal court.

Q. Fair enough. Seven times since 2004.

And it also lists your depositions; isn't that correct?

A. Yes.

Q. And I think there are 24 of those since 2003; isn't that correct?

A. It could very well be.

Q. Does that sound about right, sir?

A. Again, I have not counted them. It could be correct.

Q. Does it sound about right, sir?

A. If you say you counted them and there are 24, then there probably are 24.

Q. And most of these are Paragraph 4 litigations like this one; isn't that correct?

A. There are some of them that are Paragraph 4. I have not gone through and identified them. Some deal with contract negotiations. Some deal with infringements as it relates to irreparable harm, preliminary injunctions,

depositions regarding declarations, and so forth. So it's not all Paragraph 4.

Q. I didn't say they were all. I just said most of them are Paragraph 4 litigations like this one; isn't that correct?

A. I don't know if I would say most.

Q. I think several of them are; isn't that correct?

A. That's correct.

Q. And, in fact, the majority of them are; isn't that correct?

A. Well, again, I have not gone through and counted them specifically that way.

Q. Does that sound wrong to you?

A. Well, I do this type of Paragraph 4 litigation. No question about it. You're saying majority. That may be the case. I have not counted them.

Q. And every time you've done the Paragraph 4 litigation, you've been retained by the generic company; isn't that correct?

A. That would -- that would be correct, because as you know, you end up with conflicts. I've been approached by brand pharma, but due to conflicts, have been unable sometimes to take on those particular assignments.

Q. But every time you've given testimony, you've testified on behalf of the generic company in Paragraph 4

litigation; isn't that correct?

A. That's correct.

Q. And your testimony in those cases was always that the brand company's sales were more due to marketing than they were to the patented features; isn't that correct?

A. Well, some of the Paragraph 4 were not specifically due to commercial success. Some of the paragraph 4s that I was asked to opine on were looking at facets that related to isomers and what would happen if, indeed, marketing was related, if the marketing expenditures were committed to the racemic mixture versus the isomer.

So they're not necessarily all specifically related to commercial --

Q. Okay.

A. -- success in the legal construct of success.

Q. Fair enough.

But when it was related to commercial success, every time you testified, you testified that the branded product's sales were more due to the marketing than they were the patented features; isn't that correct?

A. Yes. I looked at all of the parameters that you would look at, which includes prescriptions and sales and competitive displacement, market share, and profitability, as well as the qualitative factors, and I would do my assessment based on those parameters.

Q. And every time you did that assessment, you testified that the branded product's success was more due to marketing than patented features; isn't that right?
A. When I evaluated all of that, it was very obvious, after spending 40 years in this business. I mean, in having the number of positions in terms of marketing and product director and market research, mine, it became pretty obvious. You could tell very clearly what was driving the sales of the product.
Q. Is that a yes to my question?
A. Yes.
Q. All right. And you were here for Mr. LeCause's testimony?
A. No, I was not.
Q. So you didn't hear him testify about his 20 years of experience in the market about glaucoma drugs?
A. No, but I read his transcript. I understand most of that time he has been in sales.
Q. And he interacts with physicians on a regular basis?
A. I'm sorry?
Q. And he testified he interacts with physicians on a regular basis?
A. I don't recall that specifically, but I'm sure he does.
Q. And he gave us his views as to why physicians

prescribe, or buy, actually, buy Lumigan?
A. Physicians don't buy Lumigan. They prescribe it.
Q. Fair enough. He gave his positions as to why physicians prescribe Lumigan?
A. I don't recall specifically those opinions in the transcript I read. I wasn't here.
Q. Okay. And you don't have experience marketing glaucoma drugs; is that correct?
A. I have not marketed glaucoma drugs. I've been involved with ophthalmics and pharma consultants. I've also consulted with a company with some ophthalmic products, but not specifically glaucoma.
Q. Actually, in your time at Roche, you did not have any experience marketing glaucoma drugs; is that correct?
A. Not glaucoma drugs, no. We had an ophthalmic solution, but not glaucoma.
Q. And in your -- well, I think you testified, isn't it true that when you were at Roche, the ocular area wasn't even a therapeutic area for Roche; isn't that right?
A. We did not focus on ocular products. We had antibiotics that were used to treat ocular infections, and that's the area that we had some experience with.
Q. And you did work on other types of products at Roche; is that correct?
A. I worked on over 40 products in multiple therapeutic

areas.
Q. And that was, I think you said, over 30 years?
A. I worked at Hoff-LaRoche from 1971 to 2001.
Q. And you're very proud of your time at Hoff-LaRoche?
A. Very proud of what we accomplished.
Q. And reflecting back on those 30 years, you don't consider any of the products you had responsibility for in some way, shape or form to be a failure; isn't that right?
A. No, that is not what I said. I've been involved with those products at various stages of development. And if I went back and had the opportunity to review all of the parameters that I normally review in these cases, then I would be able to draw specific conclusions.
Q. Isn't it true, sir, that in your time at Roche, with the drugs that you at least had responsibility for in some way, shape or form, would you consider any of the ones we've discussed at your deposition, or maybe any you have not mentioned at your deposition, a failure?
A. I'm sorry. Do you want to -- I'm not sure I understand your question. I can answer this question very easily.
Q. Let me rephrase it, sir.
A. Okay.
Q. Do you have your deposition in front of you?
A. No, I do not.

Q. It should be in your binder, the small binder that I gave you, not the big binder that your counsel gave you. It should be right at the front. And if you turn to page 103 of that deposition.

MS. ADDY: I object if he's trying to impeach him. I don't think this is a proper impeachment.

MR. SINGER: I will ask it again. I thought it was a very straightforward question.

MS. ADDY: The question moved in the middle of the question.

Q. In your time at Roche, sir, any of the products that you worked on, did you consider them a failure?

A. You're referring here to page 103?

Q. I'm asking you a question. Reflecting back on your 30 years at Roche, you don't consider any of the products you had responsibility for in some way, shape or form as a failure; is that correct?

A. Are you asking me that in the legal construct, or are you asking me that in the business sense?

Q. Sir, I'm asking you a question.

A. All right.

Q. Reflecting back on your 30 years at Roche, you don't consider any of the products you had responsibility for in some way, shape or form to be a failure; correct?

A. No, that's not correct. That's not what I said in my

deposition.

Q. Mr. Boghigian, if you could look at page 103 of your deposition.

Were you asked at your deposition at line 12:

"In your time at Roche, with the drugs that you had at least had responsibility for, in some way, shape or form, would you consider any of the ones we've discussed, or maybe any that you have not mentioned, as a failure?"

And your answer was: "No. I mean, no. I'm very proud of Roche and my tenure there at Roche."

Were you asked that question and did you give that answer at your deposition?

A. You've taken that answer out of context. That's not the intended answer. You attempted to read something into that. The answer is no. I mean I'm very proud of Roche my tenure there at Roche. It's not no, I don't believe we've had any failures, because if you go further into the deposition, you will see that I have identified where both Roche and I felt we had some products that were not commercially successful.

Q. Mr. Boghigian, were you asked that question at your deposition and did you give that answer that I read?

A. This is -- yes, but you're interpreting it differently than -- than the way I had communicated it.

THE COURT: And you're technically out of time,

but because of the back and forth, I will give you the one last question that I allowed counsel for defendant.

MR. SINGER: Just one?

BY MR. SINGER:

Q. You understand, Mr. Boghigian, that you are here today because Teva and Sandoz, two of the largest generic pharmaceutical companies in the world, want to sell generic versions of Lumigan; isn't that correct?

A. My understanding is they obviously have some interest in Lumigan, that's correct.

MR. SINGER: I have no further questions, your Honor.

THE COURT: All right.

MR. LOMBARDI: We have nothing further.

THE COURT: All right.

MR. LOMBARDI: The one thing I would raise, we had thought it would be appropriate to submit demonstratives to the Court, not for any purpose other than demonstratives, to make it easier to follow the transcript and so forth. And I'm not sure what we had asked -- we had asked the other side. I'm not sure what their position is on it.

THE COURT: I had said no demonstratives or all demonstratives.

MR. SINGER: I think we had talked it over. We don't think it's necessary or appropriate.

THE COURT: All right.

MR. LOMBARDI: Then with that, I think we're done.

THE COURT: All right.

MR. McCANN: I'm sorry, your Honor. Just so there's no procedural issue, we would renew the motion that Ms. Brooks previously mentioned about Rule 50(c).

THE COURT: All right. I reserve judgment on that.

I will let you come up with a briefing schedule for post-trial briefing.

You may step down, sir. I'm sorry.

THE WITNESS: Thank you.

THE COURT: You don't have to stick around.

(Witness excused.)

THE COURT: I know we have deadlines, and we're working very hard on the deadlines that are coming up sooner or have already passed, and so we are making progress and we should be able to make this deadline as well. But you let me know how the briefing should be submitted.

And is there anything else that we need to address yet today?

MR. LOMBARDI: No, your Honor.

MR. McCANN: No, your Honor.

THE COURT: All right. As always, it's a

pleasure, counsel. Thank you very much.

(Counsel respond, "Thank you, your Honor.")

(Court recessed at 12:38 p.m.)

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