

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

MEDA PHARMACEUTICALS, INC.,  
 and CIPLA LTD.,  
 Plaintiffs,  
 v.  
 APOTEX INC. and APOTEX CORP.,  
 Defendants.

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CIVIL ACTION  
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NO. 14-1453-LPS

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Wilmington, Delaware  
 Thursday, December 15, 2016  
*Bench Trial - Volume C*

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BEFORE: HONORABLE **LEONARD A. STARK**, Chief Judge

APPEARANCES:

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and

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23 P R O C E E D I N G S

24 (REPORTER'S NOTE: The following trial was held  
25 in open court, beginning at 2:34 p.m.)

1 THE COURT: Good afternoon, everyone.

2 (The attorneys respond, "Good afternoon.")

3 THE COURT: So have a seat, please.

4 You may or may not know, my jury is out. We got  
5 the case to them about 20 minutes ago.

6 I may at any time be interrupted with a note.  
7 If so, please bear with me while I take a look at what is  
8 sent to me, and if not, then great. But subject to the  
9 jury, other than that, I'm available until 7:00 tonight.

10 So with that, I believe we'll call the witness  
11 back to the stand, correct, Mr. Lombardi?

12 MR. LOMBARDI: I'm prepared to do that. I  
13 thought opposing counsel had something they wanted to raise  
14 with Your Honor.

15 THE COURT: I'm sorry, I should have asked that  
16 first. Good afternoon.

17 MS. EVERETT: Good afternoon, Your Honor. At  
18 the pretrial conference, we discussed that there would be  
19 certain confidential documents that will be presented during  
20 trial, and you asked for us to let you know as soon as  
21 possible.

22 Plaintiffs will have, Dr. Smyth will have some  
23 testimony that involves plaintiffs' formulation documents.  
24 Mr. John Jarosz will testify to some financial information  
25 and Apotex will have rebuttal witness Mr. Press who will

1 respond on plaintiffs' financial information. And we would  
2 seek to close the courtroom during those portions of the  
3 testimony.

4 THE COURT: Okay. Is there any objection to  
5 that?

6 MR. LOMBARDI: No, Your Honor.

7 THE COURT: Okay. So for just those limited  
8 portions of each of those witnesses testimony, I will close  
9 the courtroom. You will have to let me know when we get to  
10 that portion, and at that point we'll ask anyone who is in  
11 the courtroom who shouldn't be here to leave.

12 But keep it to the minimum that you can.

13 MS. EVERETT: Okay.

14 THE COURT: Any other issues from the plaintiff?

15 MR. EVENS: Yes, Your Honor. Just a  
16 housekeeping matter.

17 THE COURT: Sure.

18 MR. EVENS: I cleared it with Mr. Lombardi so we  
19 would not interrupt him.

20 At the end of Dr. Wedner, we were going to move  
21 some documents into evidence; two previously marked  
22 exhibits, PTX-326, and PTX-329.

23 And then we have reached agreement on four  
24 documents we used for impeachment and we marked them,  
25 provided them to counsel. They have no objection.

1           That would be PTX-1665. The Dollars For Docs,  
2           Talk With Your Doctor documents.

3           PTX-1666, the collage that shows Dr. Wedner at a  
4           meeting with his name on the slides, and his business card.

5           PTX-1667, it is advertisement for the meeting  
6           with the named Dymista azelastine hydrochloride and  
7           fluticasone propionate nasal spray, the date of the meeting  
8           the location, and the identification of Dr. Wedner as the  
9           speaker.

10          And then, finally, PTX-1668, the slide deck.

11          THE COURT: Okay. Is that all agreeable?

12          Good afternoon.

13          MR. WURMAN: Good afternoon, Your Honor. Just a  
14          couple things.

15          We, in no way -- we want to state on the record  
16          that we don't agree that the documents have been in any way  
17          authenticated or a proper foundation was laid but we came to  
18          an agreement with the plaintiffs that we don't object to  
19          their introduction of their impeachment exhibits on the  
20          condition that they do not object to our introduction of  
21          impeachment exhibits at the appropriate time.

22          THE COURT: So if I understand, the motion to be  
23          to admit them into evidence subject to what you have said,  
24          you do not object to them being admitted into evidence;  
25          correct?

1 MR. WURMAN: That's right, Your Honor.

2 THE COURT: Mr. Evens, anything further on that?

3 MR. EVENS: No, Your Honor.

4 THE COURT: All those documents that were listed  
5 are admitted. And if you have copies for us, you may pass  
6 them up if you like.

7 MR. EVENS: Thank you, Your Honor.

8 (Documents passed forward.)

9 THE COURT: Anything else from plaintiffs before  
10 we get started with this?

11 MS. EVERETT: No, Your Honor.

12 THE COURT: And nothing from defendants I  
13 understand?

14 MR. LOMBARDI: No, Your Honor.

15 THE COURT: Then we'll call the witness back,  
16 please.

17 THE COURT: Good afternoon, Doctor Donovan.  
18 Welcome back. I remind that you remain under oath, of  
19 course.

20 THE WITNESS: Yes.

21 ... MAUREEN DONOVAN, having been first duly  
22 sworn, was examined and testified as follows ...

23 THE COURT: Mr. Lombardi, you may proceed when  
24 ready.

25 MR. LOMBARDI: Thank you, Your Honor.

Donovan - direct

1 DIRECT EXAMINATION (Continued)

2 BY MR. LOMBARDI:

3 Q. Dr. Donovan, just to get us back where we were  
4 before. You were talking about some testing that had been  
5 done by the inventor. The results are her summary of the  
6 results which were submitted to the patent PTO; is that  
7 correct?

8 A. Yes.

9 Q. You remember that?

10 A. (Nodding yes.)

11 Q. Okay. Did plaintiffs' experts, Dr. Smyth and  
12 Dr. Herpin do any testing related to the same example in the  
13 Cramer reference?

14 A. Yes, they did.

15 Q. And that is Example 3?

16 A. Yes, it is.

17 Q. Okay. You understand what those two experts  
18 witnesses for plaintiffs say about that testing generally?

19 A. I read their documents, the reporting on that  
20 testing.

21 Q. And just to give us a place to start, what do you  
22 understand their position to be on that testing?

23 A. My understanding is that they also made those  
24 compositions and then they further evaluated them with  
25 additional testing and agreed with the inventor that the

Donovan - direct

1 composition was inoperable.

2 Q. Okay. Now, I want to talk to you. You have reviewed  
3 all the materials that have been provided on the testing by  
4 Dr. Smyth and Dr. Herpin; is that right?

5 A. Yes, I have.

6 Q. Have you come to a conclusion about what that testing  
7 shows?

8 A. I believe that the testing shows that the composition  
9 is certainly operable. It forms the intended composition as  
10 described by Cramer, yet it's at the very first step in what  
11 one would consider formulation development from a formulator  
12 acting as a POSA and to become a pharmaceutical product. It  
13 would need further optimization.

14 Q. Okay. Would you consider -- what do you mean by  
15 operable then?

16 A. I mean operable, again, the intention of Cramer 3 was  
17 to demonstrate you could combine triamcinolone acetonide and  
18 azelastine in the grouping of excipients described or other  
19 corticosteroids and potentially other excipients to form a  
20 composition suitable for nasal administration and indeed  
21 that composition does form something that is suitable for  
22 nasal administration, yet it's, and as Cramer states, the  
23 opportunity to modify that composition slightly for the  
24 specific need is left open as a descriptor in Cramer. That  
25 is exactly what needs to happen to turn that composition



Donovan - direct

1       into a nasal spray.

2       Q.       Are these compositions as prepared by Dr. Smyth and  
3       Dr. Herpin ready to submit to the FDA for approval, in your  
4       opinion?

5       A.       No.

6       Q.       Are they ready for commercialization?

7       A.       No.

8       Q.       What needs to be done then, just the general thing  
9       that needs to be done to get them to FDA approval or  
10      commercialization?

11      A.       They would actually need to go through a formulation  
12      development and optimization plan.

13      Q.       And is that type of work within the level of skill of  
14      the person of ordinary skill in the art in this case?

15      A.       Yes, that's exactly what formulators do, yes.

16      Q.       Let me turn to just two more fast topics. One topic  
17      and one clean-up item, Dr. Donovan. If we could have Slide  
18      DDX-5.55, which is the next slide in the presentation from  
19      where we stopped yesterday.

20               Have we asked you to review Claim 1 of the  
21      Astelin patent?

22      A.       Yes, you have.

23      Q.       The Astelin patent, just to bring us to where we were  
24      yesterday, what is the active ingredient in that patent?

25      A.       The active ingredient is azelastine hydrochloride.

Donovan - direct

1 Q. Have we asked you to compare that claim to the  
2 Dymista product?

3 A. Yes, you have.

4 Q. We have got up here, for the record, DTX-16 at Column  
5 8, Lines 1 to 6, this is the Astelin patent with the  
6 inventor Hettche on it, can you just briefly describe the  
7 elements of Claim 1 to the Court?

8 A. Claim 1 describes a method of treatment for  
9 irritations of the nose or eye which comprises applying  
10 directly to nasal tissues or the conjunctival sac a  
11 medicament that contains a member of the group that includes  
12 azelastine and its physiologically acceptable salts.

13 Q. You have compared this to Dymista. Is that right?

14 A. Yes, I have.

15 Q. Let's go to the next slide. This is DDX-5.56. On  
16 the right we have Dymista. Just for the record to bring us  
17 back where we were, what are the active ingredients in  
18 Dymista?

19 A. Dymista is a fluticasone propionate and azelastine  
20 hydrochloride combination.

21 Q. Would you walk us through your analysis of how the  
22 claims -- how Claim 1 of the Astelin patent compares to the  
23 Dymista patent?

24 A. As disclosed, to make it simpler, the first portion  
25 of the description of Claim 1 is a method of treatment for

Donovan - cross

1 irritation of disorders of the nose or eye. And that's  
2 exactly what Dymista claims to be and is approved to use, as  
3 a treatment for irritation disorders of the nose.

4 It's applied directly to the nasal tissues as a  
5 nasal spray. And finally, it contains -- it contains  
6 azelastine hydrochloride, so it contains a member of the  
7 group consisting of azelastine and its physiologically  
8 acceptable salts.

9 So on all three of the descriptors contained on  
10 that claim, Dymista is an embodiment of that.

11 Q. Now to the subject that is clean-up. I discovered  
12 that when we went through all the claims, I left out a  
13 question for a couple of the claims. To quickly clean that  
14 up, Doctor, I am going to go back to the '428 patent. As to  
15 Claims 10, 13 and 15, are those claims obvious, in your  
16 opinion?

17 A. My opinion is they are obvious.

18 Q. And with respect to the patent, the '620 patent,  
19 Claim 44, is that claim obvious, in your opinion?

20 A. Claim 44 is obvious.

21 MR. LOMBARDI: I will pass the witness, Your Honor.

22 THE COURT: Okay. Thank you. We will have  
23 cross-examination.

24 CROSS-EXAMINATION

25 BY MS. EVERETT:

1 Q. Good afternoon, Dr. Donovan.

2 A. Good afternoon.

3 Q. I would like to start with the topic you just  
4 covered, the Astelin patent.

5 Mr. Beal, may we have DDX-5.55?

6 You just testified that this covers Dymista?

7 A. Yes, it does.

8 Q. Fluticasone propionate, that is not a member selected  
9 of the group consisting of azelastine and its  
10 physiologically acceptable salts, is it?

11 A. No.

12 Q. Fluticasone propionate is not actually listed  
13 anywhere in the Astelin patent. Is that correct?

14 A. No, it's not. Not to my recollection.

15 Q. Before you offered opinions in this case, you hadn't  
16 read the prosecution history for the Hettche patent. Is  
17 that correct?

18 A. That is correct.

19 Q. And you are aware that your experts, Apotex's experts  
20 you are calling, Dr. Schleimer, is relying on the Segal  
21 reference, which is a patent application from Warner  
22 Lambert?

23 A. Yes, I understand that.

24 Q. He testified he believes it is an  
25 azelastine/fluticasone product?

1 A. I believe so, yes.

2 Q. You are aware that Warner Lambert filed a patent  
3 application on that product?

4 A. Yes, I understand that's the case.

5 Q. And you are relying on the Cramer reference?

6 A. Yes, I am.

7 Q. And you are arguing that Cramer discloses  
8 azelastine/fluticasone. Is that right?

9 A. Yes, I am.

10 Q. That is a Procter & Gamble patent. Is that correct?

11 A. That's correct.

12 Q. Procter & Gamble filed a patent application on that  
13 patent?

14 A. That's what I understand.

15 Q. Cipla, obviously, they are the patents in suit, they  
16 are an azelastine and fluticasone combination product.  
17 Correct?

18 A. Yes.

19 Q. They also filed a patent?

20 A. Yes.

21 Q. Dr. Donovan, you have never formulated a fluticasone  
22 nasal spray. Is that correct?

23 A. That's correct.

24 Q. And you haven't done that because fluticasone is not  
25 an active ingredient used in your laboratory?

Donovan - cross

1 A. That's correct.

2 Q. And that's because steroids are not simple model  
3 compounds?

4 A. Well, the compound fluticasone-propionate is not an  
5 appropriate model compound for me to pursue the research  
6 that I am conducting.

7 Q. You have also testified that the analytical methods  
8 for steroids are challenging?

9 A. Well, they were in the 1980s when I was working with  
10 them at the last time.

11 Q. Do you recall that we met in October during your  
12 deposition?

13 A. Yes.

14 Q. And that I asked you why you had not worked with  
15 fluticasone in your laboratory?

16 A. Yes.

17 Q. And do you recall what you said?

18 A. I think I said essentially what I just said, it's not  
19 an appropriate model compound. It's not a compound that we  
20 are interested in from a pursuit of the research that's  
21 being conducted in my laboratory.

22 Q. Mr. Beal, can you please pull up Dr. Donovan's  
23 deposition transcript?

24 THE COURT: Give us a page?

25 MR. EVERETT: Page 31, the back of the binder.

Donovan - cross

1 THE COURT: In the big binder?

2 MS. EVERETT: Deposition Transcript 31, in the  
3 big binder, starting at Line 3.

4 THE COURT: Give us a moment, please.

5 BY MS. EVERETT:

6 Q. Do you recall giving that testimony?

7 A. Yes.

8 Q. I asked, "Have you formulated any nasal spray  
9 products using fluticasone as an active?"

10 And you answered: "Fluticasone is not an active  
11 ingredient I've chosen to use in my laboratory in our  
12 investigations."

13 A. Yes.

14 THE COURT: Mr. Lombardi.

15 MR. LOMBARDI: That is exactly what she said.  
16 It's not impeachment.

17 THE COURT: That may be. I think counsel is  
18 going to read the next question and answer as well. Is that  
19 right?

20 MS. EVERETT: Yes.

21 BY MS. EVERETT:

22 Q. And I asked you, "Why is that?"

23 And you responded "I -- looking into using  
24 steroid products is not -- or selecting steroids as APIs is  
25 not a simple -- they're not simple model compounds. Their

1 analytical methods are challenge. That's primarily one of  
2 the reasons that I typically don't choose to use them."

3 A. That's correct. And when I used them in the 1980s  
4 they required a distinct piece of equipment that is  
5 essentially set aside only for use for the analytical  
6 methods for steroids. As a poor starving assistant  
7 professor, I didn't have the ability to have that expensive  
8 piece of equipment dedicated only for steroids. We needed  
9 to use for it other materials, also. And there was not a  
10 compelling reason to choose any of the steroids to use as  
11 model compounds for the investigations we were active in.

12 MR. LOMBARDI: For completeness, Your Honor, I  
13 would ask that counsel read Page 33, Lines 6 to 9.

14 THE COURT: Let's do that, please.

15 MS. EVERETT: There is a page between that as  
16 well.

17 THE COURT: If you wish to read all of that, you  
18 may. I do want you to read 33, 6 to 9, I believe will Mr.  
19 Lombardi asked for.

20 MS. EVERETT: The question is for Page 33, if we  
21 can pull it up.

22 THE COURT: Which line?

23 MR. LOMBARDI: Line 6 to 9:

24 MS. EVERETT: Actually, Your Honor, I am going  
25 actually go to read the whole thing. I think selecting Mr.



1 Lombardi's quote is out of context.

2 THE COURT: You can read the whole thing.

3 BY MS. EVERETT:

4 Q. You continue to state, "Detection and blood and even  
5 analysis of this dosage form itself requires more  
6 challenging HVLC assays than I like to run on daily basis,  
7 requires often back in the day, I think a very, very long  
8 time ago I worked with some steroids. Fluticasone was not  
9 one of them. And we were with -- we needed special solvent  
10 systems that weren't typically used in the labs. We had --  
11 you know, there was a waste of disposal issues. We had to  
12 have dedicated equipment. I mean it became inefficient in a  
13 small academic research lab. So there wasn't ever any  
14 reason from a focus of my research program to need to use a  
15 steroid as a model compound, so they're just not typically  
16 used."

17 I asked, You said they needed a special solvent  
18 system. What kind of a special solvent system did they need?

19 "Answer: Well, back in the day when I worked on  
20 them, standard methods to analyze steroids was something  
21 using called normal phase chromatography and normal phase  
22 chromatography used solvents like toluene and  
23 dichloromethane, other things I try not to have to use in my  
24 lab, and typically -- and I'm not sure now, I don't look at  
25 steroid analytical methods, but there are other improved

1 detection systems and better columns than there were at the  
2 time. And so, you know, our typical materials for reverse  
3 phase chromatography are now acetonitrile and methanol. And  
4 while they also have disposal issues, they don't have as  
5 many exposure issues and disposal issues as toluene  
6 dichloromethane, and their friends that get used in normal  
7 phase chromatography.

8 "Question: And you said at the time. What are  
9 the time frames?

10 "Answer: This is back in the 1980s and  
11 potentially into the early 1990s."

12 A. I see it.

13 MR. LOMBARDI: I just wanted to note that  
14 perhaps Ms. Everett misspoke when she was reading.

15 THE COURT: All right. It see it. 1980s,  
16 1990s. Let me say, the objection that it was not  
17 impeachment is overruled. And for your guidance, I am going  
18 to take a very broad view as to what might potentially ever  
19 be considered inconsistent, and so you are free to make the  
20 objections. It's very likely to be overruled. But I just  
21 give that to you for your benefit.

22 Go ahead, Ms. Everett.

23 BY MS. EVERETT:

24 Q. You also never studied or formulated azelastine; is  
25 that correct?

1 A. That is correct.

2 MS. EVERETT: May I have DDX-5.49?

3 BY MS. EVERETT:

4 Q. Yesterday, you testified that suspensions have  
5 solutions. Every suspension has a solution. Is that  
6 correct?

7 A. I would like you to rephrase that so it is something  
8 I can answer.

9 Q. Yesterday, you provided testimony that suspension  
10 products often can contain products that are in solution?

11 A. Contain materials that are in solution?

12 Q. Yes.

13 A. Yes, suspension products or suspension material --  
14 things that are in suspension will have the very item that  
15 is not dissolved, have some complement of that in solution,  
16 and they may also have other materials in solution.

17 Q. And when you meant that, you were referring to  
18 inactive ingredients; correct?

19 A. Well, yes. In addition to the active, the active  
20 ingredient is the material, it is not soluble, and it is in  
21 suspension. Some portion of that is in solution in the  
22 suspension. And if there are other inactive ingredients in  
23 the suspension, they may be in solution.

24 Q. The example you brought up did not include an active  
25 in solution; is that correct?

1 A. If we accept that the only active in Flonase is  
2 fluticasone propionate, then the fluticasone propionate has  
3 some component of it in solution and it also has material  
4 that is undissolved in suspension.

5 Q. Dr. Donovan, you used the word "active" yesterday in  
6 your testimony; correct?

7 A. I probably did, yes.

8 Q. And you used it to characterize the product that  
9 provided the therapeutic benefit; correct?

10 A. I probably did that, yes.

11 Q. So can we agree when we use the word active, we're  
12 talking about the product that provided the therapeutic  
13 benefit?

14 A. Okay.

15 Q. So in your example, DDX-5.49, you do not set forth a  
16 suspension product that includes a solution product --  
17 strike that. Excuse me.

18 You have provide an example of a suspension with  
19 ingredients in solution; is that right?

20 A. With active and inactive ingredients in solution,  
21 yes.

22 Q. You have not shown an example on DDX-5.49, DTX-33.  
23 Your example is Flonase as a suspension with ingredients in  
24 solution; correct?

25 A. Well, Flonase has ingredients in solution, both the

1 active and inactive ingredients in solution.

2 Q. Flonase is intended to be suspended; correct?

3 A. Well, there is sufficient fluticasone propionate  
4 included in that formulation, that there is excess  
5 fluticasone propionate above the solubility of fluticasone  
6 propionate in the vehicle, and therefore there is  
7 fluticasone propionate in suspension along with fluticasone  
8 propionate in solution.

9 Q. Dr. Donovan, fluticasone is intended to be suspended;  
10 correct?

11 A. The consequence of the amount of fluticasone  
12 propionate that is included in that formulation leads us  
13 to there is undissolved fluticasone propionate and it is  
14 suspended in the vehicle.

15 Q. The intention of the product is to be suspended;  
16 correct?

17 A. I can't speak to the intention of the product.

18 Q. It is an active ingredient in a suspension?

19 A. That is the result of the components in the  
20 formulation.

21 Q. It is, on the first line on the Flonase label,  
22 Flonase nasal sprays is an aqueous suspension; correct?

23 A. Correct.

24 Q. And that suspension is referring to the fluticasone?

25 A. Well, the fluticasone propionate is the undissolved,

1 is the primary active undissolved specie in that formulation  
2 and so, yes, it is aqueous suspension of the undissolved  
3 fraction of fluticasone propionate with other materials in  
4 the suspension.

5 Q. So that is a yes?

6 A. Would you like to repeat the question, please?

7 Q. You have not provided a working example of a product  
8 that has an active in solution and suspension; correct?

9 A. I have provided prior art that shows information and  
10 examples of products that or compositions that contained  
11 actives both in suspension an in solution.

12 Q. That product was never commercialized, correct?

13 A. Not to my knowledge.

14 Q. And you are referring to the Cramer reference?

15 A. Yes, I am.

16 Q. And yesterday, Mr. Lombardi asked you whether the  
17 Cramer reference showed that a person of ordinary skill  
18 would not be able to make a solution in, solution in  
19 suspension, and you testified that you believed that it did  
20 show a person can make, would be able to make a suspension  
21 because the formulation was just made and you were able to  
22 characterize it.

23 A. Can I ask, are you talking about Cramer 3 again?

24 Q. Yes, Cramer 3.

25 A. And that the composition can be made? Yes.

1 Q. And that, that is the fact a composition can be made  
2 is sufficient to show a person can make a solution in  
3 suspension?

4 A. Yes.

5 Q. You did not discuss the parameters of the formulation  
6 that would be made?

7 A. What parameters specifically?

8 Q. For example, you did not discuss whether the  
9 formulation would need dose uniformity.

10 A. Well, again, it was preparing a pharmaceutical  
11 composition, that composition was prepared. That is Cramer  
12 3 directed.

13 Q. In your testimony, you did not discuss whether dose  
14 uniformity is an important characteristic in a nasal spray  
15 formulation; correct?

16 A. Pardon me.

17 Q. Yesterday, you did not discuss the importance of dose  
18 uniformity in preparing a nasal spray, did you?

19 A. Well, if it's a nasal spray intended for specific use  
20 and specific dose, then attention would be paid to dose  
21 uniformity.

22 Q. My question was different. Yesterday, you did not  
23 discuss the importance of dose uniformity in a nasal spray,  
24 did you?

25 A. That was not part of my testimony yesterday.

1 Q. And you described Cramer Example 3 as an initial  
2 step; is that right?

3 A. That is how I described it yes.

4 Q. Cramer Example 3 doesn't refer to itself anywhere in  
5 the reference as an initial step, does it?

6 A. I'm not aware that it does.

7 Q. Dose uniformity, the ability to have a consistent  
8 dose administered is a consideration in all nasal sprays;  
9 correct?

10 A. Nasal spray is intended for human or animal use, yes.

11 Q. I'd like to turn now to your analysis of the prior  
12 art.

13 Can we have DDX-5.22?

14 Dr. Donovan, I believe yesterday, you testified  
15 that a person of ordinary skill would start with Astelin and  
16 Flonase --

17 A. Yes, I did.

18 Q. -- is that correct?

19 If a person compares Astelin, a person of  
20 ordinary skill compares Astelin and Flonase, they'll see  
21 there are two common excipients or two common ingredients  
22 between the two, is that right?

23 A. Can you be more specific, please?

24 Q. Sure. There are two overlapping excipients between  
25 Flonase and Astelin; is that right? Water is one of them.



1 A. They both contain water, yes.

2 Q. Yes. And they both contain, benzalkonium chloride?

3 A. Yes, they both contain benzalkonium chloride.

4 Q. And those are the only two overlapping ingredients?

5 A. Yes.

6 Q. Now, you discussed yesterday I believe how a person  
7 of ordinary skill would select the preservatives and their  
8 concentrations; correct?

9 A. Yes, I did.

10 Q. And you relied on the Hettche patent to arrive at  
11 concentrations, I believe?

12 A. That would be, I relied on that yesterday during  
13 testimony, yes.

14 MS. EVERETT: Can we put up DDX-5.13.

15 BY MS. EVERETT:

16 Q. And you relied on a section of the Hettche patent  
17 which says, each of these compound may be used in  
18 concentration of .002 to 0.05 for, for example, 0.02 percent  
19 weight by volume in a liquid formulation, otherwise weight  
20 by weight?

21 A. Yes, that is what I relied on.

22 Q. And that is a general statement; correct?

23 A. It gives a range of concentrations that might be  
24 appropriate, yes.

25 Q. It doesn't say anything specifically about EDTA?

Donovan - cross

1 A. No, it doesn't call up or refer only to EDTA in that  
2 list.

3 Q. You didn't testify about other sections in the  
4 Hettche patent that refer to concentrations of EDTA;  
5 correct?

6 A. Not yesterday, no.

7 MS. EVERETT: Can we pull up DTX-16? DTX-16,  
8 please? Column 4, line 4.

9 BY MS. EVERETT:

10 Q. Did you review this part of the reference,  
11 Dr. Donovan, of the Hettche reference, column 4, starting  
12 with line 4?

13 A. Yes, I did. I read that portion.

14 Q. And it says, the preservative used is preferably a  
15 combination of edetic acid, for example as a disodium salt,  
16 and benzalkonium chloride. In this combination, the edetic  
17 acid is used in a concentration of 0.05 to 0.1 percent  
18 benzalkonium chloride being used in a concentration of 0.005  
19 to 0.05 percent, preferably 0.01 percent?

20 A. That is what it says, yes.

21 Q. And you did not in your analysis discuss or disclose  
22 that the Hettche patent actually has concentrations for  
23 EDTA, edetic acid?

24 A. Well, a POSA formulator knows there is a broad range  
25 of appropriate formulations for EDTA and getting specific

1 about a particular point that is contained in the Hettche  
2 patent did not seem to be very informative.

3 Q. That is a no, you did not disclose that?

4 A. I didn't discuss that yesterday, no.

5 Q. Thank you. Can we go back to 5.33, please?

6 And you also discussed the active ingredients  
7 yesterday, how a person of ordinary skill would look to the  
8 weight by weight?

9 A. Yes. It included those two active ingredients at the  
10 concentrations that were in the prior art in the individual  
11 complement products.

12 Q. And you took the 0.5 percent weight by weight from  
13 Flonase?

14 A. That's correct.

15 Q. And you took the .1 percent by Astelin; is that  
16 correct?

17 A. Yes, and based on rounding --

18 Q. Yes, yes. That is just a yes or no question.

19 A. Yes.

20 Q. Did you compare the amount of each spray, the volume  
21 of each spray for Flonase or Astelin?

22 A. The volume of the spray in Flonase is given in  
23 milligrams and the volume of the spray in the Astelin  
24 product is given in millimeters I believe or microliters,  
25 one of the two.

1 Q. They're different, aren't they?

2 A. They are different units so, yes, they may be  
3 different.

4 Q. You didn't disclose that yesterday; correct?

5 A. I didn't describe that because the volume of the  
6 spray is a result of the match between the formulation and  
7 the spray device that is selected.

8 Q. No, you did not discuss that yesterday?

9 A. I did not discuss that yesterday.

10 Q. I'd now like to turn to pH.

11 According to this, your demonstrative, Flonase  
12 has a pH of 5 to 7?

13 A. That is what the label indicates, yes.

14 Q. And Astelin has a pH, the buffered pH, 6.5 to 7.1;  
15 correct?

16 A. As the range it describes, yes.

17 Q. And you did not discuss -- strike that. Excuse me.

18 There is an overlapping range between Flonase  
19 and Astelin; correct?

20 A. There is.

21 Q. And you did not discuss why a person of ordinary  
22 skill would or would not select an overlapping pH range that  
23 is overlapping between?

24 A. I believe in my answer yesterday, I described that if  
25 necessary, a formulator could go return to that range as the

1 range selected in an optimized formulation but to allow as  
2 much latitude as possible in early development, a formulator  
3 would choose as broad a change as possible, and then based  
4 on follow-up testing determine whether a broad range was  
5 appropriate or a much more narrow range was appropriate or  
6 if the system needed to be buffered.

7 Q. You didn't discuss the overlapping range between  
8 Astelin and Flonase; correct?

9 A. I thought I did, but perhaps I didn't make that  
10 clear.

11 MS. EVERETT: If we could go to DDX-5.34.

12 BY MS. EVERETT:

13 Q. And we're at DDX-5.34. And this is where you went  
14 through the elements in the art and matched them to the  
15 claim; is that correct?

16 A. That is correct.

17 Q. And I would like to focus on the thickening agents.

18 In your testimony yesterday you stated that a  
19 person of ordinary skill would consider MCC or CMC from  
20 Flonase or they would consider HPMC. Is that correct?

21 A. That's two possible thickening agents, yes.

22 Q. You didn't explain why a person of ordinary skill  
23 would not select HPMC. Correct?

24 A. No. I believe in my testimony I said since the  
25 Flonase formulation was formulated for the suspension, that

1 the HPMC for that formulator would be something they would  
2 start with.

3 Q. You did not discuss why a person of ordinary skill  
4 wouldn't select HPMC?

5 A. I think it is a default of selecting MCC and CMC.  
6 The formulator might not select HPMC but knows it is an  
7 opportunity if they were unsatisfied with the MCC-CMC  
8 results.

9 Q. Next I would like to go with the tonicity adjustment.  
10 Dextrose is contained in Flonase?

11 A. Yes, it is.

12 Q. You did not explain yesterday why a person of  
13 ordinary skill would not select dextrose?

14 A. I did not directly explain why a person of ordinary  
15 skill in the art might select any one of those agents over  
16 any other in my original testimony.

17 Q. That means also you are confirming you did not  
18 discuss why a person of ordinary skill would not select  
19 sodium chloride?

20 A. No, I did not, because I don't believe that a  
21 formulator would necessarily immediately select one of those  
22 agents for any particular reason over any of the others.

23 Q. I would like to go to DDX-5.35.

24 Excuse me. I am sorry, DDX-5.37, excuse me.

25 This is your analysis for Claim 15 of the '428

1 patent. Is that correct?

2 A. That's correct.

3 Q. In your view, you believe this patent is obvious. Is  
4 that right?

5 A. I believe that claim is obvious, yes.

6 Q. And you rely on the Flonase label?

7 A. I rely on the POSA knowledge and other information  
8 that I did discuss yesterday that there is knowledge in the  
9 art that pH's between 4 and 8 are acceptable for nasal  
10 dosage forms.

11 Q. Dr. Donovan, one of the references you are relying on  
12 for your opinion is the Flonase reference. Correct?

13 A. Well, Flonase has a pH between 5 and 7. Yes, it's  
14 between 4 and 8.

15 Q. The answer is yes?

16 A. Re-ask the question, please?

17 Q. You are relying on the Flonase label for your  
18 opinion, in part for your opinion that Claim 15 of the '428  
19 patent is obvious?

20 A. The Flonase label is one of the components that I  
21 rely on for my obvious formulation described there.

22 Q. You also rely on the Astelin label. Correct?

23 A. Correct.

24 Q. You rely on the Hettche patent?

25 A. Yes.

Donovan - cross

1 Q. You rely on the Handbook of Excipients.

2 A. Handbook of Pharmaceutical Excipients, yes.

3 Q. And you rely on the Allen textbook?

4 A. Yes.

5 Q. Those are five references?

6 A. They are.

7 Q. You needed to find five references picked through the  
8 art to find this claim obvious. Correct?

9 A. I used those as supportive evidence. But many of  
10 those have other pieces of information that I likely could  
11 have relied on, but I relied on that combination of  
12 information.

13 Q. Thank you.

14 THE COURT: Nothing further?

15 MS. EVERETT: Nothing further.

16 THE COURT: Any redirect?

17 MR. LOMBARDI: I have no further redirect, Your  
18 Honor. May I read a few exhibits?

19 THE COURT: Yes.

20 MR. LOMBARDI: There are some of the exhibits  
21 that the Doctor used that were already in evidence. I am  
22 going with those that weren't. I offer DTX-16, 62, 78, 114,  
23 and 293.

24 THE COURT: Objection?

25 MS. EVERETT: No objection.



1 THE COURT: Those are all admitted.

2 (Above-referenced exhibits received in evidence.)

3 THE COURT: Doctor, you may step down. Thank  
4 you very much.

5 (Witness excused.)

6 MR. LOMBARDI: We do rest our case.

7 May I remove the binders?

8 THE COURT: That would be helpful, yes.

9 Now to the plaintiffs.

10 MS. EVERETT: Your Honor, now that defendant has  
11 rested its case, we would like to move for judgment of  
12 partial findings under Rule 52(c).

13 THE COURT: If you intend to argue that or say  
14 anything more than that, you should come to the podium.  
15 That is up to you.

16 MS. EVERETT: In order to prove that the patents  
17 in suit are obvious, Apotex must prove by clear and  
18 convincing evidence that a person of ordinary skill in the  
19 art would not have been motivated to combine fluticasone and  
20 azelastine for a fixed-dose nasal spray for the treatment of  
21 allergic rhinitis. And defendants are attempting to do so  
22 by a myriad of references considered by the examiner  
23 rendering the burden higher. But, in fact, the overwhelming  
24 evidence from defendants' witnesses are doctors who  
25 prescribe and prefer to have the flexibility to prescribe

1     these medicines separately.

2             The scant reference to the doctors' desire for  
3     convenience is against the known prescribing practices and  
4     is wholly unsupported by any document or article that a POSA  
5     sought for the purposes of combining an antihistamine with a  
6     steroid, much less sought the convenience of doing so by  
7     combining two separate effective nasal sprays.

8             Your Honor, all defendants have shown is that if  
9     you presume the answer to an unestablished problem, in other  
10    words, if you presume a POSA was motivated to combine these  
11    two medicines into one, that the POSA would know how to pick  
12    and choose from the range of excipients to formulate the  
13    product.

14            This is insufficient as a matter of law to meet  
15    the defendants' high burden of clear and convincing  
16    evidence.

17            Therefore, for at least three reasons,  
18    plaintiffs request judgment under partial findings that the  
19    patents in suit are not obvious.

20            With respect to defendants' alternative theory,  
21    defendants did in their opening stress that it was an  
22    alternative of validity under Section 112. There has been  
23    no attempt by defendants to meet their burden of proof.

24            There has been no testimony that the POSA would  
25    not have believed the inventors were in possession or that

1 the claims were not enabled or that they were not found to  
2 be useful.

3 Therefore, defendants can't meet their burden to  
4 show by clear and convincing evidence that the patents are  
5 not sufficiently described and enabled.

6 Further, defendants have not presented any  
7 testimony under the *Wands* factors, and cannot show the  
8 patents are not enabled.

9 Therefore, plaintiffs move for partial findings  
10 that the patents in suit are not valid under Section 112.

11 THE COURT: Thank you. Do the defendants want  
12 to respond?

13 MR. LOMBARDI: Your Honor, I am happy to respond  
14 now. I am also happy to defer until closings or later in  
15 the case to respond.

16 THE COURT: I am going to reserve judgment on  
17 the motions.

18 MR. LOMBARDI: I will not respond at this  
19 moment.

20 THE COURT: If you choose not to respond now,  
21 that's fine.

22 MR. LOMBARDI: I will not respond.

23 THE COURT: I reserve judgment on plaintiffs'  
24 motion.

25 Plaintiffs may call their first witness.

D'Addio - direct

1 MS. EVERETT: Plaintiffs call Dr. Alexander  
2 D'Addio.

3 ... ALEXANDER DOMINIC D'ADDIO, having been duly  
4 sworn as a witness, was examined and testified as follows ...

5 THE COURT: You may proceed.

6 DIRECT EXAMINATION

7 BY MS. EVERETT:

8 Q. Good afternoon, Dr. D'Addio.

9 A. Good afternoon.

10 Q. Could you please state your full name for the record?

11 A. Alexander Dominic D'Addio.

12 Q. Where are you currently employed?

13 A. I am currently employed with Meda Pharmaceuticals.

14 Q. What is your current position?

15 A. I am vice president of scientific affairs and medical  
16 communications.

17 Q. Can you please describe your educational background?

18 A. Yes. I have a Bachelor's in chemistry from King  
19 university, and a Ph.D. from Seton Hall University.

20 Q. What year did you receive your Ph.D.

21 A. 1983.

22 Q. Where did you start your career?

23 A. I started working on pharmaceutical development with  
24 the American Cyanamid Company in 1984.

25 Q. When did you first join Meda?

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1 A. I joined Meda when it was Carter Wallace in October  
2 of 1990.

3 Q. Could you briefly summarize your employment history  
4 at Carter Wallace?

5 A. I started out in the research and development group  
6 at Carter Wallace. I then moved into a research service  
7 management position, where I supported manufacturing and  
8 stability. In mid-1990 I started working in Wallace  
9 Technical Services, was director of that group. We provided  
10 formulation development and analytical testing to support  
11 manufacturing new products.

12 Following that, when Wallace Laboratories was  
13 sold to MedPointe Pharmaceuticals, I was appointed as vice  
14 president of product and process development.

15 Q. How long did you hold your role as vice president of  
16 product and process development?

17 A. It was approximately ten years, from 2001 until 2011.

18 Q. Can you describe your role as vice president of  
19 product and process development?

20 A. Yes. We were responsible for formulation  
21 development, for analytical method development and testing,  
22 stability evaluation, manufacturing support, and development  
23 of documentation for support of regulatory filings for  
24 MedPointe.

25 Q. What are the products that you and your formulation

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1 team developed or evaluated?

2 A. We worked on a number of different formulations and  
3 dosage formulation. We worked on cough/cold products that  
4 are based on the tannate formulation that allows for  
5 sustained release.

6 We did some work on muscle relaxants, variations  
7 of carisoprodol. The name of the product was Soma. We also  
8 worked on Astelin, Astepro formulation, and we did  
9 feasibility evaluations of combination products of  
10 azelastine and steroids.

11 Q. You mentioned Astelin and Astepro. What was the  
12 active ingredient in those products?

13 A. The active ingredient in both of those products is  
14 azelastine hydrochloride.

15 Q. How would you rate your level of experience with  
16 azelastine?

17 A. I have a high level of experience. I worked on it  
18 for a number of years within the company.

19 Q. Do you have any patents related to azelastine?

20 A. I do. I have a couple of patents for azelastine  
21 reformulation, and for new devices for containing  
22 azelastine.

23 Q. When did you begin working with azelastine?

24 A. I started with azelastine when I joined Carter  
25 Wallace in October of 1990.

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1 Q. You testified earlier, I believe, that that group  
2 evaluated the feasibility of an azelastine-steroid  
3 combination product?

4 A. Yes.

5 Q. When did your group first investigate the combination  
6 product?

7 A. We started that evaluation in the middle of 2002.

8 Q. In 2002, what steps did your group do to investigate  
9 the feasibility of an azelastine-steroid combination?

10 A. We took a look at the scientific literature for  
11 anything that would help us with the development of an  
12 azelastine and steroid combination. We also evaluated the  
13 patent literature, and took a look to see if there were any  
14 commercial products that were available that contained  
15 azelastine and a steroid.

16 Q. What if anything did your group find helpful in the  
17 literature search?

18 A. Nothing that I recall.

19 Q. There was no guidance?

20 A. Not that I recall, no.

21 Q. So without guidance from the literature, did your  
22 group evaluate the feasibility for a combination nasal  
23 spray?

24 A. We based it on our experience with azelastine. As I  
25 said, we had several years of working with the molecule.

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1 And also, what we knew about what was available commercially  
2 for a steroid for the products.

3 Q. At the time in 2002 had MedPointe selected a  
4 particular steroid for the combination?

5 A. We had not.

6 Q. Did your group ever document your feasibility  
7 evaluation of the combination?

8 A. We did. We prepared a summary document for upper  
9 management for discussion.

10 Q. Can you please turn to PTX-1006 in your binder.

11 A. Yes, I have it. Thank you.

12 Q. Can you please describe this document for the Court?

13 A. This is an e-mail from Dr. William Wheeler dated  
14 Wednesday, October 30th, 2002. The recipient is Barbara  
15 Klein, who was one of our administrative assistants.

16 The subject of the e-mail is Lifecycle  
17 Management Astelin Projects. It has an attachment of the  
18 same name, Lifecycle Management Astelin Projects.

19 Q. Can you please turn to the attachment which starts on  
20 PTX-1006-00002?

21 A. Yes.

22 Q. Who generated the contents for this document?

23 A. This was a summary document that was used for  
24 discussion of ongoing projects with upper management. My  
25 group would have contributed to a couple of the major



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1 portions here, including packaging and formulation projects.

2 Q. I am going to ask you to turn to PTX-1006-00010.

3 A. Okay.

4 Q. This section begins "Formulation projects"?

5 A. That's correct.

6 Q. Is this what you were referring to a moment earlier  
7 as one of the sections you and your group contributed to?

8 A. That's correct.

9 Q. I would like you now to turn to PTX-1006-00011.

10 A. Yes.

11 Q. Can you describe this page for the Court?

12 A. Yes. This is the summary document that we put  
13 together from our evaluation of the feasibility of the  
14 development of an Astelin/steroid combination product.

15 Q. Did you contribute to this page?

16 A. I did. I contributed to the page and provided review  
17 of this document as well.

18 Q. Who else generated information for this page?

19 A. It would have been other people within our group,  
20 within the formulation development group, product and  
21 process development.

22 Q. You had personal input to it as well?

23 A. I did.

24 Q. I would like to focus on the section that starts  
25 Background.

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1 Can you read the first sentence for us, please?

2 A. "The technical aspects of developing this combination  
3 should be regarded as difficult."

4 Q. And "difficult" is underlined?

5 A. Yes.

6 Q. What did you mean by this sentence, "Technical  
7 aspects of developing this combination product should be  
8 regarded as difficult"?

9 A. We were communicating upward to our management group  
10 that undertaking a project like this was going to have a  
11 high level of difficulty.

12 Q. And then you list a number of issues that need to be  
13 addressed?

14 A. Yes.

15 Q. Can you identify the first issue for the Court?

16 A. Yes, the first issue, Astelin is a solution and  
17 virtually all nasal steroids are suspensions.

18 Q. What is the significance of Astelin -- what is the  
19 significant that Astelin is a solution and virtually all  
20 nasal steroids are suspensions?

21 A. So our product Astelin nasal spray contains  
22 azelastine hydrochloride, that is fully dissolved in a  
23 solution. Our concern was that trying to make a combination  
24 of Astelin with a nasal steroid would be very difficult.

25 Azelastine in Astelin is very near the

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1 solubility limit of the molecule in the true solution.  
2 Trying to combine that with a nasal suspension was  
3 determined to be difficult because we were worried about  
4 precipitation of the azelastine molecule in a combination of  
5 Astelin and a steroid.

6 Steroid suspensions, typically, there is very  
7 little water for hydration. These suspensions are designed  
8 to maintain the suspended material, the solid material. And  
9 any available water hydration is typically taken up by other  
10 excipients in the formulation.

11 Q. Was azelastine solubility known outside of MedPointe  
12 in 2002?

13 A. It was. It is listed in our package insert for  
14 Astelin nasal spray as being sparingly soluble.

15 Q. If you knew about the solubility limits of the  
16 materials you were considering, why couldn't you just design  
17 around that?

18 A. Being able to formulate like that and to modify the  
19 formulation is always a complicated issue. It's difficult  
20 to say what the impact would be of small changes in the  
21 formulation on other parts of the formulation, increasing  
22 the solubility of the azelastine could affect the properties  
23 of the suspension.

24 Q. Can you identify the second issue for the Court?

25 A. Azelastine is administered twice daily. Most

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1       steroids are administered once daily.

2       Q.       And what is the concern of this issue?

3       A.       This is relating to the dosing regimen that was known  
4       for the products at the time. Astelin nasal spray is dosed  
5       at two sprays per nostril twice daily. Most steroids at the  
6       time were dosed at either two sprays per nostril once daily  
7       or a single spray per nostril twice daily.

8       Q.       And what, what is the concern about these dosing  
9       issues?

10      A.       Well, this dosing regimen meant for us we would have  
11      to make some modifications to the product. To match the  
12      dosing regimen which is a lower number of sprays for a  
13      steroid would mean we would likely have to increase the  
14      concentration of azelastine to provide the same amount in  
15      the dosing regimen of the steroid.

16                   And increasing the concentration of azelastine,  
17      you have already talked about, azelastine is fairly  
18      insoluble. Increasing that concentration could lead to a  
19      higher likelihood of precipitation at a higher  
20      concentration.

21                   The other issue with azelastine, azelastine is a  
22      very bitter drug and was the target of some reformulation  
23      efforts that we had, and by increasing the concentration to  
24      a higher level in such product would probably lead to higher  
25      adverse events because of the bitterness perceived by the

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1 patient.

2 The steroids are a little bit different, so to  
3 try to match the azelastine dosing combination with --  
4 because it's a higher number of sprays would likely mean  
5 that we would have to reduce the concentration of the  
6 steroid and then it would be unknown what the efficacy of  
7 that product would be.

8 Q. Can you explain to the Court the last point you have?  
9 No. 3, that there may be compatibility issues between  
10 azelastine and steroids?

11 A. Yes, our concern here was related to what we knew  
12 about the manufacturing process for azelastine. As I said,  
13 it's azelastine is manufactured as a true solution. And as  
14 a true solution, it has to be dissolved carefully in the  
15 formulation.

16 Most steroid formulations, suspension  
17 formulations require very vigorous mixing in order to  
18 maintain or generate an even distribution of the suspended  
19 material. And the concern was that using that vigorous  
20 mixing process with azelastine had the potential to generate  
21 degradation or oxidation products.

22 Q. Next, I'm going to turn to -- and it is already up on  
23 the screen. The next section, Feasibility and Likelihood of  
24 Success. Can you explain what they mean?

25 A. Yes. Both of these were again an attempt to

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1 highlight with our management team what we thought the  
2 likelihood of success would be for a product like this.

3 The feasibility was more focused on the actual  
4 ability to generate a combination product, azelastine and  
5 steroid.

6 And the likelihood of success was intended more  
7 to discuss what the likelihood of success would be for the  
8 efficacy of the product, whether that combination product  
9 would actually be better than the single individual  
10 monotherapies.

11 Q. And in the background section you have written: Dose  
12 ranges of each component must also be explored and each  
13 component must considerable significantly to the overall  
14 effect, i.e., the FDA "combination rule." What does that  
15 mean?

16 A. So the FDA has issued a guidance about formulating  
17 combination products. And my understanding is that the FDA  
18 wants to make sure that the combination product needs to be  
19 significantly more effective than either one of the  
20 individual components that went into the combination  
21 product.

22 Q. And further down on PTX-1006-00011, you have costs.

23 A. Yes.

24 Q. And what were the total expected costs?

25 A. Yes.

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1 Q. The total development costs would likely be \$75 to  
2 \$100 million?

3 A. Yes, that was our estimate at the time.

4 Q. Was this information presented to the executive  
5 management team at Meda?

6 A. It was.

7 Q. How was it presented?

8 A. We had a meeting that was based on this briefing  
9 document, and the other products and projects contained  
10 within.

11 Q. Can you please turn to PTX-1005 in your binder,  
12 second tab?

13 A. I have it.

14 Q. What is this? Can you identify PTX-1005, please?

15 A. This is a photocopy of a PowerPoint presentation that  
16 was used at a meeting with upper management to discuss the  
17 Astelin lifecycle plans.

18 Q. What was the date this was presented?

19 A. This date was presented November 1st, 2002.

20 Q. Did you attend this meeting?

21 A. I did.

22 Q. If you could turn to PTX-1005-0011, please.

23 Dr. D'Addio, can you explain the date on the  
24 bottom right-hand corner of the page?

25 A. Yes. The date is September 26th, 2015. This is

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1     likely an error that was generated during document  
2     collection, likely due to an auto-date function built into  
3     the PowerPoint presentation.

4             The actual date of this presentation was  
5     November 1st, 2002.

6     Q.       And you know that because you attended the meeting?

7     A.       Correct.

8     Q.       What is being shown on page, Exhibit page 11?

9     A.       The header to this slide is Astelin/Steroid  
10    Combination.

11            This was intended just to be a bulleted overview  
12    for discussion with upper management, in conjunction with  
13    the summary document that we just discussed.

14    Q.       Based on your experience as a formulation scientist,  
15    can you sum up MedPointe's view of developing a combination  
16    azelastine steroid nasal spray in November 2002?

17    A.       Yes. As outlined in the bullets here, we felt that  
18    there would be a high degree of technical difficulty in  
19    formulating this solution with a suspension of a steroid.  
20    We had this high concern about the combination of the  
21    solution suspension. The differences in dosing was a  
22    major area of concern. And there was a fair amount of cost  
23    associated with the development of this product.

24    Q.       What action did MedPointe take on the combination  
25    product?



D'Addio - direct

1 A. So at this time, the management decided to make this  
2 a low priority project based on our other programs in place  
3 and then decided not to do too much with this going forward.

4 Q. What were the next development step MedPointe took on  
5 a combination product?

6 A. So even though it was a low priority, we still did a  
7 little bit of work to try to move forward with this. We  
8 did some work on trying to develop a device because of the  
9 concern we had about the solution and suspension combining  
10 those two and the stability of that product.

11 We tried to evaluate a device that would allow us  
12 to keep the solution and the steroid in separate containers or  
13 chambers that would maintain them and hopefully maintain the  
14 stability of them, combining them only at the point when they  
15 would be delivered to the patient in the form of a nasal  
16 spray.

17 This was termed as a dual chamber device.

18 Q. Was MedPointe ever able to find such a device?

19 A. No, we never found anything commercially available,  
20 and we did try to talk to some companies about the  
21 development of such a device but were unsuccessful.

22 Q. After MedPointe was unable to find a suitable device,  
23 how did your product and process group proceed?

24 A. We were then asked again by our management to try to  
25 determine if we could manufacture a formulation. So we came

D'Addio - direct

1 up with some plans that we thought would be paths forward  
2 for the formulation of the combination program.

3 Q. What year was this?

4 A. This was in March of 2006.

5 Q. Did your assessment change as to the feasibility of  
6 the formulation, a combination nasal spray product from 2002  
7 to 2006?

8 A. No, it did not. I still thought this was going to  
9 be a difficult program.

10 Q. Then why did you proceed?

11 A. It was at the request of management.

12 Q. How did your group approach the formulation this  
13 time?

14 A. Again, knowing what we did about azelastine and other  
15 steroid formulations, we tried to develop a plan that would  
16 given us a couple of options and we put that plan together  
17 for discussion with management.

18 Q. Who in your group was responsible for developing this  
19 plan?

20 A. The plan was put together by our formulation  
21 development group that was headed up by Gul Balwani and  
22 assisted by Dr. Kalidas Kale.

23 Q. What kind of formulation did Dr. Kale have in 2006?

24 A. Yes, Dr. Kale had worked in many years for  
25 formulation development in a number of different dosage

D'Addio - direct

1 forms. I think he had something like 15 to 20 years of  
2 experience at that point. He had a long career with  
3 Schering Plough working on formulation and I believe some  
4 nasal steroid formulations as well.

5 Q. You refer to him as Dr. Kale. Does he have a Ph.D.?

6 A. Yes.

7 Q. What kind of formulation experience does Gul Balwani  
8 have?

9 A. At the time, Gul had a similar background,  
10 approximately 15 to 20 years of experience. Gul had worked  
11 on a number of different dosage forms including solids,  
12 oral, oral suspensions, had worked with early on the  
13 azelastine nasal spray. Gul actually has a fair experience  
14 with Astelin and Astepro. He was leading the development of  
15 Astepro, the reformulated product that was developed for  
16 taste management product and was listed as one of the  
17 inventors on the Astepro product.

18 Q. Just to be clear on the time frame, this is the  
19 amount of experience Mr. Gul Balwani had when he had created  
20 the feasibility plan we discussed?

21 A. Yes.

22 Q. Let's turn to PTX-0151, which I believe is the third  
23 tap in your binder.

24 A. Yes.

25 Q. Can you identify PTX-0151.

D'Addio - direct

1 A. Yes. This is an e-mail dated from Dr. Kale dated  
2 March 21, 2006. This was sent to me and copied, Gul  
3 Balwani.

4 The subject of the mail is Astelin/Flonase  
5 Combination Product Feasibility Assessment Plan. And it had  
6 an attachment by the same name, Astelin Flonase Combination  
7 Product Feasibility Assessment Plan.

8 Q. Can you turn to the attachment which starts on  
9 PTX-0151-00002?

10 A. Yes.

11 Q. Is this a feasibility plan you were just speaking of  
12 a moment ago?

13 A. This is.

14 Q. Can you explain Plan A?

15 A. Yes. Plan A that is included in this feasibility  
16 assessment was an attempt to take a fluticasone propionate  
17 nasal spray, isolate the solid and then determine the  
18 solubility of azelastine in that solution.

19 Q. Can you turn to PTX-0151-0003, please?

20 A. Yes.

21 Q. And describe Plan A for the Court?

22 A. Plan B.

23 Q. Yes, Plan B. Can you describe Plan B for the Court?

24 A. The Plan B was to identify a water soluble  
25 corticosteroid compatible with azelastine hydrochloride.

D'Addio - direct

1 Q. If Meda had gone forward with Plan B, would you have  
2 ended up with an azelastine hydrochloride combination nasal  
3 spray?

4 MR. LOMBARDI: Objection. This is a fact  
5 witness and I think that is going beyond what factually  
6 actually happened. We have to establish a foundation to be  
7 more specific that they actually tried Plan B.

8 THE COURT: Do you want to respond?

9 MS. EVERETT: I can rephrase the question.

10 THE COURT: Why don't you rephrase the question.

11 BY MS. EVERETT:

12 Q. Dr. D'Addio, in Plan B, you say you are going to  
13 identify a water soluble corticosteroid; is that accurate?

14 A. Yes.

15 Q. Is fluticasone a water soluble corticosteroid?

16 A. No, it is not.

17 Q. Can you describe Plan C for the Court?

18 A. Yes. In Plan C, we were going to try to make a true  
19 solution of fluticasone/azelastine by the use of solubility  
20 enhancement agents.

21 Q. Which plan did your group move forward with?

22 A. We went ahead with Plan A.

23 Q. Why did you move forward with Plan A?

24 A. We believed that that would be the most effective way  
25 to get to a final product with azelastine and fluticasone

D'Addio - direct

1 propionate.

2 Q. Does that mean you expected Plan A to succeed?

3 A. We weren't sure. But we thought that was the most  
4 direct route for formulation development.

5 Q. Did you move forward to Plans B or C?

6 A. We did not.

7 Q. Why not?

8 A. These would be very complex programs, trying to come  
9 up with a formulation that would be acceptable for nasal  
10 delivery.

11 Q. Are what was MedPointe's next step once it decided to  
12 move forward with Plan A?

13 A. Actually, we developed plans that went into the  
14 laboratory to do some of these experiments listed in Plan A.

15 Q. Were there records of these experiments?

16 A. There were.

17 Q. Dr. D'Addio, could you turn to Tab 5 in your binder,  
18 PTX-0142?

19 A. I have it.

20 Q. Can you identify PTX-0142?

21 A. Yes. This is a photocopy of a part of one of our  
22 laboratory notebooks that we used within MedPointe.

23 Q. Who was this notebook issued to?

24 A. It's on the inside cover. The notebook was issued to  
25 John D'Aconti.

D'Addio - direct

1 Q. Who was John D'Aconti?

2 A. John was one of the formulators who worked within our  
3 formulation group, that worked in our product and process  
4 development.

5 Q. What was John's experience?

6 A. John had been with us for three or four years at this  
7 point and had worked on a number of formulation products,  
8 including Astelin and Astepro.

9 Q. I would like you to turn to PTX-0142-00017, please.

10 A. Yes.

11 Q. If you can turn to the left-hand side of the page,  
12 which is the Lab Notebook Page 114. Is this a record of  
13 MedPointe's attempt of trying Plan A?

14 A. This is the beginning. This is actually a screening  
15 experiment that we performed. The purpose of this  
16 experiment was to take a sample of a fluticasone propionate  
17 spray and add an aliquot of azelastine hydrochloride  
18 directly to the formulation for visual observation to see  
19 what the impact would be by adding azelastine hydrochloride  
20 directly to the sample.

21 Q. Can you read the last sentence on Lab Notebook Page  
22 114, which has the Exhibit No. PTX-0142-17?

23 A. Yes. The last statement is, "Final sample appears to  
24 be uniform, with no precip," that is short for  
25 precipitation.

D'Addio - direct

1 Q. At this point did Meda believe it had arrived at a  
2 feasible formulation for a combination  
3 azelastine/fluticasone nasal spray?

4 A. No. As I mentioned, this was just a screening  
5 experiment to see what would happened if we added azelastine  
6 directly to the formulation. We had really know idea what  
7 the characteristics were of this formulation. We didn't  
8 know if the Astelin had dissolved or remained as a solid  
9 material in there. There would be a significant amount of  
10 work to characterize this as a final formulation.

11 Q. Can you turn to the next page, PTX-014200018, which  
12 corresponds to Lab Notebook Page 116. The initial one may  
13 have been cut off on the lab notebook page?

14 A. I have it.

15 Q. Can you walk us through the next set of experiments?

16 A. Yes. This is John's first attempt to take a sample  
17 of fluticasone propionate nasal spray, stripping it to  
18 remove most of the solids from the formulation. Following  
19 the decanting of that liquid, he passed that through a  
20 series of filters of varying sizes until in the end he  
21 passed it through a final .45-micron filter.

22 Q. What were Mr. D'Aconti's next steps?

23 A. So John records in this notebook that at that point  
24 he had collected about 3 ml's of the sample through the  
25 filter. And that sample appeared to be a clear solution at



D'Addio - direct

1 this point. Unfortunately, during the manipulation of that  
2 sample, that sample was spilt and lost.

3 Q. What was Mr. D'Aconti's next step? I believe you  
4 might be turning, for the record, to Lab Notebook Page 117.

5 A. Yes. This is a record of the next stage. He went  
6 back into the laboratory, basically repeating the experiment  
7 he had done the day before, again, centrifuging a sample of  
8 the nasal spray followed by a series of filtration steps to  
9 obtain a solution at the end of obtaining the -- passing it  
10 through the filters.

11 Once he had that sample, John added an aliquot  
12 of azelastine hydrochloride and attempted to dissolve the  
13 azelastine in that solution.

14 He mixed it initially and then mixed overnight,  
15 he reports in here, after mixing overnight, he noted that a  
16 major portion of the azelastine had not gone into solution.

17 Q. And you are at the bottom of the lab notebook, Page  
18 117, of the lab notebook, and it has the Exhibit No.  
19 PTX-0142-0018?

20 A. Yes.

21 Q. As of April 2016, what kind of formulation experience  
22 did Mr. D'Aconti have with azelastine?

23 A. John had been working with azelastine and  
24 azelastine-containing compounds three or four years he had  
25 been with us.

D'Addio - direct

1 Q. Do you have any reason to doubt his observations in  
2 the lab notebook?

3 A. No.

4 Q. Can you continue? I think we have moved to Lab  
5 Notebook Page 118, which is on PTX-0142-00019.

6 A. I have it.

7 Q. What was Mr. D'Aconti's next steps in these  
8 experiments?

9 A. So John took the sample that he was trying dissolve  
10 the azelastine hydrochloride in. Then he performed a series  
11 of heating experiments, heating and mixing, to try to  
12 further dissolve the azelastine hydrochloride in that sample  
13 solution.

14 His initial attempt, it looks like he was able  
15 to partially dissolve some of the azelastine going from the  
16 undissolved drug to a translucent formulation. However,  
17 after on standing, that solution became a white opaque  
18 sample.

19 So John tried to dissolve it again, again by  
20 applying heat and mixing. But he was unable to change it at  
21 that point. It remained white and opaque.

22 John notes that on standing, this was the  
23 following morning, he observed that some of the solid had  
24 precipitated, what was the white opaque, some material had  
25 precipitated out of that sample.

D'Addio - direct

1 Q. That is recorded on the Lab Notebook Page 118,  
2 Exhibit PTX-1042-0019?

3 A. That's correct.

4 Q. From your perspective, as a formulation scientist,  
5 how do you interpret these results?

6 A. Well, the goal of the experiment was to isolate a  
7 solution from fluticasone propionate nasal spray and then to  
8 attempt to dissolve azelastine hydrochloride in that  
9 solution.

10 We were unable to dissolve the azelastine and  
11 ended up with a precipitate when we tried to heat it.

12 To me, this was a failed experiment. We were  
13 unable to dissolve azelastine in a solution obtained from  
14 fluticasone nasal spray.

15 Q. And you call this a failed experiment even though it  
16 was only a few days long?

17 A. Yes. It did not attain the goal of the experiment.

18 Q. Were these results ever reported to the executive  
19 management at MedPointe?

20 A. They were.

21 Q. At this point in 2006, did MedPointe want to  
22 successfully complete the contemplated formulation?

23 A. Yes, it would have been important to business.

24 Q. Was MedPointe ever able to manufacture a successful  
25 azelastine and fluticasone nasal combination product?

D'Addio - direct

1 A. Only after we had been able to identify Cipla's  
2 patents Cipla had drafted regarding combination nasal sprays  
3 and their product Duonase.

4 Q. Duonase is an azelastine-fluticasone product from  
5 India?

6 A. That's correct. It's a combination of azelastine  
7 hydrochloride and fluticasone propionate.

8 Q. At what point did you find Cipla's application and  
9 the Duonase product?

10 A. That was in, I believe it was a couple months later  
11 in May of 2006.

12 Q. What was your reaction upon the Cipla patent  
13 application and the Duonase product?

14 A. I was surprised that somebody had successfully  
15 developed a product like this. I wasn't sure what the  
16 product was. But the fact they had manufactured a product  
17 was a surprise to me.

18 Q. What did MedPointe do after finding Cipla's patent  
19 applications?

20 A. We started to develop licensing agreements with Cipla  
21 that would let us access the product for development, for  
22 distribution in the U.S. market.

23 Q. Do you know Dennis Fuge?

24 A. I do.

25 Q. Who is Dennis Fuge?

D'Addio - direct

1 A. That is the vice president of supply chain and  
2 operations for Meda.

3 Q. Is he a lawyer?

4 A. No.

5 Q. Does he have any experience in the treatment of  
6 allergic rhinitis?

7 A. Not that I know of.

8 Q. Is he a physician?

9 A. No.

10 Q. Does he have any formulation experience with nasal  
11 dosage forms?

12 A. Not that I know of.

13 Q. What were his responsibilities -- what are his  
14 responsibilities at Meda?

15 A. Dennis is primarily responsible for manufacturing and  
16 shipping of our product to our suppliers. He also works in  
17 project management and business development for the company.

18 Q. Did he work on Cipla license negotiations?

19 A. I believe he did.

20 Q. Was he in favor of licensing the patents from Cipla?

21 A. Yes.

22 Q. In your experience, would MedPointe license patent or  
23 patent applications they thought were invalid or  
24 unpatentable?

25 A. No.

D'Addio - direct

1 Q. How important were these patent applications to the  
2 license agreement?

3 A. Important. We wanted to make sure we would have some  
4 protection before we embarked into a significant development  
5 program to put together a combination product for the U.S.

6 Q. After MedPointe licensed the patent, what subsequent  
7 development steps did it take to formulate a fixed dose  
8 azelastine-fluticasone combination nasal spray?

9 A. So using the Duonase product, we worked with Cipla to  
10 finalize the manufacturing process for this product.  
11 Eventually, we were able to manufacture the product that was  
12 suitable for clinical studies.

13 Then we used the data obtained for those  
14 clinical studies to develop an NDA for the eventual approval  
15 for the Dymista product in the U.S.

16 Q. Are you aware of Medpointe's communications with the  
17 FDA regarding the Dymista product?

18 A. Yes.

19 Q. How are you aware of these communications between FDA  
20 and MedPointe?

21 A. Summaries are usually provided to the company through  
22 our regulatory affairs group.

23 Q. Are you aware that Meda went to FDA to understand  
24 FDA's position as to a combination azelastine-fluticasone  
25 therapy?

D'Addio - direct

1 A. Yes.

2 Q. Are you aware of FDA's view of such a combination  
3 product?

4 MR. LOMBARDI: I will object to, essentially she  
5 is asking for hearsay testimony here. She is asking for  
6 what the FDA said apparently in meetings he heard about.

7 THE COURT: Are you asking for hearsay?

8 MS. EVERETT: Dr. D'Addio has a basis for  
9 knowing what FDA views and their views are he was involved  
10 in the discussions, and he has his interpretation, he is  
11 going give his interpretation of those views.

12 THE COURT: Are you going ask him recite the  
13 words FDA said or was told the FDA said?

14 MS. EVERETT: No. I am going to ask for his  
15 understanding of what FDA has said.

16 THE COURT: Do you still have an objection?

17 MR. LOMBARDI: I do. I don't think asking for  
18 an understanding removes the objection. His basis is still  
19 hearsay.

20 I believe there are experts that are going to  
21 testify about the FDA issue here. But I do object to this  
22 witness relating this kind of testimony.

23 THE COURT: All right. Well, on counsel's  
24 representation, I'm going to overrule the objection. We'll  
25 see where the question goes.

D'Addio - direct

1 BY MS. EVERETT:

2 Q. Are you aware of FDA's view of a combination product?

3 A. So I know they were very concerned about the  
4 development of a combination product.

5 Some of their concerns were that the patient  
6 would not know, in such a combination product, would not  
7 know when they needed both the fluticasone and the  
8 azelastine and when they would need to switch off to just  
9 one of the monotherapies.

10 They also had a major concern about whether or  
11 not this formulation would be able to pass the combination  
12 rule, demonstrating the efficacy of that combination would  
13 be significantly better than either one of the monotherapies.

14 Q. Did MedPointe conduct any studies comparing Dymista  
15 to the monotherapies?

16 A. We did. We did an initial clinical study that  
17 compared Dymista to commercial products that were available,  
18 azelastine and fluticasone containing nasal sprays as  
19 monotherapies.

20 We also did our clinical study program support  
21 in support of the FDA which was with Dymista and monotherapy  
22 products that were developed solely for the clinical studies  
23 required by the FDA.

24 Q. What is your understanding how Dymista performed  
25 compared to the comparators?



D'Addio - direct

1 A. In all the studies, Dymista was demonstrated to be  
2 significantly better than any one of the monotherapies,  
3 either commercial or the experimental monotherapies.

4 The results that we have for the commercial  
5 products were quite surprising and much better than the  
6 therapies used in the monotherapy.

7 Q. And eventually FDA approved Dymista?

8 A. Yes. Dymista was, the NDA was submitted and approved  
9 by the FDA. I believe it was late in 2012.

10 MS. EVERETT: No further questions.

11 Your Honor, I'd like to move into evidence  
12 PTX-1006, PTX-1005, PTX-0151, PTX-01 -- excuse me.  
13 PTX-0142.

14 THE COURT: Any objection.

15 MR. LOMBARDI: No objection, Your Honor.

16 (Above-referenced exhibits admitted in evidence.)

17 THE COURT: All right. We are going to take a  
18 break. I have been advised moments ago that my jury may  
19 have a verdict. So I anticipated if that is correct that I  
20 will be busy for at least the next half hour. So you are  
21 certainly free until 4:30. If it turns out to take me  
22 significantly longer than that, we'll let you know. But we  
23 will be in a recess.

24 (Brief recess taken.)

25 \* \* \*

D'Addio - cross

1 (Proceedings reconvened after recess.)

2 THE COURT: Have a seat. As you may or may not  
3 know, we have a verdict we have a verdict in the trial  
4 upstairs. So we are done with that trial. For the time  
5 being, I am all yours. We will go till 7 tonight and we  
6 will talk about tomorrow before we break tonight. Why don't  
7 we pick up where we left off.

8 MR. LOMBARDI: We have some cross, Your Honor.

9 CROSS-EXAMINATION

10 BY MR. LOMBARDI:

11 Q. Good afternoon, Dr. D'Addio. My name is George  
12 Lombardi. We have not met, is that right?

13 A. That's correct, we have not.

14 Q. Doctor, I just want to talk a little bit about some  
15 of the things you talked about today. Not everything. But  
16 a few of the things you talked about. At first, you talked  
17 about some discussions in 2002. At that time it was  
18 MedPointe. Is that correct.

19 A. Yes.

20 Q. And became Meda at some later point in time?

21 A. That's correct.

22 Q. There were some discussions at MedPointe about doing  
23 a combination product. Is that right?

24 A. Yes.

25 Q. So at that point in time you had the idea, you

D'Addio - cross

1 meaning MedPointe, had the idea to use azelastine and a  
2 steroid in a combination product together. Is that right?

3 A. That was the direction that we had gotten from our  
4 management group, correct.

5 Q. And at that point in time, it made sense to you to do  
6 something like that, if it was technically feasible, it made  
7 sense to put azelastine and a steroid together. Isn't that  
8 true?

9 A. Azelastine was a molecule that we had a lot of  
10 experience with, again, that was with direction from our  
11 management.

12 Q. Well, did it make sense, because there were two  
13 different drugs that can be used to treat the same  
14 condition?

15 A. I don't know why you would -- I am not sure that I  
16 can answer that.

17 Q. Okay. At some point in time, Doctor, did you become  
18 aware that Astelin and Flonase were taken conjunctively by  
19 patients?

20 A. We found that out at some point. I don't know when  
21 that was.

22 Q. And when you found out that Astelin and Flonase were  
23 taken together conjunctively by patients, that made sense to  
24 you, didn't it?

25 A. I can't really speak to the clinical aspect of that.

D'Addio - cross

1 Q. Well, they are two different drugs. Right?

2 A. They are.

3 Q. And they have two different mechanisms of action.

4 Right?

5 A. I believe so.

6 Q. And it made sense to you personally to use two  
7 different drugs with two different mechanisms of action to  
8 treat a condition like allergic rhinitis. Isn't that true?

9 A. I suppose.

10 Q. Is it true, sir?

11 A. I can't say for sure. I am a chemist.

12 Q. But from your personal point of view, is it true?

13 A. My personal point of view, is it true --

14 Q. It makes sense to combine the two.

15 A. I think -- I guess it makes sense.

16 Q. Well, if there is any question, we can look at your  
17 deposition. Let's go to, I think you should have two  
18 depositions in there, Doctor. It should be the one that's  
19 dated 4th of 2016.

20 THE COURT: In the binder you handed him.

21 MR. LOMBARDI: Yes.

22 BY MR. LOMBARDI:

23 Q. If you have that?

24 A. Correct.

25 Q. Look at Page 86, if you would, please?

D'Addio - cross

1 I am looking at, starting at Line 12, Page 86,  
2 were you asked this question and did you give this answer at  
3 your deposition under oath:

4 "And there's some benefits to using two drugs  
5 that have different mechanisms of action to treat the same  
6 problem, right?

7 "Answer: It makes sense that you would use two  
8 different drugs with different mechanisms of action."

9 Did you give that answer to that question under  
10 oath at your deposition?

11 A. Yes.

12 Q. Now, Doctor, at the time in 2002 that MedPointe had  
13 this idea, you didn't do any testing at that point in time.  
14 Is that correct?

15 A. No, not that I recall.

16 Q. And no experiments of any kind?

17 A. No.

18 Q. And there was no failure of any kind at that point in  
19 time?

20 A. No. We just made an assessment of what it would take  
21 to formulate the product.

22 Q. Can we go to the Elmo, please.

23 Pardon me in advance for my handwriting. I am  
24 going to write down here "No testing." That was accurate at  
25 that point in time. Correct?

1 A. Yes.

2 Q. And your discussions that you related about the  
3 concerns that scientists at MedPointe had about this  
4 formulation, those were not publicized in 2002. Is that  
5 right?

6 A. That's correct.

7 Q. You didn't publish an article talking about the  
8 problems that you thought you had with the formulation of a  
9 compound like this?

10 A. No. I think those would have been confidential  
11 discussions within the company.

12 Q. On the right "Not public."

13 You did tell us, and I am losing the Elmo there,  
14 that goes through 2006, Doctor, if it is not clear to you.

15 You said that there was some work that continued  
16 with the idea of this combination product throughout the  
17 period 2002 to 2006, but -- I don't want to mischaracterize,  
18 but it sounded like it was discussions that didn't actually  
19 translate into doing anything like that until you got to  
20 2006. Is that fair?

21 A. I think I testified that it was a lower priority  
22 project based on other resources and other projects. There  
23 was not a lot of work done during that period.

24 Q. Certainly no formulation of a combination product  
25 during that period. Correct?

D'Addio - cross

1 A. Not that I recall, correct.

2 Q. And no testing during that period of time?

3 A. Not that I recall.

4 Q. And that's true all the way through to 2006. Is that  
5 right?

6 A. Yes.

7 Q. And then you told us about some testing that was done  
8 in 2006. Correct?

9 A. Yes.

10 Q. And there were some e-mail discussions before the  
11 testing actually began, talking about the way to go about  
12 testing of a potential azelastine hydrochloride and  
13 fluticasone product. Isn't that's right?

14 A. Which e-mails in particular?

15 Q. I am asking you generally, weren't there e-mails that  
16 were talking about the best way to go about testing?

17 A. We had developed a feasibility plan that we talked  
18 about earlier, the feasibility plan had a couple of options  
19 to pursue the combination product.

20 Q. And that was the exhibit you put on the screen, the  
21 plan. Correct?

22 A. That was the feasibility plan, correct.

23 Q. Let's cut to PTX-150. It should be in your binder.

24 If not, I am going to have it up on the screen for you.

25 Whichever you prefer. I will blow things up. I can see you

1 are squinting. This.

2 Is the?

3 A. Did you say PTX-or DTX?

4 Q. PTX.

5 A. I have it, thank you.

6 Q. Then at the very top, to identify the document, this  
7 is an e-mail where you are the recipient. Is that right?

8 A. Correct.

9 Q. That is February 6 of 2006?

10 A. Yes.

11 Q. That is before the testing that you testified had  
12 actually taken place. Is that right?

13 A. That's correct.

14 Q. Can you confirm for me for the record that this is an  
15 e-mail that is a chain of e-mails with the most recent  
16 e-mail at the top of the page and then there are earlier  
17 e-mails as you go down the page. That is the general  
18 format?

19 A. Yes.

20 Q. All right. Then if you go on the back page, there is  
21 an e-mail from Dennis Fuge dated January 30th of 2006. Do  
22 you see that one? I have put it up on the screen if that is  
23 easier for you, Doctor.

24 A. I see that.

25 Q. It should be on your screen in front of you if the



D'Addio - cross

1 screen is too far to see.

2 A. Thank you.

3 Q. Do you see that?

4 A. Yes.

5 Q. And this is in the chain that you were copied on.

6 Correct?

7 A. I was not addressed in that e-mail. But it is in the  
8 chain, yes.

9 Q. It is from Dennis Fuge, you have identified Dennis  
10 Fuge, it's to Richard, did you say Spivey?

11 A. Yes.

12 Q. It says, "As discussed, there are likely to be a  
13 number of easier formulation options for the steroid  
14 combo" -- would you understand that to be intended to be  
15 "combo" there in that azelastine-steroid combination  
16 product?

17 A. Yes.

18 Q. " -- for the steroid combo product than going the  
19 dual device chamber route."

20 There was some consideration of dual device  
21 chamber during that 2002 to 2006 time frame. Correct?

22 A. Correct.

23 Q. But he is suggesting there is an easier way to go  
24 about it than that. Right?

25 A. That is what he is writing in this e-mail. Correct.

D'Addio - cross

1 Q. Then he says, "Can we turn Gul loose to do work on  
2 whether one of the existing steroid suspensions or solutions  
3 would accept the solution of azelastine the addition of  
4 azelastine and be stable."

5 Do you see that?

6 A. I do.

7 Q. Gul is one of the people we talked about before, he  
8 is one of the people who works on formulation at MedPointe.  
9 Is that correct?

10 A. That's correct. He says, "I am not looking at a full  
11 development effort, just something small to confirm  
12 conceptually whether we are going to face major formulation  
13 issues or whether an existing formulation could be the  
14 starting point."

15 Do you see that?

16 A. I do.

17 Q. And what was decided, and you were in on this  
18 decision, was that it made sense to go with this easier,  
19 smaller development effort that is suggested in this e-mail.  
20 Isn't that right?

21 A. That was Dennis's opinion of the plan.

22 Q. And you agreed with that, didn't you?

23 A. Where was that?

24 Q. Let's go to PTX-149. It should be in binder.

25 A. Yes.

D'Addio - cross

1 Q. Do you see, we have got that on the screen as well, I  
2 am going identify for the record at the top, Doctor, do you  
3 see, am I saying this right, Edick Paul?

4 A. Paul Edick.

5 Q. I am sorry. It is to Dennis Fuge, copying yourself.  
6 Do you see that?

7 A. Yes.

8 Q. This is actually dated the same date February 6, but  
9 a little bit later in the day. Do you see that?

10 A. I do.

11 Q. Let's go down to --

12 A. I am sorry. You said 150.

13 Q. This is 149 you are looking at right now?

14 A. 150 was later in the day.

15 Q. I guess it depends on which e-mail we are looking at.  
16 Let me show you this one and see if we can clarify looking  
17 at this one.

18 Let's go to the second message down there. This  
19 one says, it's Monday, February 6 at 5:57 p.m., do you see  
20 that?

21 A. Yes.

22 Q. You are copied on it, do you see that?

23 A. Yes.

24 Q. In the last paragraph of the note, that is what I am  
25 going to read to you, it says, "Rich, Alex and I have

D'Addio - cross

1 discussed the combo product and we all feel the shortest  
2 development route would be either a simple solution or a  
3 suspension, depending on the steroid used."

4 Does that refresh your recollection that you  
5 agreed with the course set out in what we just looked at as  
6 PTX-150?

7 A. So this is a relative statement, relative to the  
8 development of a dual chamber device, this isn't stating  
9 that it's an easy program, just that it was going to be easy  
10 relative to developing a dual chamber device.

11 Q. My only question, Doctor, is did you agree, as you  
12 suggest, that you felt the shortest development route would  
13 be a simple solution or suspension?

14 A. That was our opinion at the time relative to the  
15 development of the dual chamber device.

16 Q. And it was shortly after this time that you embarked  
17 on this shortest development -- it says shortest development  
18 route. Right?

19 A. We believed that was going to be shorter than  
20 developing the dual chamber device, correct.

21 Q. You embarked on that process, and that's the testing  
22 that you described for us earlier. Correct?

23 A. That was the feasibility plan that he put together,  
24 as we mentioned before, was to assess the development of a  
25 suspension, a solution, or a water-soluble steroid, correct.

D'Addio - cross

1 Q. All right. Now, I want to talk to you a little bit  
2 the testing just briefly about the testing that you already,  
3 you went through some lab notebooks earlier; correct?

4 A. Yes.

5 Q. And that is the only testing that you know of that  
6 was done by Med -- was it MedPointe at that point in time;  
7 2006?

8 A. It was MedPointe at that point in time.

9 Q. That MedPointe, that was the only testing that  
10 MedPointe had done in 2006 were those pages of that lab  
11 notebook that you talked about earlier; is that right?

12 A. That's correct.

13 Q. All right. So let's talk about that.

14 So can we go to the Elmo quickly, please?

15 So that was in late April of 2006; correct?

16 A. Sorry.

17 Q. The testing. The testing that you reviewed earlier  
18 today took place in?

19 A. Yes, that was in April. That's correct.

20 Q. And do you remember the first day, was it April 24th?

21 A. I believe that is correct.

22 Q. All right. So I'll put here -- and what was the last  
23 day of work that you were able to find on this project?

24 A. In that series of experiments?

25 Q. Yes.

D'Addio - cross

1 A. It was three or four days later.

2 Q. So I'll put April 28th and the document will be our  
3 guide. Is that fair, Doctor?

4 A. Okay.

5 Q. All right. Now, the testing that was actually done  
6 during that period, you called it experiments I think,  
7 didn't you?

8 A. In the notebook, I did.

9 Q. So this wasn't a situation where anybody at MedPointe  
10 put together a formulation and tried to see if they could  
11 actually put together a formulation of azelastine and  
12 fluticasone; right? That is not what happened.

13 A. No, I think what we tried to do there was to perform  
14 a feasibility experiment to see if we could dissolve  
15 azelastine in the supernatant. That was the experiment.

16 Q. Right.

17 A. And --

18 Q. Go ahead, please finish.

19 A. If we were successful in doing that, then the goal  
20 would be to then formulate it with fluticasone as well.

21 Q. Okay. And I just wanted to clarify because you had a  
22 "no" in there and it might have been the way I worded the  
23 question. But there was a not an experiment where you  
24 actually formulated an azelastine and fluticasone product  
25 in this April 24th to 28th time frame; correct?

D'Addio - cross

1 A. This was a feasibility only of the solubility of  
2 azelastine, correct.

3 Q. Okay. And so the feasibility studies that you did,  
4 the first thing that -- it wasn't you personally, correct?,  
5 that did the work. You didn't?

6 A. I did not do the work, no.

7 Q. The first thing that was done was somebody bought  
8 some Flonase and just put azelastine into it. Is that  
9 right?

10 A. That was the first experiment.

11 Q. And you couldn't -- and you couldn't tell what  
12 actually happened when you did that experiment because  
13 Flonase is a suspension and you couldn't see what happened  
14 to the azelastine; correct?

15 A. It's a fairly opaque material, and it would be very  
16 difficult to be able to see what happened to the azelastine  
17 when it was added. What we did find out was that there was  
18 no gross changes in the formulation with the addition of the  
19 azelastine.

20 Q. Okay. And, yes, and you read the comment and said  
21 I think content appeared to be uniform and there was no  
22 precipitate observed, words to that effect; is that right,  
23 Doctor?

24 A. Right.

25 Q. So you then, you couldn't tell what the results were,

1 correct? For that first experiment?

2 A. I'm sorry. The result was that we didn't see any  
3 gross changes in the formulation. We couldn't identify  
4 the fate of the formulation of the azelastine in the  
5 formulation.

6 Q. Thank you. That clarifies for me. Then you moved to  
7 a second type of experiment; correct?

8 A. Yes.

9 Q. And that experiment was you had this Flonase and  
10 you decided, well, we'll take the fluticasone out of the  
11 Flonase. That was one step; correct?

12 A. Correct.

13 Q. And then you said, well, we'll put the azelastine  
14 hydrochloride in with the remainder of the Flonase  
15 formulation; is that right?

16 A. That's correct.

17 Q. So this was not a formulation that had azelastine  
18 hydrochloride and fluticasone both in it; is that right?

19 A. Not at that point, no.

20 Q. And you had some, there were some problems with  
21 centrifuging and spilling a sample and that took some time,  
22 correct?, to work through those problems?

23 A. Yes.

24 Q. And then YOU described, they did do an experiment and  
25 they ran a mixer overnight; is that right?



1 A. They tried stirring azelastine in the liquid that was  
2 obtained, correct.

3 Q. And at some point, they stopped and they had decided,  
4 well, what we need to do is analyze this sample to see what  
5 has happened to the azelastine. That is what happened  
6 according to the experimenters; is that right?

7 A. So I don't know that that is exactly the sequence. I  
8 think after the stirring, then we tried the heating experiment.

9 Q. Okay. And then you tried, the experimenters thought  
10 we ought to send this to an analytical group to study this  
11 sample; correct?

12 A. I believe that is recorded in the notebook.

13 Q. But what isn't reported is anything further that was  
14 done; correct?

15 A. I think there is another page of experiments in the  
16 notebook.

17 Q. Well, that analytical report was never completed as  
18 best you can tell; correct?

19 A. I don't know. Right.

20 Q. All right. And you don't know of any solubility  
21 enhancement technologies that were used on this sample; is  
22 that correct?

23 A. No, the only thing that was done to dissolve the  
24 azelastine was to stir it, and then we tried some heating  
25 experiments.

1           As you mentioned, we did take that sample at  
2           that point, after we observed the precipitate, and it does  
3           mention in there about sending it out for analysis, but the  
4           end result of that experiment was that we were not able to  
5           obtain a true solution of azelastine in the filtrate that  
6           we obtained from the Flonase. That was the goal of the  
7           experiment.

8           Q.       Okay. And you did not add excipients to the sample  
9           to try to promote solubility; correct?

10          A.       Not in this experiment, no.

11          Q.       No co-solvents were used in this experiment; is that  
12          correct?

13          A.       No.

14          Q.       Other than the heating process, nobody did anything  
15          to try to improve the stability of the sample; is that  
16          correct? Or the solubility of the sample. I apologize.

17          A.       That is correct. The background around that is that  
18          we knew that the Flonase formulation was a stable and  
19          commercially viable formulation, and we felt it would  
20          simplify our development effort if we could simply dissolve  
21          the azelastine in the formulation.

22          Q.       So to confirm, we talked about those are the two  
23          types of experiments that you are aware of that were done at  
24          MedPointe at this point in time; correct?

25          A.       Prior to the Cipla?

1 Q. Yes.

2 A. Yes.

3 Q. And none of them involved making a formulation that  
4 had azelastine and fluticasone together; is that right?

5 A. Except for that first experiment where we added it  
6 directly to the Flonase.

7 Q. Okay.

8 A. That was a combination of azelastine hydrochloride  
9 and fluticasone propionate.

10 Q. And it was very shortly after this April 24th to 28th  
11 time period that you found out about Cipla's patent  
12 application; is that right?

13 A. It was a couple of months later.

14 Q. Wasn't it actually May?

15 A. I believe so. I don't recall exactly.

16 Q. Well, I believe you have a declaration that you  
17 prepared in this case in your notebook up there.

18 A. Um-hmm.

19 Q. Are you able to find that? It is the very first  
20 thing in the notebook. Do you have that?

21 A. I do.

22 Q. And that was, for the record -- do we have an exhibit  
23 number?

24 This is for the record, DTX-288. Do you see  
25 that on the first page, Doctor?

D'Addio - cross

1 A. Yes.

2 Q. And it says, it's the confidential declaration of  
3 Alexander D. D'Addio. Do you see that?

4 A. I do.

5 Q. And this is a declaration that you completed in this  
6 case and you actually did it under oath; is that right?

7 A. Yes.

8 Q. And let's go to paragraph 26, just to refresh your  
9 recollection of the timing here.

10 A. Yes.

11 Q. And it says: Shortly thereafter, in May 2006,  
12 MedPointe discovered Cipla's patent application and that  
13 Cipla sells a nasal product. Do you see that?

14 A. I do.

15 Q. And that is correct, isn't it, that refreshes your  
16 recollection about the timing here?

17 A. Yes.

18 MR. LOMBARDI: Let's go back to the Elmo, if we  
19 could, please.

20 BY MR. LOMBARDI:

21 Q. So I'm just going to write in here May 2006, Cipla.  
22 And that is the timing of it; is that right?

23 A. Yes.

24 Q. Now, Doctor, you did these experiments but not on a  
25 formulation that included azelastine and fluticasone in

D'Addio - cross

1 April of 2006; correct?

2 A. I'm sorry. Restate the question.

3 Q. I'll reframe the question.

4 A. Yes.

5 Q. Prior to April of 2006, Doctor, you had come up  
6 with a formulation of azelastine and, I'm having trouble  
7 saying it, azelastine and fluticasone that you thought would  
8 work, didn't you?

9 A. I'm sorry.

10 Q. Prior to April of 2006, you had come up with a  
11 formulation that you thought would work?

12 A. I don't know what that is.

13 Q. You don't have any recollection of that?

14 A. I'm not sure I understand what you are talking about.

15 Q. Well, let's try it one more time and I will try to be  
16 more clear.

17 Prior to the time of the testing we had been  
18 talking about in April of 2006, isn't it true that you had  
19 come up with a formulation of azelastine hydrochloride and  
20 fluticasone that you believed would work?

21 A. We may have. I know that we were developing some  
22 intellectual property at the time. That's possible.

23 Q. All right. Well, let's take a look at that. I've  
24 got a document to show you.

25 May I hand this up to Your Honor as well?

D'Addio - cross

1 THE COURT: You may.

2 (Documents passed forward.)

3 BY MR. LOMBARDI:

4 Q. And, Doctor, let's just identify this for the record  
5 first. It's got DTX-313 on it. Do you see that?

6 A. I do.

7 Q. And the first page is a letter dated November 22nd,  
8 2005 to the Commissioner For Patents on Sterne Kessler  
9 Goldstein & Fox letterhead; is that right?

10 A. Yes.

11 Q. And that's the law firm that is representing you here  
12 today; is that right?

13 A. That is correct.

14 Q. All right. So let's go to page -- and you can see  
15 from the front page, it indicates that this concerns a U.S.  
16 utility patent application, down at No. 6 on the front page.

17 Do you see that?

18 A. Yes.

19 Q. Compositions comprising azelastine and methods of use  
20 thereof.

21 A. Correct.

22 Q. And do you recall that you were listed as an inventor  
23 on this patent application?

24 A. Correct.

25 Q. All right. Let's go to page DTX-313.0013 within.

D'Addio - cross

1 And those numbers are at the bottom right corner, Doctor.

2 A. Okay. Yes.

3 Q. And on that page, do you see your signature dated  
4 November 22nd of '05?

5 A. I do.

6 Q. That is before the testing we've been talking about  
7 here today; is that right?

8 A. That's correct.

9 Q. All right. And you have patents yourself? You are  
10 an inventor on patents; is that right?

11 A. That's correct.

12 Q. And you understand that when you file a patent  
13 application, you take an oath that you're providing honest  
14 accurate information; is that right?

15 A. That is correct.

16 Q. And that is what you intend to do; is that right?

17 A. Correct.

18 Q. And in this patent application, you filed claims;  
19 isn't that true?

20 A. Yes.

21 Q. And you filed claims that included the combination of  
22 azelastine hydrochloride and fluticasone; isn't that true?

23 A. I don't recall exactly which claims.

24 Q. All right. I'll show you an example. Let's go to  
25 DTX-313.0196.

D'Addio - cross

1 And let's look at claim 101.

2 A. Yes.

3 Q. And it says, a pharmaceutical composition comprising:  
4 about 0.05 percent to about 0.15 percent with weight volume  
5 azelastine hydrochloride.

6 Do you see that?

7 A. Correct.

8 Q. And then about 0.01 percent to about 0.1 percent  
9 weight volume steroid selected from the group consisting of  
10 fluticasone and others.

11 Do you see that?

12 A. I do.

13 Q. Okay. So that is a claim to formulation, a  
14 composition that includes azelastine hydrochloride and  
15 fluticasone; correct?

16 A. That is correct.

17 Q. Now, elsewhere in this patent application, you  
18 provide information about what would be appropriate  
19 excipients to use with this. Isn't that right?

20 A. Correct.

21 Q. So let's go to DTX-313.0049.

22 And I'm looking at the paragraph, it's paragraph  
23 105, Doctor. And we're getting it on the screen if that is  
24 easier for you. Just let me know.

25 A. I have it.



D'Addio - cross

1 Q. All right. And at the very top, the first line of  
2 paragraph 105 says: In one embodiment, the pharmaceutical  
3 compositions comprise (or consisting essentially of) an  
4 effective amount of azelastine (suitably azelastine  
5 hydrochloride) along with an effective amount of one or more  
6 steroids.

7 Now, we know that fluticasone is one of the  
8 steroids you referenced; isn't that right?

9 A. Yes.

10 Q. All right. So let's keep going here. Let's go down  
11 about five lines where it says such compositions.

12 You say: Such compositions can be formulated as  
13 intranasal or ocular suspensions or solutions, with a pH of  
14 about 6.0 to 8.0.

15 Do you see that?

16 A. I do.

17 Q. So you say it can be formulated as a suspension or a  
18 solution; correct?

19 A. It's possible.

20 Q. And there is nothing in this application that says  
21 that there is some kind of problem with doing that kind of  
22 formulation, is there?

23 A. It does not say that there, no.

24 Q. All right. Let's continue, Doctor. Let's go back to  
25 DTX-313.0041.

D'Addio - cross

1 Do we have that? I'm sorry. We have that.

2 At the top paragraph, Doctor. In the middle of  
3 the top paragraph, all the way over to the right. Do you  
4 see where it says "liquid?" Do you see that?

5 A. I do.

6 Q. Okay. And if we read that, it says: Liquid dosage  
7 forms that provide the active ingredient in suspension may  
8 comprise, in addition to the active azelastine compound, one  
9 or more suspending agents, such as microcrystalline  
10 cellulose. Do you see that?

11 A. Yes.

12 Q. Now, you have seen that referred to as MCC before;  
13 correct?

14 A. Correct.

15 Q. And then you see sodium carboxymethylcellulose. Do  
16 you see that?

17 A. Yes.

18 Q. You have seen that referred to as CMC before; is that  
19 right?

20 A. Yes.

21 Q. All right. Let's go now to the next paragraph.

22 Paragraph 77. And this says, at the top: Certain liquid  
23 compositions of the invention may further comprise one or  
24 more preservatives and/or one or more stabilizers.

25 Do you see that?

1 A. Correct.

2 Q. And we look down, the preservatives that you say will  
3 work with these compositions includes disodium EDTA. Do you  
4 see that?

5 A. Yes.

6 Q. And if you go down a couple more lines, it says,  
7 starting the far right, phenylethyl alcohol?

8 A. Yes.

9 Q. And benzalkonium chloride right after that. Do you  
10 see that?

11 A. I do.

12 Q. Okay. And let's go to paragraph 78, right below  
13 that:

14 Certain compositions of the invention may  
15 further comprise one or more solubility-enhancing agents  
16 that are used to improve the solubility of the azelastine  
17 compound used as an active ingredient.

18 And then it talks about solubility enhancing  
19 agents. Those are also sometimes called surfactants; right?

20 A. Some, some can be surfactants, yes. The ones listed  
21 there I believe are.

22 Q. Okay. And, in fact, one of the ones listed there is  
23 in fact polysorbate 80; is that correct?

24 A. Yes.

25 Q. And let's go to the next page, page 24, paragraph 79.

D'Addio - cross

1                   In the middle, it says: Certain compositions of  
2                   the invention may further comprise one or more agents that  
3                   are used to render the composition isotonic.

4                   Do you see that?

5           A.       I do.

6           Q.       These would be something you could call tonicity  
7                   adjusters; is that right?

8           A.       That is correct.

9           Q.       And in the list of suitable tonicity adjusters,  
10                   starting right in the middle of the paragraph, it says:  
11                   Agents that are suitable. Do you see that?

12          A.       I do.

13          Q.       And the list includes sodium chloride, which is salt;  
14                   correct?

15          A.       That is correct.

16          Q.       Go a little bit farther. It includes dextrose. Do  
17                   you see that?

18          A.       Yes.

19          Q.       And if you go a little bit farther, it has glycerine.  
20                   Do you see that?

21          A.       Yes.

22          Q.       Now, all of these statements were made to the Patent  
23                   Office -- and we can go back to the Elmo, please -- in 2005,  
24                   correct?

25          A.       Yes.

D'Addio - cross

1 Q. And that was before you had any conversation with  
2 Cipla about their patent application; correct?

3 A. That is correct.

4 Q. That is before you even knew anything about Cipla's  
5 patent application?

6 A. That is correct.

7 Q. And it is before you knew anything at all about the  
8 work that was contained in Cipla's patent application; is  
9 that correct?

10 A. That is correct.

11 MR. LOMBARDI: I have no further questions, Your  
12 Honor.

13 THE COURT: Okay. Redirect.

14 MR. LOMBARDI: And, Your Honor, maybe for the  
15 record, so we have a record of it, I'll call this D'Addio  
16 demonstrative A, if that is okay?

17 THE COURT: That's fine. And it will be  
18 accepted as a demonstrative.

19 MR. LOMBARDI: Thank you.

20 Oh, and I forgot to move in DTX-313.

21 (Counsel confer.)

22 MR. LOMBARDI: And also PTX-150 and PTX-149.

23 And that's it, Your Honor. Thank you.

24 THE COURT: Okay. Ms. Everett, any objection to  
25 the admission of those three exhibits?

D'Addio - redirect

1 MS. EVERETT: No.

2 THE COURT: Those are all admitted.

3 (Above-referenced exhibits admitted in evidence.)

4 THE COURT: We'll have redirect.

5 REDIRECT EXAMINATION

6 BY MS. EVERETT:

7 Q. Dr. D'Addio, you recall Mr. Lombardi asked you about  
8 whether it made sense to add, to combine two different drugs  
9 with two different mechanisms of action?

10 A. I do.

11 Q. Is that part of your responsibilities to make that  
12 type of determination?

13 A. I'm responsible, I was responsible for formulation  
14 development.

15 Q. So do you evaluate drugs based on their clinical  
16 properties?

17 A. Those decisions are left to our medical department.

18 Q. If you would then turn to PTX-0149.

19 A. I have it.

20 Q. Do you recall Mr. Lombardi asked you about the  
21 discussion, the section that says Rich, Alex and I discussed  
22 the combo product and we all feel the shortest development  
23 route would be either a simple solution or a suspension,  
24 depending on the steroid used?

25 A. I do.

D'Addio - redirect

1 Q. What do you recall was meant by that discussion?

2 A. I didn't know, I mentioned it before. This was a  
3 relative discussion, what would be easier than trying to  
4 develop the dual chamber device. For this we felt that it  
5 would be a more viable program to either go with the simple  
6 solution or a suspension. It doesn't mean that either of  
7 those programs would have been straightforward or taken less  
8 time. It just meant that they were going to potentially be  
9 easier than trying to develop a dual chamber device.

10 Q. And when you say a simple solution or a suspension,  
11 can you elaborate on what you meant by that?

12 A. Simple solution would be a case where both active  
13 ingredients, the azelastine and fluticasone propionate,  
14 would have been fully dissolved in a solution with no  
15 particles. A suspension, here we were talking about a  
16 product that had azelastine and a suspension of fluticasone  
17 propionate.

18 Q. So at that time you weren't sure how exactly the  
19 formulation would be solution or suspension. Is that  
20 correct?

21 A. No, we had not made that decision.

22 Q. And had Meda conducted any other tests at that time,  
23 2006?

24 A. No, not that I know of.

25 Q. You recall Mr. Lombardi asking you about whether you

D'Addio - redirect

1 had developed a formulation with azelastine and fluticasone  
2 in it? Do you recall that?

3 A. At which point in time?

4 Q. I believe he is referring to your 2006 study.

5 A. Yes.

6 Q. And you still, I believe you answered, no, that  
7 MedPointe had not developed a combination with azelastine  
8 and fluticasone?

9 A. I am sorry. There were two parts to that. The first  
10 was our screening experiment. That was a combination of  
11 fluticasone propionate as a suspension with azelastine in  
12 it, that screening experiment.

13 Then after that we had worked on the dissolution  
14 of azelastine in the supinate obtained from fluticasone  
15 propionate nasal spray.

16 Q. Is it routine or in any way unusual to conduct a  
17 number of tests while formulating with multiple actives or  
18 excipients where you just test parts of the system?

19 A. Yes.

20 Q. That's a common way of testing?

21 A. Yes.

22 Q. And you can still make decisions on whether a  
23 particular route will be successful?

24 A. Yes. As a matter of fact, that's typically done in  
25 formulation experiments, correct, pre-formulation



1 experiments.

2 Q. I am going turn to DTX-313?

3 A. Yes.

4 Q. Mr. Lombardi asked you a few questions about those.

5 Are you a patent attorney, Mr. D'Addio?

6 A. I am not.

7 Q. Are you involve in the prosecution of these patents?

8 A. Not in the progression, no.

9 Q. Do you know what's meant by a prophetic example?

10 A. Not exactly. I have an idea. It's a description of  
11 what could be a potential product.

12 Q. Did MedPointe ever develop any of the combinations  
13 that Mr. Lombardi pointed you to in 1996 or 1997?

14 A. No, not before we worked on the feasibility plan in  
15 2006.

16 Q. If MedPointe had ever developed -- if MedPointe  
17 thought it would be able to develop a fluticasone  
18 combination nasal spray, would they have needed to license  
19 it for from anyone else?

20 MR. LOMBARDI: Objection, calls for speculation.  
21 It's an "if" question, making assumptions.

22 THE COURT: Ms. Everett.

23 MS. EVERETT: I can rephrase.

24 THE COURT: Try to rephrase.

25 BY MR. EVERETT:

Kaliner - direct

1 Q. What would have been MedPointe's preference in  
2 developing a combination nasal spray, in-house development  
3 or licensing?

4 A. In-house development is always the best. You don't  
5 have to share any of the profits with a partner.

6 MS. EVERETT: No further questions.

7 THE COURT: Thank you. You may step down.  
8 Thank you very much.

9 (Witness excused.)

10 THE COURT: You may call your next witness.

11 MS. EVERETT: Thank you.

12 We call Dr. Michael Kaliner.

13 ... MICHAEL KALINER, having been duly sworn as a  
14 witness, was examined and testified as follows ...

15 THE COURT: Good evening, Dr. Kaliner. Welcome.

16 MR. VARUGHESE: Good afternoon, Your Honor.  
17 May I approach the witness to give him a pointer.

18 THE COURT: You may approach with binders. If  
19 there are others up there, perhaps you could retrieve them  
20 while you are up there.

21 DIRECT EXAMINATION

22 BY MR. VARUGHESE:

23 Q. Good evening, Dr. Kaliner.

24 A. Good evening.

25 Q. Could you state your name for the record, please?

Kaliner - direct

1 A. Michael Aaron Kaliner.

2 Q. Are you a medical doctor?

3 A. I am.

4 Q. Where are you licensed to practice?

5 A. Maryland.

6 Q. Can you turn to Tab 1 of the binder that I have just  
7 given you. Is that a copy of your curriculum vitae?

8 A. It is.

9 Q. Is it accurate as of today?

10 A. More or less. I retired from clinical practice about  
11 two weeks ago.

12 Q. Congratulations.

13 So for identification, we have marked as  
14 PTX-0027. Dr. Kaliner, can you briefly summarize for the  
15 Court your education and training?

16 A. Well, I started college at Duke and then transferred  
17 to Maryland. Graduated from Maryland in '63. Went to the  
18 Maryland Medical School. Graduated in '67. Did my  
19 internship and residency in internal medicine at Maryland at  
20 the University of California in San Francisco. And then I  
21 went to Boston and did my allergy immunology and  
22 rheumatology at the Brigham Hospital, which is part of the  
23 Harvard Medical System.

24 Q. Thank you. When you completed your training, where  
25 did you go?

Kaliner - direct

1 A. Then I had two years in the military where I was an  
2 allergist at the Kessler Air Force base in Biloxi,  
3 Mississippi.

4 Thereafter, I came to the National Institutes of  
5 Health, NIH, where I was the head of allergy. And I was  
6 there from 1975 to 1993.

7 In 1993 I completed 20 years in the military. I  
8 was part of the Public Health Service when I was at the NIH.  
9 And I started the Institute for Asthma and Allergy, which is  
10 a referral practice. We started as a place for  
11 difficult-to-manage patients to be referred to. We began  
12 that practice in 1993. I started it. When I retired two  
13 weeks ago, there were seven full time physicians.

14 Q. And in addition to your clinical practice, did you do  
15 any teaching?

16 A. Sure. We had medical students from Georgetown and GW  
17 in our office since the very beginning. We had medical  
18 residents from the hospital center, Washington Hospital  
19 center, Georgetown and GW.

20 We are part of the NIH training program so the  
21 NIH fellows come through our office.

22 Q. Have you obtained any board certifications, Doctor?

23 A. I am certified in internal medicine, allergy,  
24 immunology, and allergic rhinitis immunology.

25 Q. Have you published any articles or books?

1 A. I have.

2 Q. Approximately how many?

3 A. More than 500, articles, books, reviews, chapters,  
4 manuscripts.

5 Q. Have any of those publications published on allergy  
6 or allergic rhinitis?

7 A. Many are related to rhinitis, probably between 20 and  
8 25 percent.

9 Q. Does your CV contain an accurate list of your  
10 publications, sir.

11 A. It does.

12 Q. Have you ever served on the editorial board or any  
13 allergy-related journals?

14 A. I have been around a long time. I have served on a  
15 lot of education boards, including the Journal of Allergy  
16 and Clinical Immunology and recently the American Journal of  
17 Rhinology.

18 Q. Have you been an investigator or researcher in any  
19 clinical trials?

20 A. Yes, I have. Our office does somewhere between ten  
21 and 30 clinical trials a year covering the entire spectrum  
22 of allergy. So we have done mini-trials in allergic  
23 rhinitis, asthma, immunodeficiencies, atopic dermatitis, you  
24 name it, we have done it.

25 Q. Can you estimate in your clinical career about how

Kaliner - direct

1 many patients you have treated with allergic rhinitis?

2 A. As I said, I have been around a long time. The  
3 hardest number I can give you is based on the time at the  
4 institute for allergy. And we have consecutively numbered  
5 our patients since 1993. So we are at about 65,000.

6 And I have seen about 25 percent of the  
7 patients, give or take 15,000. And the majority of them  
8 have allergic rhinitis.

9 Q. And you're here today to testify on behalf of  
10 plaintiffs Meda and Cipla?

11 A. No.

12 Q. Were Meta and/or Cipla the first ones to contact you  
13 about this case?

14 A. They were not.

15 Q. Who contacted you?

16 A. I learn about the case by attorneys representing  
17 Apotex, who approached me about being their medical expert.

18 Q. Why didn't you take on that engagement?

19 A. I have been consulting with MedPointe and Meda for  
20 years, and I felt it was inappropriate for me to go do  
21 something that was adverse to the company.

22 Q. That consulting relationship that you had with Meda,  
23 is that a basis for any of your opinions today?

24 A. No, it is not.

25 Q. What is the basis for your opinions?

Kaliner - direct

1 A. Well, I have been in practice for many years. That  
2 is the largest part of what I am going to base my opinions  
3 upon.

4 But I also know the world's literature. That is  
5 the bulk, the data is really what I base it upon.

6 MR. VARUGHESE: Your Honor, we move to admit Dr.  
7 Kaliner as an expert in the fields of allergy and  
8 immunology, particularly in the treatment of allergic  
9 rhinitis. And we move to admit his CV into evidence.

10 THE COURT: The document you reference is  
11 admitted, and the Doctor is so recognized.

12 (Exhibit received in evidence.)

13 BY MR. VARUGHESE:

14 Q. Dr. Kaliner, you just represented your consulting for  
15 Dymista?

16 A. It does.

17 Q. Does that have anything to do with the drug?

18 A. It does.

19 Q. Can you explain what you have done in terms of  
20 Dymista, consulting for them?

21 A. Well, actually, I predate Dymista so, it also  
22 involves Astelin And Astepro. And I have visited the  
23 company periodically over the years and talked about  
24 primarily marketing, product development.

25 In terms of ideas, I have been assisting them

Kaliner - direct

1 with speaking, I have lectured for them the years many  
2 times.

3 I have been with the speakers bureau with the  
4 slide productions.

5 A lot of what I deal with is teaching other  
6 physicians.

7 Q. You just mentioned speakers bureau and slide  
8 productions. What do you mean by that?

9 A. Well, the company has a group of physicians that they  
10 enlist to represent them and present information to other  
11 physicians or sometimes nurses and sometimes pharmacists  
12 about products, so they have what's called a speakers  
13 bureau.

14 Q. And the attendees of this group, are they M.D.'s?

15 A. The physicians presenting the slides are all M.D.'s,  
16 yes.

17 Q. Do you mind turning to Tab 30 of the book that I have  
18 given you? Can we go to PTX-1668, please?

19 A. Sure.

20 Q. Do you recognize this document?

21 A. I do.

22 Q. Would you identify it?

23 A. It's the first slide in one of the slide decks in a  
24 recent year. I am not certain what year it is, but a recent  
25 year.



Kaliner - direct

1 Q. Have you used this slide deck before?

2 A. Yes, I have.

3 Q. In what way do you use the slide deck?

4 A. Well, the company prepares slides and presents them  
5 to the FDA. The FDA has to approve those slides.

6 Once the FDA and the company have come to an  
7 agreement about the slides that can be used, then they are  
8 given to us and we present those slides.

9 It's a branded product. It's called a  
10 promotional presentation, so you give the slides as  
11 presented to you.

12 You have to present every slide. You can't  
13 change a word on the slides.

14 Q. When you say they were given to us, what do you mean?

15 A. Well, the speakers bureau.

16 Q. Were you in the courtroom the other day when Dr.  
17 Wedner was testifying?

18 A. I was.

19 Q. Did you know Dr. Wedner from before this litigation?

20 A. I have known Jim for many years.

21 Q. How do you know him?

22 A. Well, we are colleagues. We have been around  
23 together. It's a small community. We all know each other.  
24 So I have known Jim for many years. But when we were  
25 discussing this case a year ago, whenever it was, nine

Kaliner - direct

1 months ago, and I was presented that Jim was going to be  
2 opposing us, I made a comment, gosh, I think he is on the  
3 speakers bureau. I remembered him as being part of the  
4 speakers bureau.

5 Q. When you heard his testimony the other day, where he  
6 said he didn't recall being part of the speakers bureau,  
7 what was your reaction?

8 A. I was a little surprised.

9 Q. This is an "if" question. If Dr. Wedner had spoken  
10 on behalf of Dymista, given a talk, would this have been the  
11 deck that he would have used?

12 MR. KLEIN: Objection. Calls for speculation.

13 MR. VARUGHESE: Your Honor, this goes to the  
14 witness' knowledge. We was a trainer of the speaking  
15 bureau. He has testified that slides are not altered. And  
16 I asked an "if" question. As an expert.

17 THE COURT: Your response.

18 MR. KLEIN: My response is he has no idea if Dr.  
19 Wedner presented this or he was paid a very small amount or  
20 whether Dr. Wedner made any presentation.

21 THE COURT: I overrule the objection.

22 BY MR. VARUGHESE:

23 Q. Can you answer that?

24 A. Say it again?

25 Q. If Dr. Wedner had presented or given a talk on behalf

Kaliner - direct

1 of Dymista, would this have been the slide that you would  
2 have used?

3 A. So each of the slide decks is different one year to  
4 another year. There are minimal changes. So if it was in  
5 the year that this slide deck represents, he would have  
6 presented this deck of slides.

7 Q. And year to year, how many changes were there?

8 A. It depends on how much data they have.

9 So they do change. My guess is that they change  
10 a few percent, five percent, ten percent a year.

11 Q. Thank you, Dr. Kaliner.

12 Let's switch gears. What were you asked to do  
13 in this case?

14 A. I was asked to respond to Dr. Schleimer's contentions  
15 of obviousness.

16 Q. Were you in the courtroom when Dr. Schleimer  
17 testified?

18 A. I was.

19 Q. Did you hear his testimony that in his view the  
20 patents in suit would have been obvious to a person of  
21 ordinary skill in the art at the time of the invention?

22 A. I did.

23 Q. Do you agree with him?

24 A. I don't.

25 Q. Dr. Kaliner, did you prepare any slides to aid in

Kaliner - direct

1 your testimony today?

2 A. Yes.

3 Q. Would you go to the slides, please.

4 Can you summarize for the Court your opinions in  
5 this case, please?

6 A. Sure. As I put on the slides, the person of ordinary  
7 skill in the art at the time of the invention I do not  
8 believe would have found the claims to be obvious.

9 The weight of data at that time and for many  
10 years indicated that antihistamines added no additional  
11 benefit to nasal corticosteroids. The POSA would not have  
12 found any motivation or reason to combine azelastine and  
13 fluticasone into a single formulation.

14 Moreover, the POSA would have had no reasonable  
15 expectation of success in such a combined single  
16 formulation.

17 Q. Do you have any other opinions with respect to  
18 nonobviousness in this case?

19 A. I do. I am going to show you a lot of data later on  
20 that experts in the field consistently expressed skepticism  
21 that an antihistamine would add benefit to a nasal  
22 corticosteroid.

23 I have been treating patients for a long time,  
24 and I realized that in 2002 we had more efficient medicines  
25 than when I started treating. But there was no question

Kaliner - direct

1     that patients wanted better medications. They were  
2     symptomatic. They wanted more effective medications.

3             It is my opinion that Dymista satisfies, when it  
4     came to fruition, satisfies a long-felt need in the art.

5             Duonase, which is the -- the expression of the  
6     patent brought forth in India, was a successful product.  
7     And within a limited period of time, somewhere between six  
8     and 11 Indian companies made imitator products mimicking  
9     Duonase, which I think is a clear reflection of a success in  
10    India.

11    Q.     You just mentioned some products, Dymista, Duonase,  
12    and what you pointed out as Indian imitator products. Do  
13    you have an understanding as to whether those products are  
14    related to the patents here?

15    A.     I do. Dymista, Duonase, and the Indian imitator  
16    products that we will cover later on are all fixed-dose  
17    combinations of azelastine and fluticasone and they are all  
18    used to treat allergic rhinitis.

19    Q.     Dr. Kaliner, in forming your opinions in this case,  
20    did you review the patents in suit?

21    A.     I did.

22    Q.     And those would be the '620 patent?

23    A.     Yes.

24    Q.     And the '428 patent?

25    A.     Yes.

Kaliner - direct

1 Q. And those are PTX-1 and PTX-3 respectively?

2 A. Yes.

3 Q. Also in formulating your opinions, did you consider  
4 the perspective of a person of ordinary skill in the art at  
5 the relevant time of the invention?

6 A. I did.

7 Q. And for purposes of our discussions, is it okay if I  
8 refer to this person as a POSA? Would you understand what  
9 I'm talking about?

10 A. Please do.

11 Q. Do you have an understanding of the appropriate POSA  
12 in this case?

13 A. Well, it is a clinical -- we're talking about a  
14 clinical problem, allergic rhinitis. In my opinion, the  
15 person to best evaluate issues related to this patent would  
16 be a physician. Most patients seek care from their primary  
17 care physicians. So about 75 percent of the patients with  
18 allergic rhinitis are seen by their internist or family  
19 practitioner or pediatrician, so I think it should be a  
20 primary care physician, but he needs enough time in practice  
21 to understand the disease and the treatment of the disease  
22 and the nuances therein.

23 So I think it is two to four years of clinical  
24 experience would be a minimum.

25 So I think it should be a physician with some

Kaliner - direct

1 experience, primarily a primary care physician.

2 Q. Now, you heard Dr. Schleimer's definition of a POSA  
3 yesterday?

4 A. I did.

5 Q. Do you agree with his definition?

6 A. In part. He mentioned an MD, and I totally agree  
7 with that.

8 But I don't think a Ph.D. or a Pharm.D is  
9 appropriate. I think you have to have clinical acumen to be  
10 able to judge these patents.

11 Q. So in your experience, Dr. Kaliner, how would a  
12 patient with allergic rhinitis present at your office?

13 A. Well, a patient with allergic rhinitis would have,  
14 would come to the office because of symptoms.

15 I'm an allergy sufferer and I'm having some  
16 experience with symptoms right now.

17 And so nobody comes, nobody wants to go to the  
18 Doctor. So they come to the Doctor only when they have to.  
19 So it means that patients are really uncomfortable in order  
20 to take time off from school or work to seek a physician's  
21 care.

22 So although the symptoms, itching, sneezing,  
23 runny nose, and congestion sound trivial, if you are an  
24 allergy sufferer like I am, and like I think Dr. Schleimer  
25 is, you know that this can be an fairly incapacitating

Kaliner - direct

1 problem.

2 It can bother you particularly in court when  
3 you are trying to speak clear, if you have postnasal drip,  
4 clearing the throat, like I'm going to do all morning,  
5 coughing, headaches, sleep loss because you can't breathe  
6 through your nose and hoarseness.

7 So these symptoms may be trivial but they're  
8 very important to the patient that has this problem and can  
9 be very devastating.

10 Q. Okay. And you cited a couple documents on the far  
11 right from this demonstrative. That is PTX-22.

12 BY MR. VARUGHESE:

13 Q. Is that the Dykewicz article?

14 A. So the Dykewicz is the practice parameter which was  
15 published in the United States.

16 Q. And the other one is PTX-326. That is ARIA?

17 A. That is an ARIA guideline published in Europe.

18 THE COURT: Doctor, we're going to take a break.  
19 It's not because you sound like you are sick or anything. I  
20 need a break.

21 But before we do, let me just say something  
22 about the schedule because I want you to think about this,  
23 and if you need to confer with one another either during the  
24 break or later this evening, but I'm going to be available  
25 tomorrow from 8:30 in the morning until 7:00 p.m., if



Kaliner - direct

1 needed. I'm hopeful that that means we won't need Saturday  
2 at all.

3 Further, what I'm contemplating is maybe taking  
4 back an hour from each side for closing argument and putting  
5 off closing argument, instead of tomorrow, putting it off  
6 until February after you complete your briefing, and I do  
7 have some time on February 28th in particular in the  
8 afternoon.

9 And so I would like you, to the extent you have  
10 time over the next hour, to look at your schedules and  
11 confer perhaps during the break, or you can get back to me  
12 as late as tomorrow morning. But the most pressing thing is  
13 whether or not you all think we're going to need Saturday  
14 and whether in light of this we might be able to figure that  
15 out tonight.

16 In any case, we'll take a short break and then  
17 we'll be back.

18 (Brief recess taken.)

19 \* \* \*

20 (Proceedings reconvened after recess.)

21 THE COURT: Have a seat.

22 BY MR. VARUGHESE:

23 Q. So, Dr. Kaliner, before the break, I did ask you  
24 about your differences in opinion between the difference in  
25 opinion between you and Dr. Schleimer in terms of how a POSA

Kaliner - direct

1 is defined.

2 If we were to adopt Dr. Schleimer's definition,  
3 would that change your opinions?

4 A. No, I don't think so.

5 Q. Okay. Now, do you recall yesterday in  
6 Dr. Schleimer's testimony, he suggested that treatment  
7 decisions would about based on the early/late phase  
8 classification of the action? Do you recall that?

9 A. I do.

10 Q. Do you agree with his assessment?

11 A. No, not really.

12 Q. And can you explain to the Court why that is?

13 A. Well, first of all, let me preface that by I've been  
14 treating patients for 50 years and just finished 50 years of  
15 practice. And so the appreciation of the early and late  
16 phase in which experimentally I was involved in was a  
17 terrific breakthrough, a major breakthrough in how we  
18 understand allergy and allergic reactions to go forward and  
19 explained a lot of phenomena that we had seen clinically  
20 that we really didn't understand completely before we  
21 understood early and late phase.

22 But it turns out, first of all, it is an  
23 experimental model. It is a terrific teaching tool. It is  
24 very useful, and I'm not minimizing late phase and early  
25 phase at all.

Kaliner - direct

1 But in clinical practice, it is not relevant.

2 So let me explain why I make that statement.

3 If I brought you into the laboratory, if brought  
4 me into the laboratory and I inhaled allergen, I would  
5 develop asthma, and then some hours later I might definitely  
6 a second phase of asthma. It is pretty reliable for asthma.

7 But I do the same thing, and I have done the  
8 same thing, and take allergen in my nose, I would have an  
9 immediate reaction but I never get a late phase reaction,  
10 and only 20 to 40 percent of patients ever get a nasal late  
11 phase reaction. It is just not reliable on the nose.

12 So it is impossible to determine where a patient  
13 is in late phase. Let me tell you what I mean about that.

14 In practice, you are allergic to, let's say,  
15 pollen and during the springtime there could be literally  
16 thousands of pollen grains in a cubic meter, nine feet by  
17 nine feet around you.

18 And every time you breathe, you are breathing in  
19 pollen grains or allergens, and so I might have an allergic  
20 reaction right now, and then a half hour ago and two hours  
21 from now, I might be initiating a reaction. So they're all  
22 superimposed on each other, and it is impossible to tell  
23 where a patient is outside the laboratory model with respect  
24 to early and late phase.

25 The other complicating factor is that the

Kaliner - direct

1 symptoms of late phase and early phase overlap: Sneezing,  
2 itching, runny nose, and congestion. You can get all of the  
3 phenomena.

4 And to make things even worse, the medicines  
5 we use to treat early and late phase overlap. Some of the  
6 medicines have effects on both sides of the reaction.  
7 Corticosteroids, which are very good antiinflammatory  
8 medications, also affect the immediate reaction.

9 As a matter of fact, that work came from the  
10 laboratory that Dr. Schleimer is part of at Hopkins. And so  
11 it is well appreciated that medicines that we use have  
12 effects on one phase but also overlap on the other phase.

13 So it is a great teaching tool, great  
14 understanding what we do in medicine, but it does not relate  
15 to clinical practice.

16 Q. So in the real world, clinical practice, you know, in  
17 your experience, what factors do you and what factors do you  
18 think a POSA would have considered in determining treatment  
19 options?

20 A. We treat symptoms. That's the bottom line.

21 And I have got on the next slide, I have at  
22 least the primary symptoms, sneezing, itching, runny nose,  
23 and congestion. I didn't list all the medicines, we'll  
24 get to that in a few minutes, but I listed the major  
25 medication.

Kaliner - direct

1           So we have been using antihistamines since 1955  
2   or so, and they're very good for itching, sneezing and runny  
3   nose. They don't have reliable effects on congestion, but  
4   along the way, we discovered decongestants like Sudafed --  
5   probably everyone of us had taken Sudafed -- work on  
6   congestion.

7           In fact, the pharmaceutical industry, which is  
8   not so dumb, has been able to combine antihistamines and  
9   decongestants into a single tablet, and they block itching,  
10   sneezing runny nose, and congestion. Those are probably the  
11   most prevalent treatments for the symptom complex that are  
12   used around the world.

13           On this slide, I have included corticosteroid  
14   which blocks sneezing, itching, running nose, and  
15   congestion, just like antihistamines and decongestant  
16   tablets. So you would see a patient that has, they have the  
17   symptoms. The way we treat, try a medicine, you try another  
18   medicine, you try another medicine and hopefully patients  
19   get better. That's the way it works.

20   Q.       So, yesterday, do you recall, during Dr. Schleimer's  
21   testimony, he suggested that a POSA in or around the  
22   2001-2002 time frame would most likely go on to combine  
23   azelastine and fluticasone? Do you recall that?

24   A.       I heard that, yes.

25   Q.       Do you agree?

Kaliner - direct

1 A. Well, I mean we did do, we did combine azelastine and  
2 fluticasone, amongst many, many, many other treatment  
3 options that we did. I'm not saying we didn't do that. But  
4 the treatment options were enormous, and that was a tiny,  
5 tiny portion of our treatment modality. And I'm going to  
6 give you very hard data to support that comment.

7 The treatment options we had in 2002 were  
8 enormous. So we had 24 antihistamines, many decongestants,  
9 mast cell stabilizers, anticholinergics, leukotriene  
10 receptors, and corticosteroids.

11 So we used every one of these medicines. Every  
12 one of the medicines on the slide was used in some context  
13 earlier.

14 Now, I heard yesterday that we only did a few of  
15 the antihistamines.

16 Well, I would be very happy to take the income  
17 from diphenhydramine, which is Benadryl, and that sells  
18 hundreds of millions of dollars per year. That is not a  
19 trivial market.

20 It's true that in 2002, we were looking to use  
21 primarily the non-sedating antihistamines. So that is  
22 cetirizine, loratadine, fexofenadine, and they were sold a  
23 Claritin, Allegra, and Zyrtec. And those were the primary  
24 antihistamines we were using but we used these other  
25 antihistamines for other conditions.

Kaliner - direct

1           We used every medicine that is listed on the  
2           slide in one context or another. I personally used oral  
3           antihistamines as my primary treatment, and then I would add  
4           a nasal steroid, and the nasal steroid at the bottom of the  
5           slide, I used every one of them including fluticasone.

6           But I had another preferred product that I used  
7           primarily, overwhelmingly primarily, triamcinolone, which  
8           was Nasacort AQ, and I will go into the reasons later on why  
9           I made that choice.

10          Q.       From where did you assemble the list of drugs?

11          A.       This is from the Dykewicz and ARIA guidelines. This  
12           is combining the wealth of knowledge in the two major  
13           guidelines.

14          Q.       Do you follow the guidelines?

15          A.       I do follow the guidelines.

16          Q.       Switching gears slightly, Dr. Kaliner. At the time  
17           of invention, based on your experience, how satisfied were  
18           patients with existing therapies?

19          A.       Well, what I have done is I went to the literature  
20           and drew a review that was published in Europe  
21           contemporaneously with that 2002 and one in the United  
22           States. There are other surveys as well.

23                    So these are two patient surveys. And what  
24           they show is that between 80 and 92 percent of the patients  
25           consider themselves impaired in work and daily life. 74

Kaliner - direct

1     were not well controlled with the medicines they were using,  
2     74 were using more than two medicines, 23 percent were using  
3     three medicines.

4             And with that, many patients were concerned  
5     about side effects. 65 percent of the patients tried to  
6     medications to avoid side effects, primarily sedation from  
7     antihistamines?

8     Q.       So you mentioned some surveys that you used to arrive  
9     at this information. Are the cites there the surveys?

10    A.       These are Demoly and Storms.

11    Q.       Can you explain to the Court a little bit about  
12    Demoly and Storms?

13    A.       These are both physicians, that you did  
14    patient-related surveys, actually quite large numbers of  
15    patients, thousands of patients and asked them a series  
16    of questions and derived from those questions this data.

17    Q.       And those surveys are PTX-20 and PTX-42 respectively?

18    A.       Yes.

19    Q.       You reviewed them?

20    A.       I did.

21    Q.       Going back to your recollection of Dr. Schleimer's  
22    testimony. Yesterday, he suggested that Flonase or  
23    fluticasone was a preferred steroid in 2002. Do you recall  
24    that?

25    A.       I do.



Kaliner - direct

1 Q. Do you agree with him?

2 A. Well, let's talk about the field at the time.

3 What Dr. Schleimer pointed out, and he did  
4 some of the work, that he was absolutely right, is that  
5 fluticasone was the most potent of all the nasal steroids.  
6 There is no doubt about that. It still is.

7 However, the manufacturers of these nasal  
8 products, as I said, are not so dumb. And what they did  
9 is they made each of the products, concentration in the  
10 products so that the products were equally effective.

11 So every nasal steroid was equally effective.  
12 There wasn't one that was any bit better than the other.  
13 Head-to-head comparison showed them to be totally equivalent,  
14 one to the other.

15 So potency of Flonase had nothing to do with how  
16 it worked in patients. They were equally effective. And,  
17 in fact, many of us made a decision on what steroid to use  
18 not based on potency or effectiveness but on the other  
19 attributes that the steroids have.

20 So most of the nasal steroids have no smell, no  
21 taste. They were not unpleasant to use. Flonase has this  
22 floral smell that many of the patients, particularly  
23 patients that I took care of, that didn't like. So Flonase,  
24 to me, was a product that had unpleasant attributes and,  
25 therefore, I used other products.

Kaliner - direct

1 I tended to use pretty exclusively Nasacort AQ.  
2 I am a super-POSA, so I did not use a lot of Flonase. I did  
3 use Flonase. I had patients on Flonase, but my preference  
4 was for another product.

5 Now, around the same time, we also appreciated  
6 that the steroids had potentially very important systemic  
7 effects. There was publications that show growth suppression  
8 in children from nasal steroids, and so all of us were trying  
9 to use products that have the fewest systemic effects. We  
10 were using the lowest dose we could possibly get away with.

11 Q. Okay. Now, you site a study on the bottom right. Do  
12 you see that?

13 A. I do.

14 Q. Can you identify that?

15 A. Yes, Michael Blaiss. What Michael did was to have a  
16 review of a studies that had looked at attributes of nasal  
17 steroids and his conclusion was that Nasacort was the  
18 preferred nasal steroid.

19 Q. That is PTX-0058?

20 A. Yes.

21 MR. VARUGHESE: Can we go to PTX-58, please?  
22 Specifically, page 6 of the PTX.

23 BY MR. VARUGHESE:

24 Q. And focusing your attention, Dr. Kaliner, this is Tab  
25 8 in your book, if you want to refer to it. But it's going

Kaliner - direct

1 to be on the screen. I want to focus your attention to the  
2 graph or the chart there.

3 Can you blow it up?

4 Can you describe for the Court what is being  
5 shown here in this graph?

6 A. Well, the core of the data where the significance is  
7 in the center part here. And what happened is the patients  
8 were sprayed with one of the steroids or another steroid and  
9 within two minutes later, a series of questions was asked.  
10 And, for example, one of the questions was, the strength of  
11 the odor. And you can see that patients felt that the  
12 fluticasone and benzalkonium chloride was unpleasant where  
13 the triamcinolone was less unpleasant, it was quite  
14 acceptable.

15 If you look at taste, you can see that Nasacort  
16 was significantly preferred in respective taste compared to  
17 Flonase which is the middle bar.

18 That is pretty much the data. There is more,  
19 other sensations that were asked, but that is the core of  
20 this table.

21 Q. Thank you. Let's go back to the slides, please.

22 Yesterday, do you recall that Dr. Schleimer  
23 suggested that a POSA would prefer azelastine as the  
24 preferred antihistamine? Do you agree with that?

25 A. I don't.

Kaliner - direct

1 Q. Do you agree with that assessment?

2 A. No.

3 Q. Can you tell the Court why?

4 A. There are a lot of reasons why. Let me take you  
5 through the first problem with azelastine. That is that the  
6 molecule has itself has a taste, I think Alex mentioned this  
7 earlier, that it has a bitter taste.

8 Let me tell you, if you taste the Astelin -- I  
9 use Astelin, I use it all the time and I don't taste it. If  
10 you are one of the people who taste it, its taste is  
11 repugnant enough that you won't use the product. That taste  
12 sensation is found in about 19 percent of the patients, that  
13 is one out of five.

14 What happens with the physicians, if you give  
15 them a product they don't like, you lose their confidence.  
16 There are a lot of physicians that didn't use Astelin, in  
17 large part because of the side effects. It also got  
18 absorbed from the nose, through the stomach, in the  
19 bloodstream, and caused somnolence in about 11 percent of  
20 the patients. That is the systemic effect.

21 The taste from the nasal spray I guess you could  
22 say was expected. But what was unexpected was from the  
23 eyedrop before you get very little in the nose. That also  
24 caused bitter taste in ten percent of the patients.

25 This product had, in the view of many, many

Kaliner - direct

1 physicians, unacceptable side effects.

2 Q. Somnolence and headaches, are those systemic side  
3 effects?

4 A. Somnolence is systemic side effect. Headache can  
5 be caused by nasal trigger. So it's not necessarily  
6 systemic.

7 Q. Dr. Kaliner, you cite PTX-11. Is that the Astelin  
8 label?

9 A. Yes, that is the Astelin and the Optivar label.

10 Q. That is PTX-103?

11 A. Yes.

12 Q. You reviewed those documents and rely on them?

13 A. Yes.

14 Q. As of 2002, Dr. Kaliner, do you have an understanding  
15 as to how prevalent azelastine's use was?

16 A. I do. This is an important slide in relationship to  
17 the impression that may have been given that azelastine was  
18 being used a lot.

19 What this slide -- IMS, the data report, they  
20 monitor the pharmaceutical industry. It's pretty routine.

21 This is data that was published in 2004. But it  
22 comes from 2003. And the reason we chose that is in 2003,  
23 they cleaved out this category of RIA6 that includes  
24 azelastine, that is that little blue box here that I have  
25 circled in red.

Kaliner - direct

1           Let me take you through the slide.

2           By the way, this is the year after Claritin went  
3 over the counter. So Claritin is only three percent. It  
4 would have been 20 percent had it not gone over the counter.

5           In terms of the oral antihistamines, they  
6 comprise 56 percent of the prescriptions. Nasal steroids  
7 comprise 25 percent.

8           And this group of R1A6 of which there are four  
9 nasal products, which represents two percent, we went back  
10 and checked the sales figure for azelastine in 2002, which  
11 was less than one percent.

12           So azelastine is one percent of the market.  
13 That means that there were 56 prescriptions for an oral  
14 antihistamine for every prescription of azelastine.

15           There were 25 corticosteroid prescriptions for  
16 one prescription of azelastine. And any impression that you  
17 have that azelastine was being used as a major force in the  
18 market is just incorrect.

19           It was a tiny part of the market.

20 Q.       Forgive me if you have answered this. You used the  
21 word one percent. How did you derive that?

22 A.       It's based on the exact sales of azelastine in the  
23 year 2002.

24 Q.       Dr. Kaliner, where did you derive this data from?

25 A.       This comes from the IMS Data Monitor. It's a widely

Kaliner - direct

1       respected analysis of the pharmaceutical industry.

2       Q.       And that's PTX-98?

3       A.       Yes.

4       Q.       Can we go to PTX-98, please.

5               Is this the document, Dr. Kaliner?

6       A.       It is.

7       Q.       Do you have an understanding of what the purpose of  
8       this document was?

9       A.       This was an assessment by people who do  
10      pharmaceutical accounting and forecasting of what the  
11      prospects were for antihistamines after OTC Claritin. I  
12      don't remember the number of patients, but it's a good sized  
13      document full of data.

14              They are looking at the worldwide perspective.

15      Q.       What does this document say about azelastine and the  
16      future of antihistamines?

17      A.       It says nothing. Azelastine is hardly mentioned in  
18      this document. This document focuses on where  
19      antihistamines were in 2003 and what's going to happen in  
20      the future. And azelastine is hardly mentioned in this  
21      document. It has no presence whatsoever in this document.

22              So it's another confirmation that at least the  
23      people who looked at the pharmaceutical industry did not  
24      think that azelastine was important enough to even mention  
25      in this document.

Kaliner - direct

1 Q. Let's go back to the slides, please.

2 In 2002, Dr. Kaliner, what was the route of  
3 administration for fluticasone treatment of allergic  
4 rhinitis?

5 A. They were both nasal sprays.

6 Q. In your experience, especially around that time  
7 frame, do you have an understanding as to whether the dosage  
8 form affects patient acceptability or patient compliance?

9 A. Yes, it does.

10 So again, looking at data from the literature,  
11 75 percent of patients preferred oral treatments to nasal  
12 treatments. And I will tell you, there are some people that  
13 you can talk to till your blue in the face, or red in the  
14 face in my case, and you will never get to the use of nasal  
15 spray. They just what won't use a nasal spray.

16 The second thing is that, at least Fluticasone  
17 was a steroid, and patients are afraid of steroids. They  
18 don't know the difference between the steroids that make the  
19 Russians that make the Olympics and the steroids we use as  
20 anti-inflammatory agents. So you have to talk the patient  
21 into using a steroid.

22 As I said before, we were using the lowest dose  
23 we could when we were using steroids, ever.

24 I think I will stop there.

25 Q. Now, yesterday you may have heard Dr. Schleimer



Kaliner - direct

1 suggest that combining azelastine and fluticasone would have  
2 been a preferred approach to treating allergic rhinitis. Do  
3 you recall that?

4 A. I do.

5 Q. Do you agree with that assessment?

6 A. I don't.

7 Q. Can you explain to the Court why not?

8 A. I said it now several times. We were titrating  
9 steroids to the lowest dose we could possibly get away with.  
10 If you used fluticasone as your steroid, you would wanted to  
11 use it at the lowest dose that the patient needed to control  
12 the symptoms. That could have been two sprays once a day or  
13 one spray once a day or every other day or one spray less  
14 than that.

15 Azelastine is a 12-hour product. Once steroids  
16 start working, they have a long duration of effect. They  
17 work for days or weeks.

18 The dosing of two products with very, very  
19 different pharmacokinetics is extremely difficult to  
20 project.

21 So you have a hard time figuring out the dosing  
22 schedule.

23 What we were trying to do was to step up. We  
24 would do high dose, get the patient under control and step  
25 down. When you have a product series that has different

Kaliner - direct

1 kinetics like 12 hours, several days, you have an extremely  
2 difficult time figuring go out a step-up and step-down.

3 Finally, you would anticipate given azelastine,  
4 which has unpleasant side effects, and fluticasone, which  
5 has unpleasant side effects, together to give you additive  
6 side effects profile, that would definitely affect  
7 compliance.

8 Q. I want to identify for the Court some of the  
9 documents you relied on in assembling this information.  
10 PTX-42, is that the Storms article?

11 A. Yes.

12 Q. PTX-11, is that the Astelin label?

13 A. Yes.

14 Q. PTX-59, that is the Flonase label?

15 A. Yes.

16 Q. And PTX-326, that is ARIA?

17 A. The ARIA guidelines.

18 Q. You reviewed those documents in preparing the slide?

19 A. Yes.

20 Q. Dr. Kaliner, at the time that we are talking about,  
21 2002, were there any studies that combined oral  
22 antihistamines and corticosteroids?

23 A. Yes.

24 Q. Can you describe them for the Court?

25 A. This is a busy slide. I apologize. It has a lot of

Kaliner - direct

1 data that is important.

2 So what I have put together here is, along the  
3 blue box is part of the time scale from '88 to 2008. This  
4 red vertical line is when the patents became to date.

5 What I have summarized here is all the studies  
6 that looked at the potential benefit of adding an oral  
7 antihistamine to a nasal corticosteroid. And that is these  
8 gray boxes.

9 The authors here, the steroid here BDP is one of  
10 the steroids, and then there is an antihistamine, and in red  
11 is my interpretation of the data.

12 So we can talk about that.

13 So these are the studies that were done prior to  
14 2002. There were a couple more studies that were done after  
15 2002.

16 In the clear boxes are systemic reviews of the  
17 literature, Howarth and Nielsen before 2002, Nielsen did  
18 another review as did Akerlund in 2005.

19 Those are post-invention reviews that looked  
20 back over the world's literature.

21 Q. So, Dr. Kaliner, before I ask any further questions  
22 on this, I want to identify the PTX's that you relied on.  
23 The Juniper study, that is PTX-336?

24 A. Yes.

25 Q. Benincasa is 313?

Kaliner - direct

- 1 A. Yes.
- 2 Q. Simpson is PTX-39?
- 3 A. Yes.
- 4 Q. Drouin is 333?
- 5 A. Right.
- 6 Q. Brooks is PTX-332?
- 7 A. Yes.
- 8 Q. Ratner, 1998, is PTX-331?
- 9 A. Yes.
- 10 Q. Howarth is PTX-337?
- 11 A. Yes.
- 12 Q. Nielsen 2001 is PTX-36?
- 13 A. Yes.
- 14 Q. Nielsen 2003 is PTX-85?
- 15 A. Yes.
- 16 Q. The Di Lorenzo study is PTX-21?
- 17 A. Yes.
- 18 Q. Akerlund PTX-53?
- 19 A. Yes.
- 20 Q. Barnes is PTX-12?
- 21 A. Yes.
- 22 Q. And then the Ratner study in 2008 is PTX-330?
- 23 A. Yes.
- 24 Q. Did you review all these studies?
- 25 A. Yes.

Kaliner - direct

1 Q. In preparing this slide?

2 A. Yes.

3 Q. I want to direct you to just a few slides, a few of  
4 the studies.

5 Let's start with Nielsen 2001. Can we go to  
6 PTX-36, please.

7 Dr. Kaliner, can you read for the Court the  
8 sentence beginning with Combining antihistamines?

9 A. So Nielsen is a comprehensive review of the  
10 literature to date, 2001.

11 And he concluded from the world's literature  
12 that "Combining antihistamines and intranasal  
13 corticosteroids in the treatment of allergic rhinitis does  
14 not provide any additional effect to intranasal  
15 corticosteroids alone."

16 Q. You made a point that it's a comprehensive review to  
17 date as of 2001, did you not?

18 A. Yes.

19 Q. Can you explain to the Court the significance of  
20 that?

21 A. What he did was to look over all the articles on  
22 actually looking at oral antihistamines and nasal steroids  
23 and the combination of antihistamines and nasal steroids and  
24 made this conclusion based on their appreciation of the  
25 literature.

Kaliner - direct

1 Q. What does this statement mean, to your knowledge?

2 A. What it means that if you had a patient on a nasal  
3 steroid, and you gave him an antihistamine, you shouldn't  
4 predict any additional benefit from the antihistamine.

5 Q. Let's now turn to PTX-53, the Akerlund study,  
6 specifically, Page 17, right column, first paragraph, about  
7 ten lines down, I want to draw your attention, Dr. Kaliner,  
8 to the sentence that begins with Four double-blind, can you  
9 read that sentence?

10 A. "Four double-blind, double-dummy trials in 1250  
11 patients with allergic rhinitis have failed to show any  
12 significant difference on nasal symptoms between intranasal  
13 corticosteroid with and without oral antihistamine."

14 Q. Can you explain to the Court what that statement  
15 means to you?

16 A. The same thing as Nielsen. That is that, you would  
17 anticipate, if you had a patient on an intranasal  
18 corticosteroid and you gave him an antihistamine, you  
19 shouldn't anticipate any additional benefit from the oral  
20 antihistamine.

21 Q. Now, Akerlund published in 2003. Correct?

22 A. That's correct.

23 Q. That's after the 2002 invention time frame that we  
24 have been discussing?

25 A. Correct.

Kaliner - direct

1 Q. Why did you include a study that published afterwards  
2 in your analysis?

3 A. Just to show that nothing had changed after 2002, and  
4 as a matter of fact, with more information in hand, the  
5 conclusion is still the same. I may have missed. It might  
6 have been 2005. I apologize.

7 Q. Do you see at the end of the sentence you just read,  
8 there is footnotes, 227 to 230?

9 A. I do.

10 Q. Can we go to those footnotes.

11 Can we also put up PDX-4.50 side by side please.

12 Dr. Kaliner, what are these footnotes?

13 A. So these are the four double-blind -- the placebo  
14 controlled trials that were reviewed from which the  
15 conclusion that adding an oral antihistamine gave no  
16 additional benefit to a nasal steroid.

17 Q. Do you recall seeing those same studies in Dr.  
18 Schleimer's demonstrative yesterday?

19 A. I did. If you look at the -- I don't know how to say  
20 it -- the bottom right part, you can see that the four  
21 double-blind studies that were included in this review that  
22 concluded that antihistamines, oral antihistamines added  
23 nothing to nasal steroids are four of the studies that were  
24 relied upon by Dr. Schleimer to say the exact thing.

25 Q. Let's go to one other article. Drouin 1995, that is

Kaliner - direct

1 PTX-333. Do you recall Dr. Schleimer discussing Drouin in  
2 his demonstratives?

3 A. I do.

4 Q. Do you recall what his testimony was regarding  
5 Drouin?

6 A. I think Dr. Schleimer relied heavily on Drouin as  
7 showing positive results of adding Claritin Loratadine to  
8 their nasal steroid, which was Nasonex mometasone.

9 Q. Mr. Beal, can we go to Page 5 of the PTX.

10 If we can blow up the top part of the table.

11 Dr. Kaliner, can you explain to the Court what's  
12 being shown on this table?

13 A. First of all, I misspoke. I said Nasonex. This is  
14 data of a Schering study looking at the Schering Claritin  
15 and beclomethasone, Beconase, that was the Schering nasal  
16 steroid at this time.

17 What you are looking at here, the core of this  
18 data is looking at Claritin and the nasal steroid versus  
19 placebo and the nasal steroid.

20 And you can see that along the P Value Column,  
21 NS is not significant, that many of the issues are not  
22 significant.

23 There is a .05 significance value for several of  
24 the symptoms, and that means that they were statistically  
25 significant.



Kaliner - direct

1           So when I looked at this data, I have to tell  
2   you, this is the weakest positive data I have ever seen in  
3   my life. And I wish I had a statistician who could do this.

4           You are looking at statistical significance of  
5   48 percent improvement versus 55 percent improvement, or any  
6   of these numbers, 48 versus 61. In some magical way, they  
7   are statistically significant. I can't argue with that.  
8   They did it somehow.

9           But in terms of clinical significance, I am not  
10   about to change my treatment regimen to a patient when they  
11   can get a ten or 7 percent improvement if I put them on a  
12   different combination of medicines. This is clinically  
13   insignificant. This is the weakest positive data that you  
14   can have. And that is why on my summary slide I said weak  
15   positive data. This is as weak as it gets.

16   Q.       Let's go back to the slides, please. Looking back at  
17   your summary slide, what is your opinion on whether any of  
18   the studies would have suggested to a POSA in 2002 that  
19   there would have been a benefit in combining oral  
20   antihistamines and nasal corticosteroids?

21   A.       I think that a POSA would have looked at this data  
22   and said that there is no predictable improvement of adding  
23   a nasal steroid -- an oral antihistamine to a nasal steroid,  
24   that the efficacy that you get is from the nasal steroid,  
25   and that overwhelmingly the oral histamine would not have

Kaliner - direct

1 given you additional benefit.

2 Q. Now, yesterday, going back to Dr. Schleimer's  
3 testimony, do you recall Dr. Schleimer testifying that in  
4 his view conjunctive use of azelastine and fluticasone  
5 before 2001 were the closest prior art?

6 A. I heard that, yes.

7 Q. And did you also hear him testify that to show that  
8 prior use he relies on Dr. Accetta's patient records?

9 A. Yes.

10 Q. Did you look at Dr. Accetta's patient records?

11 A. I did.

12 Q. In your view, do Dr. Accetta's patients records  
13 reflect a fixed dose use of azelastine and fluticasone?

14 A. No. Dr. Accetta was using the azelastine in much the  
15 same way that I did. I used it as a basis, as well as he  
16 did.

17 I may not have used Flonase. But I used a nasal  
18 steroid.

19 What you do is you cycle patients.

20 I know this sounds contradictory to what I just  
21 said about oral antihistamines. But we have been using oral  
22 antihistamines since 1955. The traditional approach, and  
23 what's in the guidelines, is to use oral antihistamines, and  
24 if the patients are not well controlled add a nasal steroid.

25 What would happen is if they had oral

Kaliner - direct

1 antihistamines and they were well, that's all we did. If we  
2 added a nasal steroid and they got better, we were happy.  
3 We couldn't tell at clinical practice whether the nasal  
4 steroid was the effective medicine or the antihistamine was  
5 the efficient medicine.

6 But if they weren't better, we would then go to  
7 some additional modalities, decongestants, drying agents,  
8 what have you. And eventually we would try azelastine, and  
9 some of the patients got better with azelastine.

10 When you added azelastine it was usually a late  
11 addition, I think Dr. Accetta's data also showed that he  
12 added azelastine months or years after using nasal steroids,  
13 the same thing I did.

14 And you would use it and patients would use it  
15 for a period of time, but it was never a fixed dose. You  
16 never said to the patient use this product first and then  
17 use this product, wait a period of time between the  
18 products. You use it precisely together. We never did  
19 that. That was just not part of the practice.

20 Q. Now, Dr. Kaliner, when was the first time you became  
21 aware of any study assessing the efficacy or safety of  
22 conjunctive azelastine/fluticasone combination?

23 A. The first time that I and I think anybody else ever  
24 heard about it was Ratner 2008. Ratner 2008 was an epical  
25 study.

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1 Q. Did you say ethical?

2 A. Epical. Seminal.

3 Q. And that is six years after the invention date;  
4 right?

5 A. Yes.

6 Q. So can you discuss for the Court your impressions on  
7 the findings of the Ratner 2008 study?

8 A. Yes. Well, first of all, Ratner was 2008. So that  
9 is six years after 2002. Ratner is what we call a proof of  
10 concept study. Ratner's colleagues had the concept, despite  
11 what was in the literature about oral antihistamines not  
12 being particularly useful with nasal steroids, that maybe a  
13 nasal antihistamine combined with a nasal steroid would be  
14 useful. So that is a concept, and the Ratner study proved  
15 the study that adding a nasal antihistamine to a nasal  
16 steroid was particularly effective.

17 Now, Ratner is not at all what we were doing in  
18 2002. The Ratner study was, first of all, it is a clinical  
19 trial. Patients had high compliance rates. They did  
20 precisely what they were told to do: two sprays of Astelin,  
21 wait 15 to 30 minutes, two sprays of Flonase in the morning.  
22 In the evening, they would do two sprays of Astelin.

23 So that protocol, nobody did that protocol in  
24 clinical practice, and no patients would do it either. If  
25 you pause 15 to 30 minutes between two medicines, that

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1 second medicine never gets used. So there is no compliance  
2 whatsoever.

3 So this is no way reflects what we were doing in  
4 clinical practice, but it was a wonderful clinical design  
5 for this particular study.

6 Q. So as a practicing clinician, treating allergies,  
7 does that summarize your reaction when you became aware of  
8 the study?

9 A. I'm sorry. I didn't follow the question.

10 Q. So when you first became aware of the findings of  
11 Ratner, what was your reaction? Let me ask it that way.

12 A. I was blown away by it. I mean it was an amazing  
13 confirmation that this combination would be effective.

14 Q. Now, you mentioned increased side effects observed  
15 with the Ratner investigators; correct?

16 A. Well, I have. That we predicted that if you combined  
17 the medicines, you get increased side effects.

18 Q. And can you elaborate a little bit further for the  
19 Court?

20 A. So this is from Ratner. And what you are seeing  
21 here is that in the arm of Ratner where they had azelastine  
22 alone, adverse taste was only 8 percent in the study and  
23 headache was 4.

24 In the arm where it was fluticasone alone, the  
25 taste was 2 and headache 4.

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1                   When you did azelastine, waited 15 minutes and  
2                   did fluticasone, the taste aversion was up to 13.5 percent,  
3                   which was a synergistic increase.

4                   And headaches were at 5.8, and that is a  
5                   near-additive.

6                   So as you would expect, spritzing the nose, you  
7                   get additive or synergistic side effects.

8           Q.       Now, do you recall Dr. Schleimer testifying yesterday  
9                   that combining azelastine and fluticasone would enhance  
10                  compliance?

11          A.       I think I remember him saying that.

12          Q.       Do you agree with his assessment?

13          A.       Based on what I just showed, if you used these  
14                   medicines conjunctively, I would expect the acid side effect  
15                   we just showed and that would effect the side effects. The  
16                   more side effects you have, the less compliance you have.  
17                   So my expectation would be conjunctive use would increase,  
18                   would lead to increased side effects as confirmed by Ratner.

19          Q.       And are you aware of any other considerations that a  
20                   clinician, POSA at the relevant time would have considered  
21                   in determining whether or not to combine azelastine and  
22                   fluticasone?

23          A.       So now we're going back to pre-Ratner, because Ratner  
24                   changed everything. But in 2002, I would have expected that  
25                   there would have been an extraordinary difficulty in showing

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1     that the antihistamine added anything to the nasal steroid,  
2     particularly in light of the FDA's combination rule.

3     Q.     And can you explain to the Court a little bit more  
4     what the FDA's combination rule is?

5     A.     So the FDA has a long standing policy that if there  
6     is a product that combines two drugs, each of the drugs has  
7     to make a significant contribution to the efficacy of the  
8     product. And so that basically if you put an antihistamine  
9     with a steroid, both of the products have to contribute to  
10    it. That means that the combined product is statistically  
11    significantly better than each of the components.

12    Q.     Dr. Kaliner, do you recall Dr. Schleimer yesterday  
13    testifying that in his opinion, the Howarth study and the  
14    Nielsen study we covered on the previous slide were contrary  
15    to what the ARIA authors were suggesting? Do you recall  
16    that?

17    A.     I heard him say that. I did.

18    Q.     And do you agree with him?

19    A.     Oh, no. No. I mean Howarth and the senior authors,  
20    such as Ronald Dahl, are some of the senior physicians in  
21    Europe, and what is more, they're authors of the ARIA  
22    guidelines. They're authors in the ARIA guidelines. They  
23    wouldn't be contrary to the ARIA guidelines. They wrote the  
24    ARIA guidelines.

25    Q.     So let me ask you this. And I guess this ties into

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1 Dr. Wedner's testimony.

2 Can you just explain to the Court, in 2001, when  
3 a patient first presents to you with allergic rhinitis, you  
4 mentioned cycling. How does the cycling of treatments, how  
5 does that work? How would you approach treatment?

6 A. So we're talking about before 2002?

7 Q. Correct.

8 A. So what I would do is to use an oral antihistamine  
9 first and then I would add something else if they weren't  
10 totally satisfied. Generally, it would be a nasal steroid,  
11 and I would use a dose of nasal steroid. It might be a  
12 higher dose than I eventually end up with, but then I would  
13 lower the dose to the lowest effective dose I could get away  
14 with.

15 If I added azelastine as part of the combination,  
16 I would do the same thing and try to use the lowest dose of  
17 medicine that worked.

18 Q. Now, yesterday, do you recall Dr. Schleimer  
19 testifying that in his opinion, the patents themselves  
20 didn't provide any dosing guidelines?

21 A. Yes, I heard him say that.

22 Q. Do you agree with his assessment?

23 A. Well, okay. Before 2002, I wouldn't have thought to  
24 put azelastine and fluticasone in the same bottle and use it  
25 as a combined nasal spray. You know, we were just starting



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1 with azelastine, and I don't think that anybody appreciated  
2 what happened with Ratner.

3 But as I look at the patent, I have been a  
4 scientist and I'm a clinician now. I look at this and I see  
5 a nasal spray. It has got azelastine and fluticasone in it,  
6 I know both of those products, and the dose of azelastine is  
7 pretty comparable to the dose that is in azelastine. And  
8 the dose -- sorry, the concentration of azelastine is what  
9 is in the concentration of Astelin and the concentration of  
10 fluticasone is the same as in Flonase.

11 So I look at this and I say, well golly, if I  
12 had this in practice, how would I use it? I wouldn't want  
13 to use more Flonase than I have to. So I wouldn't exceed  
14 the Flonase dosing. It would be either two sprays once a  
15 day or one spray twice a day, and that is what I would start  
16 with.

17 And, lo and behold, that turns out to be Dymista.  
18 So it wouldn't be that difficult to figure out how to use  
19 this product.

20 Q. Now, we have heard a lot about ARIA. Can you speak  
21 to the Court, briefly, the recommendation in the ARIA  
22 guidelines for how to approach treatment?

23 A. Do you want to give me some help with this?

24 Q. Sure. Let's go to PTX-336.

25 And I apologize, Dr. Kaliner. Bear with me for

1 a moment.

2 Can we go to page 119? PTX-326, 119.

3 So, Your Honor, I'll probably have to spend a  
4 couple minutes on this. Would you prefer?

5 THE COURT: I think it is best if we stop then.  
6 Thank you for that.

7 So before we break, any thoughts on the schedule  
8 in light of what I had said before the break?

9 MR. VARUGHESE: So for plaintiffs --

10 (Ms. Everett rises.)

11 MR. VARUGHESE: I'm sorry, go ahead.

12 THE COURT: Anyone and everyone.

13 MR. VARUGHESE: So for plaintiffs, Your Honor,  
14 we certainly agree with that, and we accept their proposal.  
15 I'm sure defendants will.

16 MR. LOMBARDI: And, Your Honor, we're fine  
17 with tomorrow, no problem. We do have some issues on the  
18 schedule of, I think you said, the 28th due to some trials  
19 that were previously scheduled, but we're willing to be here  
20 early in the morning, late at night or whatever other time  
21 we work out, but for tomorrow we're completely fine.

22 THE COURT: So we will finish tomorrow. We won't  
23 do closings tomorrow, and I'll look at my calendar more  
24 closely and we'll confer, you know, over the coming days to  
25 find a date that you all can come back post-briefing for oral

1 argument.

2 Is that acceptable to defendants?

3 MR. LOMBARDI: That is, Your Honor.

4 THE COURT: And acceptable to plaintiffs?

5 MR. VARUGHESE: Yes, Your Honor.

6 THE COURT: And assuming we start at 8:30  
7 tomorrow, is there any sense as to how much of the day we're  
8 likely to need? And if no sense, then that is fine. I'm  
9 available until 7:00.

10 MR. VARUGHESE: I think our guess is we'll  
11 definitely finish before 7:00, Your Honor.

12 MR. LOMBARDI: If you are looking for more  
13 specificity, I think there is a chance we will have time to  
14 spare. We tried to work this out. I think we came up with  
15 we might be done in the 5:00ish range.

16 THE COURT: Okay.

17 MR. LOMBARDI: I hope you won't hold us to it.

18 THE COURT: No, I won't hold you to it. I just  
19 know one reason I'm going to cut out now is I told people in  
20 the building they can expect us to be done at 7:00, and that  
21 is what I told them tomorrow. So I'm going to continue to  
22 tell them that about tomorrow, and hopefully we'll get done  
23 at least a little bit before 7:00.

24 Okay. Well, thank you all very much. We'll see  
25 you at 8:30 tomorrow morning.

(Proceedings adjourn at 7:00 p.m.)

I hereby certify the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Brian P. Gaffigan  
Official Court Reporter  
U.S. District Court

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