

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

NO. 14-1453-LPS

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Wilmington, Delaware
 Tuesday, December 13, 2016
Bench Trial - Volume A

- - -

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

APPEARANCES:

RICHARDS LAYTON & FINGER, P.A.
 BY: FREDERICK L. COTTRELL, III, ESQ., and
 SELENA E. MOLINA, ESQ.

and

STERNE KESSLER GOLDSTEIN & FOX, LLP
 BY: UMA N. EVERETT, ESQ.,
 DENNIES VARUGHESE, ESQ.,
 RAMI BARDENSTEIN, ESQ.,
 ADAM C. LaROCK, ESQ.,
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 (Washington, District of Columbia)

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1 APPEARANCES: (Continued)

2
3 PROCTOR HEYMAN ENERIO, LLP
4 BY: DOMINICK GATTUSO, ESQ.

5 and

6 WINSTON & STRAWN, LLP
7 BY: GEORGE C. LOMBARDI, ESQ.,
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17 Counsel on behalf of Defendants

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

20 (REPORTER'S NOTE: The following bench trial was
21 held in open court, beginning at 3:32 p.m.)

22 THE COURT: Good afternoon.

23 (The attorneys respond, "Good afternoon, Your
24 Honor.")

25 THE COURT: Please have a seat.

On this first day of trial, let's begin by
noting your appearances for the record, starting with

1 plaintiffs.

2 MS. EVERETT: Your Honor, Uma Everett on behalf
3 of plaintiffs. With me this week, you will hear from my
4 colleagues, Mark Evens.

5 MR. EVENS: Good afternoon, Your Honor.

6 MS. EVERETT: Dennies Varughese.

7 MR. VARUGHESE: Good afternoon, Your Honor.

8 THE COURT: Good afternoon.

9 MS. EVERETT: And Adam LaRock.

10 MR. LaROCK: Good afternoon.

11 THE COURT: Good afternoon.

12 MS. EVERETT: Your Honor, we also have client
13 representatives here this week to attend trial. We have
14 client represents from Meda. From your left, Your Honor we
15 have Marten Osterlund from Sweden.

16 MR. OSTERLUND: Good afternoon.

17 MS. EVERETT: We have Gabrielle Endler from
18 Germany.

19 MS. ENDLER: Good afternoon.

20 MS. EVERETT: We have Matthew Polley from New
21 Jersey.

22 MR. POLLEY: Good afternoon.

23 MS. EVERETT: We also have representatives from
24 Cipla Limited.

25 Again, from your left, Your Honor, we have

1 Bhakti Patil.

2 MS. PATIL: Good afternoon.

3 MS. EVERETT: And we have Aarti Deodhar.

4 MS. DEODHAR: Good afternoon.

5 MS. EVERETT: From India.

6 THE COURT: Welcome to all of you.

7 All right. Mr. Cottrell, do you want to put
8 your appearance on the record?

9 MR. COTTRELL: I'm sorry. Fred Cottrell from
10 Richard Layton, Delaware counsel. Thank you.

11 THE COURT: Thank you. And now the other side
12 of the room.

13 MR. GATTUSO: Good afternoon, Your Honor.

14 THE COURT: Good afternoon.

15 MR. GATTUSO: Dominick Gattuso from Proctor
16 Heyman Enerio on behalf of Apotex.

17 I also have with me George Lombardi.

18 MR. LOMBARDI: Good afternoon.

19 MR. GATTUSO: Charles Klein.

20 MR. KLEIN: Good afternoon, Your Honor.

21 MR. GATTUSO: Ilan Wurman.

22 MR. WURMAN: Good afternoon.

23 MR. GATTUSO: Kevin Warner.

24 MR. WARNER: Good afternoon.

25 MR. GATTUSO: And in the back, we have Ryan

1 Hauer who isn't with us now but will be before Your Honor.

2 And then from the client Apotex, we have Robert
3 Shapiro, senior patent counsel.

4 (Mr. Shapiro nods greetings.)

5 THE COURT: Welcome and good afternoon to all of
6 you.

7 MR. GATTUSO: Thank you.

8 THE COURT: Thank you very much. So we are here
9 for trial. As I think you all know, I have another trial
10 going on upstairs I guess that is. And so that is,
11 hopefully you're aware, moving along at the pace we
12 anticipated, meaning as of now we expect we will close the
13 evidence tomorrow some time. I'll certainly be with you by
14 3:30 tomorrow.

15 If it turns out that I could be here sooner than
16 that, we'll let you know. If it works out for all of you,
17 we'll start sooner, but since that is a little bit up in the
18 air, we won't force you all to come in before 3:30 but if
19 it does work for me and it works for all of you and your
20 witnesses, we might be able to get started earlier than
21 3:30.

22 We plan to have closing argument in the jury
23 trial Thursday morning, and so if all goes according to
24 plan, we'll get the case to the jury by around lunchtime
25 Thursday, which means we could start early in the afternoon

1 on Thursday and hopefully be with you most of Friday, all
2 subject to if the jury has a question or needs me for some
3 other reason.

4 Are there any questions about any of that? No?
5 No.

6 Before we get started with openings, any issues
7 from plaintiffs?

8 MS. EVERETT: No, Your Honor.

9 THE COURT: And from defendant?

10 MR. LOMBARDI: No, Your Honor.

11 THE COURT: And do both sides intend to give an
12 opening?

13 MR. LOMBARDI: Yes, Your Honor.

14 MS. EVERETT: Yes, Your Honor.

15 THE COURT: Then we'll I believe we were going
16 to hear from defendants first.

17 MR. LOMBARDI: Your Honor, I do have copies of
18 slides. I'm not sure how many copies.

19 THE COURT: If you have three, that would be
20 very helpful. Thank you.

21 (Demonstratives passed forward.)

22 MR. LOMBARDI: And, Your Honor, one note. And
23 for the record, George Lombardi on behalf of Apotex. One
24 note about the slides, Your Honor.

25 In order to correct some objections or respond

1 to some objections, we changed some of the slides. I think
2 the copy I just gave you might have a couple of slides that
3 actually will be corrected, and we will substitute that
4 tomorrow for you so that the slides you will see on the
5 screen is the slide that is appropriate.

6 THE COURT: Okay. Thank you.

7 MR. LOMBARDI: And, again, may it please the
8 Court. George Lombardi on behalf of Apotex.

9 Your Honor, I want to talk to you a little bit
10 about the basics of this case.

11 First of all, Apotex is the defendant here and
12 the only defendant here. The other parties here are Meda,
13 Cipla, and they are, I will describe who they are. But what
14 has brought us here is that Apotex has filed an ANDA and is
15 seeking the right to sell the generic version of a drug
16 called Dymista. And you are going to hear a lot more about
17 Dymista obviously as we go long and we go along today.

18 Cipla, the Indian company that was introduced
19 here before is the patent holder. Meda has an exclusive
20 license and is the distributor of the product in the United
21 States.

22 Meda, you will see, from time to time, you will
23 see a company called MedPointe in the documents. That Med
24 Point is Meda. MedPointe became Meda over time, and it is
25 our understanding Meda was acquired by a company called

1 Mylan recently. So that is the corporate layout of the
2 various defendants.

3 And here is the gist of the case.

4 Your Honor, our central defense in this case is
5 obviousness. And that is what we're going to spend most of
6 our time talking about in this case. The claims cover the
7 co-formulation, meaning the combination of two known FDA
8 approved drugs combined with known excipients or inactive
9 ingredients for a known use.

10 So let me talk about that in a little bit more
11 detail. The two known FDA drugs here are azelastine
12 hydrochloride and fluticasone propionate. They were known
13 to treat a condition known as allergic rhinitis, which I
14 will talk about a little bit more. It's hayfever is what it
15 is commonly known as.

16 They both treated it separately. They both
17 had separate mechanisms of action for treating allergic
18 rhinitis. So they operated in different ways on the same
19 condition but they were both treatment for allergic
20 rhinitis.

21 And the evidence here will be it was taught in
22 the art specifically to combine azelastine hydrochloride and
23 fluticasone propionate together to treat allergic rhinitis.

24 As to the excipients, all of the excipients, and
25 again, the excipients are the inactive ingredients, as I'm

1 sure Your Honor is aware. All the excipients claimed here
2 were known in the art. And, in fact, all of the excipients
3 that are part of the claimed formulations were used with
4 either azelastine hydrochloride or with fluticasone
5 propionate, and the excipients that are used in the claimed
6 formulation here operate exactly as they did in the prior
7 art, operate in the same way.

8 And this combination, this formulation that is
9 combined is being used for a known purpose. It is being
10 used to treat allergic rhinitis.

11 The fluticasone and azelastine hydrochloride --
12 and Your Honor, we'll probably have a tomato, tomato thing
13 with azelastine and we will try to conform things as we go
14 along. But azelastine hydrochloride and fluticasone, as I
15 said, were used to treat allergic rhinitis. So there is
16 literally nothing new about what has been put together and
17 claimed as an invention here. There is no surprising
18 results. Everything works as it was taught to work in the
19 prior art. And the claims as a result are obvious.

20 So let me give you some of the background about
21 the dates, background information you are going to hear a
22 lot more about as we go along.

23 There are two patents at issue in the case. And
24 plaintiffs have chosen to assert 15 claims, so we're going
25 to have to deal with all 15 claims.

1 The first, the patents are slightly different but
2 really go to the same basic principle. So the '620 patent,
3 which is the one on the left, is a formulation patent which
4 literally sets forth the azelastine hydrochloride, the
5 fluticasone, and various excipients together as a combination,
6 combination formulation.

7 The '428 patent is a method patent, a method of
8 treatment patent, but the patent is a method of treatment
9 that employs the formulation. So the fundamental issue is
10 the same from the method of treatment claims to the claims
11 that are for the formulation.

12 Now, I'm not going to go through all the claims
13 here in detail this morning, but to give you a representative
14 example, Your Honor, I took one of the most complete claims in
15 terms of the number of elements that it refers to just to give
16 you an example.

17 And this is from the '428 patent, claim 1 which
18 is one of the method of treatment patents for seasonal
19 allergic rhinitis. And you can see the first two elements
20 there are azelastine hydrochloride and fluticasone
21 propionate. Those are the active ingredients I have been
22 talking about.

23 And from that point down are various excipients
24 that have different purposes. Each of them has a different
25 purpose. So we'll talk about what the preservatives do,

1 with those first two there, what a thickening agent does,
2 what a surfactant does and so forth.

3 And the claim, while there are 15 claims, all
4 of the claims are essentially this or some subset of this.
5 Sometimes there is a claim relating to pH in there and
6 sometimes there is a claim related to the size of the
7 particles in there as well, but this is fundamentally what
8 is going to be at issue throughout the entirety of the 15
9 claims that are at issue here.

10 So what is the fundamental story on the prior
11 art? And, Your Honor, this is what fundamentally happened.

12 Azelastine hydrochloride was marketed as a drug
13 called Astelin, commercially available well before the
14 critical date. And just so you have it in mind, Your Honor,
15 the critical date here is in 2002.

16 And so azelastine hydrochloride, Astelin, was
17 available before 2002. It is, azelastine hydrochloride is an
18 antihistamine, and antihistamines were known as treatments
19 for allergic rhinitis, and azelastine hydrochloride was
20 specifically known as that kind of treatment.

21 Also on the market before the critical date was a
22 drug called Flonase, and Flonase was fluticasone propionate.
23 That was the active ingredient. That is a corticosteroid, and
24 corticosteroids are known to treat allergic rhinitis as well
25 and Flonase, in particular, fluticasone propionate, treats

1 allergic rhinitis.

2 Those two, our position is all that happened
3 here is that those two formulations were put together to
4 create the drug that is at issue here, Dymista. Dymista
5 includes azelastine hydrochloride as one active ingredient
6 and includes fluticasone propionate as the other active
7 ingredient. That is fundamentally what happened here.

8 Now, Dymista, as was the case with azelastine
9 hydrochloride and fluticasone propionate is a nasal spray,
10 sprayed into the nose to treat allergic rhinitis.

11 So what is allergic rhinitis? I made reference
12 to this before, Your Honor. It is what is commonly known as
13 hayfever. And what happen is that the patient, that the
14 person who is victimized by allergic rhinitis is exposed to
15 allergens like pollen and on exposure to allergens starts to
16 experience symptoms, symptoms sneezing, wheezing, coughing
17 irritation of the nasal mucous and so forth, and this can go
18 on for quite some time.

19 And so the way the two prior art drugs worked,
20 Astelin and fluticasone -- and Flonase is as follows.
21 Astelin was known to be particularly good for the early
22 phase response to the allergen. So if somebody with
23 allergic rhinitis was exposed to pollen and started to
24 react, the antihistamine, Astelin, would have a relatively
25 fast effect and would address those early phase symptoms.

1 With respect to Flonase, the fluticasone
2 compound, it was known that that would have more of an
3 effect on the late phase, the late phase symptoms. And so
4 it was actually viewed that Flonase or fluticasone component
5 of steroid treatment, what was considered the first line of
6 defense.

7 And the second line of defense was putting in
8 the antihistamine because the steroid frequently didn't take
9 effect for a few days and the patient would need some relief
10 in the few days before this steroid could take effect. That
11 was the fundamental way the two worked in the art and not
12 surprisingly, given the way I described that to you, it is
13 no surprise at all that doctors concluded that these drugs
14 should be prescribed together to patients.

15 And sometimes you will hear that referred to,
16 Your Honor, as conjunctive treatment, meaning the two are
17 prescribed together, meaning not as part of the same
18 formulation but prescriptions to both together. And what
19 I put up on my screen is again in the prior art, and it's
20 called the ARIA guidelines, and ARIA stands for Allergic
21 Rhinitis Impact on Asthma.

22 And there were guidelines put together by
23 persons skilled in this art by doctors skilled in the art to
24 advise how to treat allergic rhinitis. And you can see, and
25 you are going to hear the witnesses talk about this, that

1 before the critical date, the priority date in this case,
2 on the left you can see it is advised to use intranasal
3 glucocorticosteroids, that is what fluticasone or Flonase
4 is, as a first line treatment.

5 And the second column, you can see that you --
6 you can see the reference to adding HI antihistamines, and
7 that is what kind of product Astelin was, azelastine
8 hydrochloride.

9 So the prior art specifically suggested adding
10 these two types of drugs together to treat an individual
11 patient. That was known in the art.

12 And you're actually going to hear evidence in
13 this case that doctors before the critical date actually did
14 prescribe Flonase and Astelin, the prior art compounds here
15 together to their patients.

16 So the first witness you are going to hear
17 from today is Dr. Accetta, and he is going to show you some
18 patient records that evidence the fact that back before the
19 critical date, you can see at the top, allergic rhinitis is
20 what is being treated, and the medicines are Flonase and
21 Astelin.

22 So this was being done in the art, this kind of
23 conjunctive treatment using the two drugs was being done in
24 the art.

25 And, again, given all that I have told you, it

1 is no surprise that there were calls in the art that if
2 we're going to be prescribing these two drugs, conjunctively
3 to patients, there ought to be a drug that puts them both in
4 the same bottle and treats people from the same bottle with
5 those same drugs.

6 And so the Spector reference from 1999 sets that
7 forth. And you can see there is a reference to the symptoms
8 observed in EPR are most effectively managed by an H1
9 receptor antagonist.

10 EPR is early phase rhinitis which is what we
11 referred to before, saying those symptoms from early phase
12 rhinitis are most effectively managed by an antihistamine.
13 That is what an H1 receptor antagonist is. That is what it
14 is talking about as azelastine hydrochloride.

15 Whereas the effects of LPR, which stands for
16 late phase rhinitis, are best managed with a corticosteroid.
17 And that is what fluticasone is, a corticosteroid.

18 So here is the important point and what is
19 perfectly logical that the art would be saying this is,
20 therefore, the ideal pharmacologic therapy would be a drug
21 that possessed not only the H1 receptor antagonist activity,
22 meaning the antihistamine activity, but also the
23 antiinflammatory activity, and that is the activity of the
24 corticosteroid.

25 So the art was specifically calling for the

1 combination of these types of drugs together. And beyond
2 that, Your Honor, the art was specifically calling for and
3 teaching the combination of the precise active ingredients
4 that are at issue in this case.

5 So in 1997, Proctor & Gamble filed an EPO, a
6 European patent application; and in that patent application,
7 they called for a treatment which consisted of fluticasone
8 and azelastine from a very small group of corticosteroids
9 and from a very small group of antihistamines to be used
10 as an intranasal carrier, to be used to treat allergic
11 rhinitis.

12 So the art specifically taught the use of these
13 active ingredients.

14 So when plaintiffs talk to you about being the
15 first with this, what they'll never be able to establish is
16 that they were the first to have the idea. This idea was
17 out there in the art. This idea to combine fluticasone
18 and azelastine hydrochloride was out there, known in the
19 art, taught in the art, and claimed by people like Proctor &
20 Gamble. And there are other examples of this as well, Your
21 Honor.

22 So what will plaintiffs say about this?
23 Plaintiffs will present, based on what we have seen in
24 discovery, Your Honor, plaintiffs will present evidence that
25 there are articles out there that teach away. I put

1 asterisks by the articles that are relied on by plaintiffs;
2 and we will go through with the experts these articles and
3 the conclusion from these articles is that they don't teach
4 away, and, in fact, encourage the use of fluticasone and
5 azelastine hydrochloride.

6 But for simplicity sake, just so you understand
7 the timeline, the ARIA guidelines that I referred to that
8 call for a combination of these types of drugs came after --
9 came before the priority date and after all of those studies
10 were issued. So the point is that even given whatever
11 plaintiff wants to say about those studies, the ARIA
12 guidelines was still recommending them.

13 And with that, Your Honor, we believe it is
14 beyond obvious that azelastine hydrochloride and fluticasone
15 should be suggested in the art and were obvious over the art.

16 Your Honor is very aware of the case law on this
17 area, and I won't dwell on this at this point. But just as
18 a reminder, the *Richardson-Vicks* case was a case that
19 originated in this District and the Federal Circuit, and
20 actually the District Judge in this case overturned jury
21 verdict of validity.

22 It involved a situation where two active
23 ingredients had been used separately and prescribed for the
24 same purpose and then were put in the same tablet, which
25 is the same situation that we have here, and it was ruled

1 obvious in that instance.

2 There are other things as part of the
3 formulation. There are excipients that are part of the
4 formulation. What effect do these excipients have on the
5 obviousness analysis here?

6 And the short answer, judge, is it doesn't
7 change the analysis. And I'm not going to go through
8 everything on this chart, but I'll describe to you what can
9 be taken from this chart is we put up the excipients from
10 the Flonase label, the prior art fluticasone label, and from
11 the Astelin label, the prior art azelastine label, and we
12 put adjacent to that one of the claims of the patent.

13 What you will find in summary in this case, Your
14 Honor, is that with one exception, all of the excipients
15 were used with either Flonase -- all the excipients that are
16 claimed here were used with either Flonase or azelastine, or
17 Astelin, in those two labels. All of them but one of them
18 were used.

19 And with respect to that one, it's an excipient
20 that is called a tonicity adjustor, and we're going to talk
21 a lot about that, Your Honor. But at a high level, a
22 different tonicity adjustor was used and was in the Flonase
23 level or the Astelin label, but when you look at the art,
24 there is a patent that covers the Astelin product and covers
25 azelastine hydrochloride, and that patent specifically

1 mentions glycerin which was the excipient that was used in
2 these claims. So the art completely discloses the use of
3 these excipients with these components.

4 So at the end of the day, Your Honor, when we
5 look at these formulations, and we look at these excipients,
6 we are going to find that all the excipients that are used
7 were known in the art, all of the excipients were known to
8 have particular purposes in their use, and all of the
9 excipients as used in Dymista, as used in the claimed
10 invention, work in the same way as was taught in the art.
11 There was nothing new about the excipients that were used
12 here.

13 So what did plaintiff say about that and
14 throughout the discovery and expert portions of this case,
15 leading up to this trial?

16 Well, they generally said that this is
17 formulation, Your Honor. And when you put components
18 together, you never know whether they're going to work until
19 you actually put them together.

20 But that kind of general unpredictability has
21 been rejected by the Federal Circuit as a way to avoid
22 obviousness, Your Honor.

23 The question here is would one reasonably expect
24 it to work? And an assertion that generally the art is
25 unpredictable or you can't know until you put things

1 together is not sufficient.

2 There will not be any art presented that
3 indicates that any of these excipients could not work with
4 any of the other excipients or could not work with the
5 active ingredients.

6 Now, there is another argument that plaintiffs
7 are going to make here, Your Honor, about this formulation.
8 And they're going to say, well, this formulation, because it
9 involves fluticasone, which is a compound that is suspended,
10 is in suspension normally when you formulate it. Suspension
11 just means the particles, for lack of a better word, are
12 suspended in the water, which is the vehicle, and azelastine
13 hydrochloride is dissolved, it goes into solution. So those
14 are two different ways of being carried.

15 They're going to say, well, that creates
16 problems for a formula here. But there is nothing in the
17 art that teaches that there is any issue with a solution and
18 a suspension being in the same formulation. And, in fact,
19 the evidence will be to the contrary, and the evidence will
20 be that azelastine hydrochloride and fluticasone function
21 exactly as one would expect them to function based on how
22 they function in the prior art. In other words, azelastine
23 is dissolved and fluticasone is in suspension.

24 Now, what plaintiffs did when they were in the
25 Patent Office and faced with an obviousness rejection in the

1 Patent Office, they did some testing to try to show that
2 there were problems in doing this kind of formulation. And
3 the testing that they did in that context came from Cramer,
4 which was the Proctor & Gamble patent application I pointed
5 out to Your Honor earlier. And they went to an example
6 there that involved different components that are at issue
7 in this case, and they did the testing based on that example.

8 Now, the Patent Office, at the time this testing
9 was submitted, had indicated that the claimed invention was
10 considered prima facie obvious. And they submitted this
11 testing as an attempt to try to overcome the obviousness
12 finding.

13 And they did overcome the obviousness finding
14 but not with the testing, Your Honor. The Patent Office
15 did not even mention this testing in the reasons for
16 allowability of the patent. They are going to mention some
17 other things which I'm going to talk about shortly but they
18 didn't mention the testing, and that is because the test was
19 flawed.

20 The testing they submitted to the Patent Office
21 was incomplete. It was testing that was done with making no
22 attempt to optimize the formula, and the criticisms they
23 make of the testing are criticisms that don't relate to
24 anything other than optimization.

25 But this is not a case about optimization or FDA

1 approval. This is a case, a patent case and about whether
2 claims were obvious. So the testing other is not relevant
3 as is indicated by the way that the Patent Office handled it.

4 You can see that in the notice of allowability,
5 there is reference to certain secondary considerations,
6 which played a big part in the Patent Office's decision to
7 approve the patent to allow the patent here.

8 Your Honor I know is supremely familiar with the
9 law of secondary considerations, so I'm not going to talk
10 about that. And there are a lot, there has been a lot of
11 discussion of secondary considerations in various ways
12 throughout this case. I'm not going to try to anticipate
13 every secondary consideration.

14 I will have something to say at the end of the
15 case about anything that is referenced, but I do want to
16 reference a few things for Your Honor to keep in mind as
17 you hear the evidence that is pertinent to secondary
18 considerations.

19 The first is the existence of blocking patents.
20 There is going to be a lot of talk about how Dymista was
21 the first drug of this kind to get to the market, to be
22 commercially sold, but that is in part explained by the
23 patent landscape that existed at the time.

24 So the PTO didn't have this patent landscape
25 before it, did not consider these blocking patents in

1 considering the secondary considerations. And this is what
2 that landscape was.

3 The patent covering -- there was a patent
4 covering fluticasone, one of the two active ingredients
5 here, that issued way back in 1982 and ran to the early
6 2000s.

7 There was a patent covering Astelin which ran
8 from 1992 and, when you include pediatric exclusivity,
9 barred people from the market until 2011.

10 So anybody who might have considered using a
11 combination of those two active ingredients would have been
12 faced with those two patents during that period of time.

13 And on top of that, Your Honor, on top of that,
14 in 2003, in the middle of the screen there, December 24th,
15 2003, the application for the patents that matured into --
16 for the patents that are in suit today was published. So
17 anybody looking at this landscape at the time would know
18 that there were two patents out there, one each on
19 fluticasone and azelastine, and would know that somebody had
20 already gotten a patent on file covering the two together.

21 And one thing further to keep in mind, Your
22 Honor, is that the azelastine patent was something that
23 plaintiffs had rights in, so that didn't block them. That
24 didn't, didn't block them.

25 So somebody of skill in the art, looking at this

1 landscape, would know that they faced huge hurdles in
2 trying to get to market with the combination drug. So when
3 plaintiffs in this case say that they were the first to
4 commercially market it, this patent landscape had a lot to
5 do with that.

6 I believe there will likely be some reference to
7 testing that was done to show that the Dymista formulation,
8 of the claimed formulation in this case was superior,
9 unexpectedly superior. But it's important to keep in mind
10 what the testing was they did, because I don't think the
11 testing that they have done here will be proved took the
12 legally necessary testing.

13 The testing that is necessary. And, Your Honor,
14 we'll get into the law when we get into the law, but the
15 testing that is necessary is to compare the claimed
16 invention to the closest prior art. The closest prior art
17 in this case would be the combination treatment, the
18 conjunctive treatment of Astelin and Flonase as two separate
19 products but prescribed at the same time to a patient. That
20 would be the relevant testing.

21 But the testing that plaintiffs did was not
22 that testing. The plaintiffs' testing was Dymista, their
23 combination product, versus fluticasone, and Dymista
24 separately, their combination product, versus azelastine.

25 And so there is not a big surprise, Your Honor,

1 that Dymista is going to be superior in some tests to either
2 of those separately. That is why people wanted to make the
3 combination.

4 The testing that plaintiffs did is not the kind
5 of testing that establishes what needs to be established for
6 purposes of secondary considerations.

7 And, finally, Your Honor, I think we're going
8 to hear some testimony about a failure of others. Meda, the
9 plaintiff in this case, but not the inventor, the licensee,
10 did some work with fluticasone and azelastine before they
11 got their license from Cipla in the case. Now, the first
12 thing that that tells you is -- and before, and I should say
13 before they knew about this Cipla patent, before they knew
14 about the Cipla patent. So they say they independently came
15 up with this, this idea.

16 The first thing that that tells us is that Meda
17 helps contribute to a finding of obviousness here because
18 they are yet another party that thought it was a good idea
19 to add fluticasone propionate and azelastine hydrochloride
20 together.

21 And they did start to talk about doing
22 development, but in the whole course of time that they
23 talked about doing some development, they ended up doing
24 what they say on their own was preliminary testing. It
25 lasted three to four days, Your Honor. It stopped in the

1 middle, and the next week they dropped it completely and
2 got the license from Cipla.

3 So, any attempt to use the Meda experience as an
4 instance of failure of others in our view completely fails.

5 That's the obviousness defense, Your Honor, in
6 summary.

7 We do have an alternative theory which is
8 enablement 112. And it is an alternative theory, Your
9 Honor. Our main theory is clearly obviousness.

10 But if plaintiff is right and this was not
11 obvious, then these patents run into a serious enablement
12 problem. Because if they are right that persons of skill in
13 the art would not have known how to combine these elements
14 to make a successful formulation, if the art did not teach
15 that, the patent doesn't teach it either. And so the patent
16 wouldn't enable a person of skill in the art to create these
17 products, this formulation.

18 To the extent they claim that the art doesn't
19 teach that azelastine hydrochloride and fluticasone would be
20 successful together in treatment of allergic rhinitis, they
21 provide no clinical data in their patent either.

22 So to the extent it is not obvious, there is an
23 enablement problem in the case.

24 And very quickly, Your Honor. Just a preview.
25 I won't go through this in much detail. But just so you

1 know, we're going to have four live witnesses. It's a
2 little up in the air as to what depositions will be
3 necessary.

4 I will say that I think that some total, the
5 whole universe, I don't think we will play all this, will be
6 less than an hour of depositions, but I expect we'll play
7 some.

8 Four live witnesses:

9 Dr. Accetta on the left is a fact witness who
10 will testify about his prescribing habits on allergic
11 rhinitis to allergic rhinitis patients. You will hear from
12 him immediately.

13 Dr. Wedner is a secondary considerations witness
14 who is going to testify today, Your Honor, out of order
15 because of scheduling issues, but just so you are not
16 surprised and startled to hear some secondary consideration
17 evidence today.

18 Dr. Schleimer is here and is the Chief of
19 Allergy and Immunology at Northwestern; and he will be
20 talking about the obviousness of azelastine hydrochloride
21 and fluticasone propionate used together as treatments.

22 And Maureen Donovan is a professor, a Ph.D. at
23 the University of Iowa and has been there for 30 years. She
24 is an expert specifically in formulation and in formulation
25 of nasal sprays, and she will be explaining why these

1 formulations were not obvious.

2 So, Your Honor, that is what I expect our
3 evidence to be in this case.

4 THE COURT: Okay. Thank you very much.

5 I'll hear plaintiffs' opening.

6 MS. EVERETT: Good afternoon, Your Honor.

7 THE COURT: Good afternoon.

8 MS. EVERETT: Uma Everett on behalf of
9 plaintiffs.

10 Mr. Lombardi painted a very nice and simple
11 story; and if the case was actually that simple, we wouldn't
12 be here this week with many witnesses going through many
13 documents.

14 The reason the case sounds so simple is because
15 Apotex's theory is based on hindsight. We're here 14
16 and-a-half years after the critical date of the invention
17 with the patents and products in hand.

18 Other than the passage of a decade and-a-half, how
19 do we know Apotex's theory is based on hindsight? Because
20 it is inconsistent with the statements, the contemporaneous
21 statements made years before this litigation, completely
22 outside the context of the litigation.

23 This is going to be an interesting case, Your
24 Honor, because we'll have documents and evidence of people
25 who considered an azelastine/fluticasone combination nasal

1 spray in 2002, 2006, and when FDA was first presented it in
2 2008. And they did not think that was an obvious invention,
3 and the documents will show that.

4 The facts of the case will show that Cipla was
5 the first in the world to invent a fixed dose combination
6 nasal spray.

7 Now, Mr. Lombardi made a comment in his openings
8 about Cipla not being the first to have the idea, but it is
9 unquestionable that Cipla was the first in the world to
10 actually come up with an a fixed dose combination nasal
11 spray for allergic rhinitis.

12 Now, first in the world, this isn't a litigation
13 phrase. This is actually how they advertised their product
14 when it first launched in 2004.

15 During this case, we'll also hear about
16 plaintiff Meda and their story, their efforts to develop a
17 fixed dose combination azelastine product.

18 As Mr. Lombardi indicated, Meda, they're the
19 makers of Astelin which is a prior art product in this case.
20 And in 2002, the makers of Astelin assessed whether they
21 could make a combination azelastine/steroid nasal spray, and
22 they determined they could not. That the project was too
23 technically difficult. And because of this, they passed.

24 Then later in 2006, they conducted some
25 experiments which failed. And it was only after Meda

1 entered into a licensing partnership with Cipla that they
2 were able to develop Dymista, which is sold and marketed in
3 the U.S. and is the first and only combination nasal spray
4 for allergic rhinitis.

5 Dymista has had unexpected results. Not only
6 does it have better, more complete symptom relief than
7 either Astelin or Flonase, it has faster onset of action
8 without increased side effects.

9 This week from plaintiffs' experts, you will
10 hear about the state of the art, the full state of the art.

11 Mr. Lombardi talked about two classes of drugs
12 that were available in 2002, but the treating guidelines
13 discussed six possible classes of drugs, including
14 decongestants, mast cell stabilizers, anticholinergics, and
15 leukotriene receptors, and there are many options within
16 those classes.

17 Despite these statements from 2002, there is a
18 need for better and more complete symptom relief.

19 Your Honor, I'm going to turn to address
20 Apotex's obviousness case, but before I do, it is worth
21 noting that a lot of references you will hear about this
22 week, Astelin, Flonase, the Cramer reference, some of these
23 conjunctive studies. They were all before the Patent
24 Office. And the Patent Office found this to be a valid
25 patentable invention.

1 There is no reason or motivation to combine
2 Astelin, azelastine, and fluticasone into a fixed dose
3 combination as of June 2002. There is no benefit. The
4 studies in the art showed no benefit from the conjunctive
5 use. Physicians prefer flexibility and dosing azelastine
6 was not a preferred antihistamine and the practice just
7 wasn't in the art.

8 Starting in about 1989 through 2002, and past
9 the critical date, there were a number of studies looking
10 at conjunctive use of intranasal corticosteroid and
11 antihistamines and they found no benefit.

12 How do we know that? Because, right around,
13 these are the blue boxes, right around the critical date
14 there are a number of review articles where experts and
15 person of ordinary skills look at the entire state of the
16 art and concluded there was no benefit, this despite the
17 fact there was clinical practice to some extent to use the
18 conjunctive use.

19 The review article, one at the top, for example,
20 found the common clinical practice of combining intranasal
21 corticosteroids and oral antihistamines in the treatment of
22 allergic rhinitis has no support in the clinical evidence as
23 the combination has not provided effects beyond intranasal
24 corticosteroids alone and so it cannot be considered cost
25 effective. This is not a reason to combine.

1 In addition, some of these studies, they studied
2 a number of corticosteroids, including fluticasone, and
3 there was no benefit from the fluticasone, the combination
4 studies as well.

5 Your Honor, in 2002 as Mr. Lombardi explained,
6 there were some prescriptions where the physicians
7 prescribed multiple medications and physicians preferred the
8 flexibility in dosing, and because they preferred the
9 flexibility in dosing, that counseled against a fixed dose
10 combination. Individual therapies were prescribed on an as
11 needed basis. There was an approach called stepwise
12 treatment where physicians would add and take patients off
13 medications to achieve symptom relief, and physicians
14 preferred this approach because it allowed them to titrate
15 up for symptom relief and titrate down for most effective
16 dose. It also allowed them to take advantage of different
17 dosing schedules so the drugs could be optimized. None of
18 this could be in fixed dose combination.

19 You will hear a lot about azelastine this week,
20 but in reality, compared to the antihistamine market in
21 general, it was not as preferred. It was a fraction of the
22 market, and that's because there were significant systemic side
23 effects such as somnolence, headaches, bad taste, and there
24 was at the time known to be no material clinical difference
25 in efficacy onset of action or duration of action from the

1 much more popular oral histamines.

2 Now, this week again I think you're going to
3 hear a lot about the use of prescription, use of azelastine,
4 and perhaps Apotex is going to tell you about the benefit
5 and their argument that it's no better than Dymista. But to
6 make this argument about the alleged prior art practice,
7 they'll need to rely on an article that we in the case have
8 all been calling Ratner 2008.

9 So it's significant here a few things about
10 Ratner 2008. First, your Honor, the critical date is 2002.
11 So to discuss the prior art practice, they'll need to rely
12 on an article six years after the critical date. Putting
13 the data side, Ratner doesn't show the prior art practice,
14 nor does it show a motivation to combine the two actives
15 into a fixed dose combination.

16 The Cramer reference. You've heard Mr. Lombardi
17 talk about the Cramer reference. This was a reference that
18 the PTO considered the closest prior art. It was considered
19 by the PTO and overcome. It was considered by the EPO, the
20 European Patent Office, the foreign counterpart. It was
21 overcome there, and now we are going to discuss it for a
22 third time this week.

23 The key point about Cramer is it discloses
24 allegedly a combination is nasal spray. Apotex will tell
25 you it discloses a combination nasal spray potentially with

1 Azelastine. Cramer is inoperable. The patentee submitted
2 declarations to the Patent Office, and we'll have testing
3 this week to show you Cramer does not disclose a nasal spray
4 that a person of ordinary skill in the art would have been
5 able to use as guidance to develop this invention.

6 Now, you'll hear again a lot that Astelin was
7 known, Fluticasone was known, the combination was known,
8 Cramer was known. Your Honor, there's a number of years
9 between the public disclosures of those pieces of prior art
10 and June 2002, when Cipla filed its patent application,
11 again, suggesting that this invention is not obvious.
12 People didn't have a motivation to combine, didn't have a
13 reasonable expectation of success.

14 Your Honor, there were a number of formulation
15 challenges with the fixed dose combination. These weren't
16 general challenges as Mr. Lombardi has characterized them.
17 They were particular challenges with this formulation and
18 Azelastine and a Fluticasone formulation in a nasal spray,
19 and this is something people in the art would have known and
20 understood.

21 The first issue is the solution suspension
22 problem. Azelastine is sparingly soluble. That means you
23 have to work to keep it in solution, and the goal of an
24 active like Azelastine, you need to keep it fully dissolved
25 for it to work. That's how it was known.

1 And then fluticasone has to stay insoluble.
2 It's suspended in the medium and you don't want it
3 dissolved. And to put those together in the same container
4 would have been a formulation challenge.

5 In addition, there are a number of competing
6 nasal sprays. So even putting aside the solution suspension
7 issues, a formulator would have needed to adjust these
8 multiple parameters, and these aren't just general
9 formulation difficulties. For example, the Cramer
10 reference, the testing in that would show just how
11 difficult it is to adjust these parameters when you have
12 these two drugs.

13 And, finally, there were dosing differences that
14 would have dissuaded a person of ordinary skill. Azelastine
15 and Fluticasone had different dosing schedules, and
16 essentially a person of ordinary skill would have had to
17 make the decision should they double the amount of
18 Fluticasone beyond what was known to be safe and effective
19 or should they have the amount of Azelastine that had been
20 shown to be therapeutically effective. And these all would
21 have dissuaded a person of ordinary skill from formulating
22 this invention.

23 Now, Apotex's theory is based on hindsight and
24 ignores the real word challenges that Cipla faced. There
25 were no working examples of combining slightly soluble

1 actives with a suspended active in a nasal spray. There was
2 no guidance in the literature, including Cramer. Cramer
3 didn't work. Cramer does not disclose a suitable nasal
4 spray. There's no instruction in the art, including from
5 FDA, how to reconcile. There were no studies showing a
6 clinical benefit with Azelastine added to Fluticasone. To
7 the extent Apotex was going to show you anything again, it
8 is a 2008 reference. There's no combination nasal spray for
9 treating allergic rhinitis before Duonase and Dymista.

10 Apotex's theory is ignoring all of these real
11 world challenges. But, your Honor, you know who did not
12 ignore these challenges? Meda. In 2002 MedPointe, again,
13 the makers of Astelin assessed whether to make an Astelin
14 steroid combination and they determined that it had a high
15 degree of technical difficulty. There was a need to
16 reconcile combination of solution and suspension and their
17 dosing differences and they passed on making this
18 formulation. In addition to the prima facie case, we have a
19 number of objective, a number of objective indicia of
20 nonobviousness that support the validity of this invention.

21 As Mr. Lombardi also mentioned, we do have --
22 Meda failed. Now, after 2002, Meda assessed whether to make
23 the combination nasal spray. They passed. They decided
24 again in 2006. This time they decided to conduct some
25 tests, and they conducted those tests and they failed. The

1 fact that we're going to hear this week potentially that
2 Meda ten years later, in 2016, we're going to hear that Meda
3 experiments were not a failure is yet more evidence of their
4 theory, their arguments based on hindsight.

5 Meda entered into a -- entered into a licensing
6 arrangement with Cipla and was able to finally develop
7 Dymista, and it presented Dymista to the FDA for approval.
8 And when Meda approached FDA for approval, they explained,
9 have to explain the basis of this combination and why it
10 should achieve approval. And some of the arguments that
11 were made are similar to the ones you'll be hearing this
12 week such as, there's a justification for this product based
13 on mechanism of action.

14 FDA heard that and disagreed. They didn't think
15 there was a basis. They said, rationale based on
16 pharmacodynamic reasoning such as mechanism of action, onset
17 of symptom relief are also not sufficient to justify this
18 combination product. Your Honor, this was in 2000, I
19 believe, eight, years before we are all here today.

20 In addition, FDA was also concerned about the
21 lack of flexibility from a fixed dose combination. They
22 stated, as stated before, combining products eliminates
23 flexibility with dosage titration and potentially exposes
24 patients to unnecessary medication and thus unnecessary
25 risk. So when FDA was presented with a fixed dose

1 combination, they were very skeptical about it.

2 Dymista, as we all know, was eventually
3 approved, and it has had unexpected results and met an unmet
4 need for better and more complete symptom relief.

5 Dymista, as you can see from the left-hand box,
6 it acts within 15 to 30 minutes, much faster than Astelin
7 and Flonase. It reduces the middle boxes, so the higher the
8 negative, the better. It reduces symptoms much more than
9 either Astelin a Flonase or Flonase alone. And you can see
10 that its side effects are lower than Astelin or Flonase. So
11 essentially Dymista, which is an Astelin-Fluticasone
12 combination, works faster, improves symptoms more
13 completely, and has fewer side effects. And, of course,
14 this leads to praise in the industry. The leading allergy
15 journal referred to Meda as the drug of choice for the
16 treatment of AR.

17 And, your Honor, there are a number of copycats
18 in this case. I appreciate in a Hatch-Waxman case we no
19 longer talk about copies, but in this case it's worth noting
20 that Duonase has no patent protection in India and shortly,
21 about a year -- not shortly. A year or so after its launch,
22 copycats began entering in the market. And from 2005 to
23 present, 11 copycats have entered the Indian market.
24 Dymista and Duonase are commercial successes. Their sales
25 are extensive along with the imitator products.

1 Having recognized the weight of the prima facie
2 and the commercial success and all of the other objective
3 considerations, Apotex is now arguing that there's a
4 blocking patent here. Blocking patent doesn't go to all the
5 objective considerations. As Mr. Lombardi's slide said
6 something like the weight of secondary considerations is
7 weak. Blocking is a limited doctrine. It goes to
8 commercialization only. And, in any event, there is no
9 blocking here. There is no, there will be no evidence of
10 blocking patent. There will be no evidence that anybody was
11 blocked. And in any event, Cipla, this is Cipla's patent.
12 They were not blocked. They were first in the world.

13 Now, your Honor, Mr. Lombardi mentioned that in
14 the alternative they plan to argue that these claims are
15 not -- there's a 112 issue and these claims are not
16 adequately described or enabled. But a person of ordinary
17 skill would still know Azelastine and Fluticasone were
18 products approved for the treatment of allergic rhinitis.
19 They wouldn't doubt that those individuals assays would have
20 some effect.

21 And looking at the specification as a whole and
22 the claims as a whole, they would know this invention was
23 useful. There are examples and claims that would allow them
24 to formulate the combination, and the person of ordinary
25 skill would know how to dose the combinations to find a

1 therapeutically effective amount.

2 And, your Honor, you'll be hearing this week
3 from five of Meda's witnesses. Dr. Alexander D'Addio,
4 Meda's Vice President of Scientific Affairs, will explain
5 Meda's development of a fixed dose combination.

6 Michael Kaliner will testify. He's an allergist
7 with 50 years of practice, will talk about the prima facie
8 case and how this is not an obvious invention and it met a
9 long-felt need.

10 Dr. Warner Carr is also a long-practicing
11 allergist who works at FDA's division of Allergy
12 Pulmonology, and he'll be speaking about the objective
13 considerations of nonobviousness from a clinician's point of
14 view.

15 Hugh Smyth is our expert formulator. He's from
16 the University of Texas and will be discussing how a person
17 of ordinary skill would have understood and been dissuaded
18 by the challenges this invention posed. He'll also be
19 addressing objectives considerations.

20 And finally you'll hear from John Jarosz, our
21 economist, who will explain why the copycats are a
22 commercial success.

23 Thank you, your Honor.

24 THE COURT: Thank you very much.

25 Call your first witness.

Accetta - direct

1 MR. LOMBARDI: And, your Honor, Mr. Klein will
2 be presenting our first witness.

3 MS. EVERETT: Your Honor, I realize I didn't
4 hand up copies.

5 THE COURT: You may do so.

6 (Ms. Everett handed slides to the Court.)

7 MR. KLEIN: Your Honor, Apotex's first witness
8 is Dr. Donald Accetta. I believe we're looking for him
9 right now.

10 THE COURT: Okay. He can't be far.

11 ... DONALD ACCETTA, having been duly sworn as a
12 witness, was examined and testified as follows ...

13 THE COURT: Good afternoon, Dr. Accetta. Thank
14 you for being here.

15 THE WITNESS: Good afternoon.

16 THE COURT: You may proceed.

17 DIRECT EXAMINATION

18 BY MR. KLEIN:

19 Q. Good afternoon, Dr. Accetta. What is your full name?

20 A. Donald Accetta.

21 Q. Where do you live?

22 A. Walpole, Massachusetts.

23 Q. And what do you do for a living?

24 A. I'm an allergist.

25 Q. Where do you practice?

Accetta - direct

- 1 A. Taunton, T-a-u-n-t-o-n, Massachusetts.
- 2 Q. What is the name of your company?
- 3 A. Allergy and Asthma Care.
- 4 Q. And how long have you been an allergist?
- 5 A. A little under 30 years.
- 6 Q. On the screen is a demonstrative that has PTX-231.
- 7 Do you recognize this document?
- 8 A. I do.
- 9 Q. And is it a copy of your C.V.?
- 10 A. It is.
- 11 Q. Where did you go to medical school?
- 12 A. I went to -- I graduated from the University of
- 13 Brussels in Belgium.
- 14 Q. When did you graduate?
- 15 A. 1975.
- 16 Q. Are you board-certified in allergy medicine?
- 17 A. Yes.
- 18 Q. Now, Dr. Accetta, this case concerns allergic
- 19 rhinitis. Are you familiar with disease?
- 20 A. Yes.
- 21 Q. What is it?
- 22 A. It's nasal symptoms due to allergies, typically what
- 23 people call hayfever.
- 24 Q. Are there different types of allergic rhinitis?
- 25 A. Well, the symptoms can be caused by different

Accetta - direct

1 allergens, but symptoms are pretty much the same.

2 Q. Are there seasonal versus non-seasonal allergic
3 rhinitis?

4 A. It can be seasonal or year-round or year-round with
5 seasonal exacerbations.

6 Q. And what is the difference?

7 A. In terms of the symptoms, none. In terms of -- it's
8 only in terms of what triggers it and for what length of
9 time.

10 Q. And do you treat patients suffering from allergic
11 rhinitis?

12 A. Yes.

13 Q. Since when?

14 A. Since I was a pediatrician in the late 1970s.

15 Q. Now, Dr. Accetta, had you done work for Apotex in the
16 past on an unrelated matter in the capacity of an expert
17 witness?

18 A. Yes.

19 Q. And did Apotex's counsel reach out to you earlier on
20 in this case?

21 A. Yes.

22 Q. And did they ask you to see if you could pull some
23 patient records?

24 A. Yes.

25 Q. And did you actually pull some records?

Accetta - direct

1 A. I did.

2 Q. And are you prepared to testify about them today?

3 A. Yes.

4 Q. Now, to be clear, are you testifying today as an
5 expert witness or a fact witness?

6 A. Fact witness.

7 Q. Has Apotex agreed to compensate you for your time
8 collecting documents and spending time testifying?

9 A. Yes.

10 Q. And do you have a typical hourly rate for consulting
11 work?

12 A. I do.

13 Q. And what that rate?

14 A. \$400 per hour.

15 Q. Is that what Apotex is paying you?

16 A. Yes.

17 Q. Okay. Now, have you been consulting with Apotex on
18 litigation strategy for this case?

19 A. No.

20 Q. Do you have any ongoing relationship with Apotex
21 outside the context of this case?

22 A. No.

23 Q. And do you have any interest in the outcome of this
24 case?

25 A. No.

Accetta - direct

1 Q. Now, have you treated allergic rhinitis patients with
2 a drug called Flonase?

3 A. Yes.

4 Q. And since when have you used that drug?

5 A. Shortly -- probably shortly after it was released.

6 Q. Around mid 1990s? Does that sound about right?

7 A. That sounds right.

8 Q. And what's the active ingredient in Flonase?

9 A. Fluticasone.

10 Q. How is it administered?

11 A. In the nose. Intranasally.

12 Q. And what type of drug is Fluticasone?

13 A. It's a steroid.

14 Q. Have you also treated allergic rhinitis patients with
15 a drug called Astelin?

16 A. Yes.

17 Q. Since when?

18 A. Probably shortly after it was released as well.

19 Q. Mid-1990s or so?

20 A. That sounds right.

21 Q. What's the active ingredient in Astelin?

22 A. Azelastine.

23 Q. How is it administered?

24 A. Intranasally.

25 Q. And what type of drug is Astelin?

Accetta - direct

1 A. It's an antihistamine.

2 Q. Now, I'd like to focus your attention on a particular
3 period, 1997 until June 2002. Now, during that period, did
4 you treat allergic rhinitis patients with drug combination
5 therapy?

6 A. Yes.

7 Q. Generally speaking, what types of combination
8 therapies did you use during that period?

9 A. Typically, it would be a nasal steroid. I might add
10 on an oral antihistamine, the intranasal antihistamine, or
11 decongestant, or any combination of both.

12 Q. Did you prescribe Flonase combined with Astelin to
13 treat allergic rhinitis before June of 2002?

14 A. Yes.

15 Q. And when do you think you first started prescribing
16 Flonase with Astelin to treat allergic rhinitis?

17 A. I would guess it was probably about a year after
18 Astelin was released. It could have been a little earlier
19 than that.

20 Q. Roughly 1997 or so?

21 A. That sounds about right.

22 Q. And why did you prescribe Flonase with Astelin to
23 treat patients with allergic rhinitis? And, again, I'm
24 focusing on before June of 2002.

25 A. Well, it seemed to me to be obvious we were already

Accetta - direct

1 treating people with the nasal steroid and with an oral
2 antihistamine, and this seemed like a good idea because
3 instead of having to give people medication that went
4 through their entire system, you spray it in the nose and it
5 would act locally.

6 Q. When you say "medication through the entire system,"
7 what are you referring to?

8 A. In other words, a pill, or a liquid if it was a
9 child.

10 Q. And before June 2002, did you prescribe any
11 intranasal antihistamine other than Astelin?

12 A. No.

13 Q. Before June 2002, did you prescribe any intranasal
14 steroids other than Flonase?

15 A. Yes.

16 Q. And what were the top intranasal steroids that you
17 used?

18 A. Well, Flonase was probably one of the major ones.
19 Then there was Nasacort, Nasonex, Rhinocort. I think
20 there may have been a few others, but those were the big
21 ones.

22 Q. On the screen is another demonstrative, and you
23 should have a binder there if you would like to look at the
24 actual document.

25 A. I don't have a binder.

Accetta - direct

1 THE COURT: We will give him one.

2 (A binder was handed to the witness.)

3 THE WITNESS: Thank you.

4 MR. KLEIN: Your Honor, may I approach?

5 THE COURT: You may. I think we just gave him
6 one, although now we don't have one. You may want to
7 approach.

8 MR. KLEIN: Thank you.

9 (Mr. Klein handed a binder to the Court.)

10 BY MR. KLEIN:

11 Q. Now, on the screen is a demonstrative with DTX-2. Do
12 you recognize this document?

13 A. Yes.

14 Q. And what is it?

15 A. It's a copy of an office visit note.

16 Q. Okay. And towards the bottom, not in the callout,
17 there's an examining practitioner, Donald Accetta. I assume
18 that's you?

19 A. Yes.

20 Q. Did you prepare this document?

21 A. Yes.

22 Q. What is the date?

23 A. It's 24 April, 2001. No. I'm sorry. 3/26/01.

24 Q. And when did you prepare the document?

25 A. It would be that date.

Accetta - direct

1 Q. When did you see the patient?

2 A. That date.

3 Q. And I see the patient's name is redacted.

4 A. Yes.

5 Q. Is that for privacy reasons?

6 A. It is.

7 Q. And what was your diagnosis of this patient?

8 A. There were two diagnoses, allergic rhinitis and
9 chronic rhinitis.

10 Q. What's the different difference between allergic and
11 chronic rhinitis?

12 A. Well, the symptoms would be the same, but the cause,
13 in the case of the number one diagnosis, it was allergic
14 rhinitis. So these were nasal symptoms caused by allergic
15 factors, and the chronic rhinitis would be just about
16 everything else. So it could be weather changes, strong
17 odors, perfumes, hairsprays, cigarette smoke, et cetera.

18 Q. Did you prescribe medications for this patient?

19 A. I did.

20 Q. What did you prescribe?

21 A. Flonase and Astelin.

22 Q. And I see there's a plus right before the Astelin.

23 What does that mean?

24 A. Yes. That shows that the patient was already on the
25 Flonase and on that visit I added the Astelin.

Accetta - direct

1 Q. What is the dose that you used for Flonase?

2 A. It was two sprays twice a day.

3 Q. Was that -- did you ever prescribe a dose for Flonase
4 that was different than two sprays twice a day?

5 A. Generally, that would be the way I would write the
6 prescription.

7 Q. And what dose of Astelin did you prescribe?

8 A. Astelin? It was two sprays twice a day.

9 Q. All right. Is that the FDA approved dose for
10 Astelin?

11 A. For adults, yes.

12 Q. Did you prescribe Flonase to be taken together with
13 Astelin at the same time to treat allergic rhinitis?

14 A. I did.

15 Q. Is this the only time you prescribed Flonase combined
16 with Astelin before June 2002?

17 A. No.

18 Q. All right. Let's take a look at another record.

19 This is DTX-4.

20 Did you prepare this document?

21 A. I did.

22 Q. When?

23 A. 12/18 2000.

24 Q. And, again, the patient's name is redacted for
25 privacy reasons; right?

Accetta - direct

- 1 A. Yes.
- 2 Q. What was your diagnosis?
- 3 A. Chronic rhinitis and allergic rhinitis.
- 4 Q. And did you prescribe medications for this patient?
- 5 A. I did.
- 6 Q. What did you prescribe?
- 7 A. The patient was already in Flonase at that time,
8 and I added Astelin and Allegra, which is an oral
9 antihistamine.
- 10 Q. Okay. So sometimes when you prescribe Flonase and
11 Astelin, did you prescribe other medications as well?
- 12 A. I did.
- 13 Q. And why would you prescribe an oral antihistamine?
- 14 A. Why would I prescribe an oral antihistamine?
- 15 Q. Yes.
- 16 A. You know, I don't recollect why in this case. It
17 would really be a guess.
- 18 Q. Okay. I meant just generally speaking, why would you
19 combine Flonase, Astelin and then add an --
- 20 A. I might give the patient both of them and perhaps
21 say, try them and see which one or ones work.
- 22 Q. Well, what Astelin dose did you prescribe for this
23 patient?
- 24 A. Two sprays twice a day.
- 25 Q. And you see there's a discussion section that is

Accetta - direct

1 called out there?

2 A. Yes.

3 Q. Can you read the last sentence?

4 A. She will also try using Astelin spray either daily or
5 as needed.

6 You know, if I can go back and just amend
7 the question that you asked me before about why I might
8 prescribe both. My guess is in this particular patient,
9 perhaps the patient was already on Allegra from another
10 physician. I added it and then added the Astelin at this
11 point.

12 Q. Okay.

13 Now, with regard to the Astelin spray at either
14 daily or as needed, can you give us an example of what you
15 mean by "as needed"?

16 A. Sure. And I think the best is an example. In a
17 person who has year-round nasal symptoms, I would typically
18 be prescribing the Flonase for daily use, and let's say
19 they're allergic to grass as in this patient. They may
20 typically have increased symptoms during May and June, and
21 so I will tell them, you know, come 1st of May or the end of
22 April, start your Astelin.

23 Q. And how much Astelin would they then use?

24 A. Well, I would tell them to start with the full dose,
25 two sprays twice a day, and then use it through their

Accetta - direct

1 season, and then if they were feeling well, in this example
2 would be perhaps early July, then they can stop it.

3 Q. And would you tell patients to use doses that were
4 lower than two sprays twice daily?

5 A. I would typically tell them to start at the full dose
6 and then, yes, they could taper it if they felt that it was
7 working well for them.

8 Q. And what type of alternative dosing did you suggest
9 the patient?

10 A. I would tell them that they could -- take it either
11 on an as needed basis, for example, so not every day if they
12 didn't feel the need for it. I would tell them to -- they
13 could take it once a day, two sprays, or one spray twice a
14 day.

15 Q. Did you find that alternative dosing to be effective
16 for your patient?

17 A. For different people, they would find different
18 combinations worked best. I can't really say that one
19 worked best for most patients.

20 Q. Now, Dr. Accetta, your binder contains Defendants'
21 Trial Exhibits marked DTX-1 to DTX-10; is that right?

22 A. Yes.

23 Q. All right. Now, we went through DTX-2 and 4. Are
24 you familiar with the others, DTX-1, 3, and 5 through 10?

25 A. Yes.

Accetta - direct

1 Q. And generally speaking, what are those documents?

2 A. Those are also copies of office notes.

3 Q. And do those exhibits show eight additional times
4 where you prescribed Flonase combined with at least Astelin
5 before June 2002?

6 A. It does.

7 Q. And did you prescribe Flonase combined with Astelin
8 only ten times before June 2002?

9 A. No.

10 Q. Why do you say that?

11 A. Well, these are the records that are left over where
12 we're all electronic now, and we've slowly been shredding
13 old records over the years, so that's -- a lot of the
14 records are no longer in existence.

15 The second thing is that I was trying to be very
16 efficient and I have two huge file cabinets, so I had to
17 check each record individually. So from the upper, upper
18 left all the way down to the lower right, and I'm sure I
19 missed additional examples.

20 Q. I'd like to again focus your attention on the period
21 of 1997 through June 2002. When you used drug combinations
22 to treat allergic rhinitis, how often did you use Flonase
23 combined with Astelin?

24 A. Probably about a third of the time.

25 Q. And before June 2002, did you find that Flonase

Accetta - direct

1 combined with Astelin effectively treated your allergic
2 rhinitis patients?

3 A. There was a set of patients for whom the combination
4 worked well.

5 Q. To this day, do you still prescribe the combination?

6 A. I do.

7 Q. Now, Dr. Accetta, have you heard of a drug called
8 Dymista?

9 A. Yes.

10 Q. And what is Dymista?

11 A. It's a combination of Fluticasone and Azelastine.

12 Q. Have you given Dymista to patients who are suffering
13 from allergic rhinitis?

14 A. Yes.

15 Q. And based on your experience, how does Dymista
16 compare to using Flonase combined with Astelin?

17 A. In terms of its effectiveness, it's probably similar.

18 Q. I guess it's more convenient?

19 A. Absolutely more convenient.

20 Q. Now, do you currently prescribe them?

21 A. Do I currently prescribe Dymista?

22 Q. Correct.

23 A. No.

24 Q. Why not?

25 A. Massachusetts has a heavily regulated health

Accetta - direct

1 insurance industry and virtually none of our major carriers
2 will cover Dymista.

3 Q. Have you served on a pharmacy committee for a major
4 health plan in Massachusetts?

5 A. Yes.

6 Q. Which one?

7 A. Tufts Health Plan.

8 Q. And from time to time have you made efforts to get
9 drugs covered by insurance in Massachusetts?

10 A. I have.

11 Q. And have you made any such effort to try to get
12 Dymista covered by insurance in Massachusetts?

13 A. No.

14 Q. Why not?

15 A. Except for the convenience, it was really -- I didn't
16 feel that it was any better than the two drugs taken
17 separately.

18 MR. KLEIN: Your Honor, we move to admit DTX-1
19 through 10 and PTX-231, and also for the record, I used
20 Demonstrative Exhibit DDX-2.00 through 2.03.

21 THE COURT: I assume you're not offering the
22 demonstratives into evidence, just as an aid to me?

23 MR. KLEIN: That's correct, your Honor.

24 THE COURT: All right. Is there any objection
25 to any of those?

Accetta - direct

1 MR. VARUGHESE: Your Honor, we don't object to
2 DTX-1 and 2 and PTX-326. However, I think for DTX-2 through
3 10, the witness needs to go through and establish that that,
4 in fact, is reference. They have not provided us a summary
5 for such a bulk entry.

6 THE COURT: For DTX-2 through 10?

7 MR. VARUGHESE: Correct.

8 THE COURT: Mr. Klein?

9 MR. KLEIN: Your Honor, we went through them,
10 explained they were his records, explained they all
11 included, reflected prescriptions for Astelin and Flonase.
12 We could spend the time to go through them one at a time,
13 but I suspect that they are just trying to have us eat up
14 some time.

15 THE COURT: Mr. Varughese, what is it that you
16 think is missing?

17 MR. VARUGHESE: Well, your Honor, if they enter
18 2 through 10 into evidence, I'm going to have to go through
19 and examine the witness on them.

20 I think it's only fair that defendants spend
21 some time authenticating and establishing why they think
22 they should be entered in.

23 THE COURT: I don't have a copy of them.
24 They're in that binder there? Do you have another set of
25 the binder?

Accetta - direct

1 MR. KLEIN: May I approach (handing a binder to
2 the Court).

3 THE COURT: So they all look the same and
4 the witness said they all came from his records. I'm sort
5 of lost on what it is you think that they have not
6 established.

7 MR. VARUGHESE: Well, I think in each one of
8 these records Dr. Accetta actually just admitted that its
9 usage varies, it's different. They're trying to establish
10 that he prescribes them together in a fashion that's
11 relevant to the patent, and I'm going to have to examine,
12 just like Mr. Klein did on the first two records, on how and
13 when he prescribed them and the practice of prescribing
14 this.

15 THE COURT: All right. Well, I understood the
16 objection to be to its admission. I believe the foundation
17 was established. They are all admitted.

18 Mr. Klein, if you want to go through them
19 further before without the witness, you may. Otherwise
20 that's your choice.

21 (Exhibits admitted into evidence.)

22 MR. KLEIN: No further questions.

23 THE COURT: You can question him to whatever
24 extent you wish on cross.

25 MR. VARUGHESE: Thank you, your Honor.

Accetta - cross

1 THE COURT: You may approach.

2 (Binders handed to the witness and to the
3 Court.)

4 CROSS-EXAMINATION

5 BY MR. VARUGHESE:

6 Q. Good afternoon, Dr. Accetta.

7 A. Good afternoon.

8 Q. How are you?

9 A. I'm doing fine. Thank you.

10 MR. VARUGHESE: Can we put up defendants'
11 demonstrative, please.

12 BY MR. VARUGHESE:

13 Q. I'm going to ask you to turn to Tab 1 in the book
14 that we just gave you, Dr. Accetta.

15 Now, this is defendants' demonstrative which you
16 just testified regarding; is that correct? Let's go to
17 Defendant's DDX-2.03.

18 A. I'm sorry. Which one are we looking at?

19 Q. What's up right here, Tab 1.

20 A. DTX-4, that's Tab 1.

21 Q. Correct.

22 A. Right.

23 Q. Now, the patient that's captioned on this record, you
24 diagnosed this patient with allergic rhinitis back in
25 December of 1998; is that correct?

Accetta - cross

1 A. I'm sorry. My hearing is not the best here.

2 Q. You may regret asking that. I was admonished a few
3 weeks ago.

4 You diagnosed this patient with allergic
5 rhinitis back in December of 1998; is that correct?

6 A. Yes.

7 Q. And it wasn't until February 8, 2000 that you
8 prescribed Flonase?

9 A. I couldn't tell you that without -- that's what this
10 shows, so I would have to say that probably was when I
11 started it.

12 Q. Sir, that was a yes-or-no question. We're talking
13 about your records.

14 A. Yes.

15 Q. Okay. And it wasn't until eight months later, in
16 December, that you decided to add on Azelastine?

17 A. Correct.

18 Q. And for this patient, you instructed this patient to
19 take Azelastine on an as needed basis; is that correct?

20 A. Yes. Well, either daily or as needed.

21 Q. And is Astelin in your experience also referred to as
22 PRN use?

23 A. The as needed part would be PRN.

24 Q. Okay. And as needed would mean you're instructing
25 the patient to take the Azelastine whenever the patient

Accetta - cross

1 deemed necessary; is that correct?

2 A. Could you repeat that question?

3 Q. The as needed part of the instruction, you were
4 telling the patient to take the Astelin when the patient
5 deemed it necessary; is that correct?

6 A. Well, that could be --

7 Q. Dr. Accetta, I'm sorry to interrupt you. We're on
8 the clock here. Your counsel can give you an opportunity to
9 explain. I'm just asking you a yes-or-no question.

10 A. I can't answer that question.

11 Q. You can't answer that question?

12 A. Not without some additional explanation.

13 Q. Did you understand the question?

14 A. I did.

15 Q. Did you have a sense for when the patient would have
16 deemed it necessary to take Astelin?

17 A. When they were having additional symptoms, and that
18 might be daily. It might be seasonally.

19 Q. Thank you.

20 It would vary; is that right?

21 A. It could vary.

22 Q. And as needed does not mean that it was a fixed
23 regimen you put that patient on; is that correct?

24 A. Possibly.

25 Q. I'll ask my question one more time. The as needed

Accetta - cross

1 part of that instruction, you just testified that the usage
2 would vary, so that was not a fixed regimen; correct?

3 A. On the "as needed" part, yes.

4 Q. Thank you. Looking at this record, Dr. Accetta,
5 there is nothing in this record that reveals how you are
6 instructing the patient -- or strike that -- when you were
7 instructing the patient to take the Astelin in relation to
8 when the patient would take Flonase, right?

9 A. Not written in the record, it isn't.

10 Q. And again focusing on this record, there is nothing
11 in this record to indicate the sequence in which the patient
12 was to take those two drugs; correct?

13 A. Correct.

14 Q. Let's turn to Tab 2. Let's turn to DDX-2.02, please.

15 Now, Dr. Accetta, this is the other patient
16 record that you testified about regarding just now; correct?

17 A. I believe so, yes.

18 Q. And you diagnosed this patient in March of 1998 with
19 allergic rhinitis?

20 A. Yes.

21 Q. And then you prescribed Flonase in January of 2000?

22 A. That is what the record says.

23 Q. And it wasn't, it wasn't until more than a year later
24 that you decided to add Astelin on to this therapy?

25 A. Yes.

Accetta - cross

1 Q. And here, in the instructions, you told the patient
2 that he can try adding Astelin?

3 A. Well, I think the full comment is springtime --

4 Q. I'm sorry, Dr. Accetta.

5 THE COURT: Let's not interrupt the witness.
6 When he answers, let him answer.

7 MR. VARUGHESE: I apologize, Your Honor.

8 BY MR. VARUGHESE:

9 Q. You instructed the witness to try taking Astelin; is
10 that correct?

11 A. Yes.

12 Q. And in this record, too, looking at just the record,
13 there is no indication as to when you told to take the
14 Flonase or the Astelin in relation to one another; correct?

15 A. No, I would disagree.

16 Q. What is your basis for disagreeing?

17 A. For the springtime symptoms, he can try adding
18 Astelin. So that is pretty clear in my mind.

19 Q. Sure. Let me try my question one more time. Looking
20 at this record, you didn't tell the patient when to take the
21 Astelin in relation to when the patient takes the Flonase;
22 correct?

23 A. In other words, which would come first?

24 Q. That's one that would be sequence.

25 A. No, I didn't.

Accetta - cross

1 Q. Okay. How about in terms of the time interval
2 between the two different medications?

3 A. I didn't specify that either.

4 Q. And in this particular record, you're prescribing
5 Flonase, two sprays twice daily; correct?

6 A. Yes.

7 Q. And do you have an understanding as to whether that
8 is higher than the FDA approved dosage?

9 A. It is higher.

10 Q. So looking at just these two records that we have
11 covered, none of these records indicate whether or not you
12 observed any improvement or lack of improvement in these
13 patients once you prescribed Astelin; correct?

14 A. I was just taking a snapshot in time, so if I was
15 just starting the medication, I obviously wouldn't know
16 whether it was working.

17 Q. I understand. And also looking at these records,
18 there is nothing in here to indicate the incidents of side
19 effects that patients experienced, right?, when you add
20 Astelin?

21 A. Again, it would be the same thing, yes. I just
22 prescribed it.

23 Q. And there is no documentation of compliance?

24 A. No.

25 Q. And in looking at these records, there is no

Accetta - cross

1 indication as to whether the patient has complied with
2 your direction to add Astelin to Flonase, is there?

3 A. No, but we generally never know that.

4 Q. Let's turn to Tab 3, please.

5 A. You said Tab 3?

6 Q. Yes.

7 MR. VARUGHESE: Can we go to DTX-1, please.

8 BY MR. VARUGHESE:

9 Q. Dr. Accetta, this is a document that has been marked
10 as DTX-1 for identification. Do you recognize this as one
11 of your records?

12 A. Yes.

13 Q. This has just been admitted into the case?

14 A. I'm sorry. What did you ask?

15 Q. Did you understand this has been entered into the
16 case as evidence?

17 A. Yes.

18 Q. Now, here this patient record --

19 Can we blow up the medications, please?

20 Here, you diagnosed this patient with allergic
21 rhinitis in April of 1998?

22 A. Yes.

23 Q. And the first drug that you prescribed this patent
24 was Zyrtec?

25 A. Correct.

Accetta - cross

1 Q. And then you added fluticasone in 2000?

2 A. Yes.

3 Q. It was almost a year later in 2001 when you added
4 Astelin?

5 A. Yes.

6 Q. And here, too, you told the patient to take it as
7 needed?

8 A. Well, I said daily or as needed.

9 Q. But you included as needed?

10 A. Yes.

11 Q. And if the patient is taking it as needed, it is not
12 in a fixed dose regimen; correct?

13 A. If they were using it as needed.

14 Q. And here, Astelin was actually the last drug that you
15 prescribed this patient; correct?

16 A. Yes.

17 Q. Okay. Thank you. You can turn to Tab 5, if you
18 don't mind.

19 This is Exhibit DTX-005. Do you recognize this
20 as one of your other patient records, Dr. Accetta?

21 A. Yes.

22 Q. And here, the diagnosis was polyps and allergic
23 rhinitis; correct?

24 A. Yes.

25 Q. And looking at the notes below, it appears you took

Accetta - cross

1 the patient off what they were previously on, Seldane D and
2 Nasacort at this visit?

3 A. Correct.

4 Q. And you put the patient on a high dose of Flonase
5 which is two times a day?

6 A. Yes.

7 Q. And that was to address the polyps; correct?

8 A. Yes. Well, it was, the high dose was for the polyps.

9 Q. Thank you. And here, too, Astelin was the last drug
10 you prescribed for treatment?

11 A. Well, it was just the last on the list here, but they
12 both were prescribed on the same day.

13 Q. If you turn to Tab 6, please?

14 A. Tab 6?

15 Q. Yes. The diagnosis for this patient was in May of
16 1998?

17 A. Yes.

18 Q. And on that day -- I'm sorry. On an initial visit,
19 you prescribed Flonase and Claritin; correct?

20 A. I did.

21 Q. And Claritin is an oral antihistamines?

22 A. Yes.

23 Q. And it wasn't until about two years later that you
24 added Astelin to the prescription?

25 A. I did.

Accetta - cross

1 Q. And here, too, Astelin was the last drug that you
2 prescribed?

3 A. Yes.

4 Q. And in the instructions, you said that: If Astelin
5 works, the patient can try stopping the Flonase; correct?

6 A. That is what I wrote, yes.

7 Q. Now, looking at some of these records that we just
8 covered together, it appears that you have never prescribed
9 Astelin as the first drug of choice; correct?

10 A. Not in these exhibits, but I have prescribed Astelin
11 as a first drug.

12 Q. Thank you. But I'm just focusing on these exhibits
13 because that is what is in evidence. Thank you.

14 A. I have to go through each one of these, but I think
15 there is one, there may be one of them where I did start
16 with the Astelin first, but without looking at all of the
17 rest, I couldn't tell you that for sure.

18 Q. Again, your counsel will give you an opportunity on
19 redirect to go through that, if needed.

20 Now, based on the records that we looked at, you
21 prescribed Astelin as add-on therapy or an as needed
22 therapy; correct?

23 A. Yes.

24 Q. And in all the records that we just looked at, you
25 never instructed the patient on a fixed dose regimen,

1 specific time or a specific sequence; correct?

2 A. I have never instructed the patients on the specific
3 sequence, but I, as in these records, I think have already
4 established that I told them to take, in the case of
5 Astelin, two sprays twice a day, Flonase two sprays
6 generally once a day.

7 Q. But in these records, you never told patients when
8 to take Astelin in relation to when they took the Flonase;
9 correct?

10 A. No.

11 Q. Thank you. And I think you may have answered this
12 question in your earlier testimony but I will ask it anyway.
13 As a physician, you seek to dose titrate; correct? Is that
14 a concept you are familiar with?

15 A. That is a general concept that we all I think ascribe
16 to.

17 Q. So if a patient is on Flonase and Astelin and if you
18 feel the patient is controlled, you take them off one of
19 those drugs or reduce the dose; right?

20 A. Yes.

21 Q. And that is what you were doing?

22 A. Well, they may need both, but generally, yes. If I,
23 if I have a second drug on and suddenly it works much
24 better, I may tell them they can try stopping the first
25 drug. And I think that may have been the case in this

Accetta - cross

1 particular one because I said if this helps, she can try
2 stopping with Flonase.

3 Q. So for those instances that we discussed that you
4 didn't specify a fixed dose regimen for those patients, you
5 would want the flexibility to be able to titrate the agents
6 up or down or on and off; correct?

7 A. I think that is a general good concept for any
8 medication.

9 Q. Because if not, you would expose the patient to
10 unnecessary risk?

11 A. You might.

12 MR. VARUGHESE: Your Honor, I don't have
13 anything further.

14 THE COURT: Okay. Redirect?

15 MR. KLEIN: Nothing further, Your Honor.

16 THE COURT: All right. Doctor, thank you. You
17 may step down.

18 (Witness excused.)

19 THE COURT: We're going to take a short recess
20 before the next witness.

21 (Brief recess taken.)

22 * * *

23 (Proceedings reconvened after recess.)

24 THE COURT: Have a seat.

25 You may call the next witness.

Wedner - direct

1 MR. WURMAN: Your Honor, Apotex calls as its
2 next witness, Dr. H. James Wedner.

3 THE COURT: Okay.

4 MR. WURMAN: Your Honor, for context,
5 Mr. Lombardi mentioned Dr. Wedner earlier today. He is the
6 out of order witness. He is testifying on secondary
7 considerations, but due to scheduling conflicts, we're
8 having him testify today with no objection from the plaintiffs.

9 THE COURT: Hold on one second.

10 ... H. JAMES WEDNER, having been first duly
11 sworn, was examined and testified as follows...

12 THE COURT: Good evening, Dr. Wedner.

13 You may approach.

14 (Binders passed forward.)

15 DIRECT EXAMINATION

16 BY MR. WURMAN:

17 Q. Dr. Wedner, good afternoon.

18 A. Good afternoon.

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

20 A. My name is H. James Wedner.

21 Q. Has Apotex retained you as an expert in this case?

22 A. Yes, they have.

23 Q. Did you bring some slides today to assist in your
24 presentation?

25 A. I did.

Wedner - direct

1 Q. And if we go to the first slide. Is that the cover
2 of your CV and the background and it's labelled as DTX-292?

3 A. It is.

4 Q. Could you please tell the Court where you currently
5 work?

6 A. I work at Washington University School of Medicine in
7 St. Louis.

8 Q. What do you do there?

9 A. I'm a professor of medicine and chief of the division
10 of allergy and clinical immunology.

11 Q. What does that entail exactly?

12 A. Actually, it entails four different things:

13 I'm the director of the division, so I have
14 to run the division and make sure that it runs smoothly.

15 I'm a training program director, so I train
16 young physicians in the practice of allergy and clinical
17 immunology.

18 I do clinical research.

19 And I see patients.

20 Q. And how long have you been treating patients?

21 A. Since 1971.

22 Q. And where did you get your medical education?

23 A. I went to Cornell University medical college in New
24 York City. It's now called Weill Cornell.

25 Q. And I see that you are a member of a number of

Wedner - direct

1 academic and professional organizations. Do any of these
2 relate to the subject of allergic rhinitis?

3 A. Yes. I'm a fellow of the American Academy of Allergy
4 and Immunology. I'm a member of the American College
5 Allergy, Asthma and Immunology. I'm also a member of the
6 American Association of Immunologists, American College of
7 Allergy Asthma and Immunology, the Clinical Immunological
8 Society, European Academy of Allergology and Clinical
9 Immunology, and the St. Louis Metropolitan --

10 Q. And -- sorry to interrupt.

11 A. -- Medical Society.

12 Q. And you have been an editor on journals before. Do
13 any of those relate to the subject of allergy rhinitis?

14 A. Many of them do. I have been Associate Editor of the
15 Journal of Immunology, a Topic Editor For Clinical
16 Immunology, quarterly survey. I've been a Volume Editor For
17 the Year in Immunology. I was on the Editorial Board of the
18 journal of Allergy and Immunology. I was the Editor for the
19 Clinical Immunology Society Newsletter, and the Editor of
20 Current Allergy Reports, Anaphylaxis and Drug Allergy
21 Section.

22 Q. Do you have any of your own publications related to
23 allergic rhinitis?

24 A. I published over 130 articles. Two of those are
25 shown here. Those are two textbooks that I wrote with my

Wedner - direct

1 colleague Phil Korenblat dealing with the practice of
2 allergy and immunology.

3 Q. I want to focus a bit on your current practice.
4 About how many patients do you see per year?

5 A. I see about 4,000 patient visits per year.

6 Q. How many of them present with allergic rhinitis?

7 A. About a third or 1,300.

8 Q. And I think you mentioned a fellowship program. Do
9 you have fellows at your hospital?

10 A. We do we have a training program in allergy and
11 clinical immunology.

12 Q. What is your role with respect to that program?

13 A. I'm the training program director.

14 Q. Do you teach fellows about treating allergic
15 rhinitis?

16 A. I do everyday.

17 Q. Can you estimate how many fellows you trained over
18 the year?

19 A. Over the years, I trained 73 fellows, not including
20 the six that are in the program right now.

21 Q. How long does this fellowship program go back to?

22 A. The fellowship program itself goes back many years.
23 It was the first fellowship program that was west of the
24 Mississippi. We're not much west of the Mississippi but we
25 are west of the Mississippi. The formal training program

Wedner - direct

1 started in 1985.

2 Q. What did your fellows do after training at your
3 hospital?

4 A. About a third of our fellows stay in academic
5 pursuits, either as investigators or as clinician educators.
6 About two-thirds go out and practice allergy in the
7 community.

8 MR. WURMAN: Your Honor, we would like to tender
9 Dr. Wedner as an expert in the treatment of patients
10 suffering from allergic rhinitis.

11 THE COURT: Any objection?

12 MR. EVENS: No objection, Your Honor.

13 THE COURT: He is so recognized.

14 BY MR. WURMAN:

15 Q. Dr. Wedner, were you asked to give opinions in this
16 case related to Meda's purported evidence of nonobviousness?

17 A. Yes.

18 Q. Have you reviewed Meda's expert reports by Drs.
19 Kaliner and Carr with regard to so-called secondary
20 considerations of nonobviousness?

21 A. I have.

22 Q. Have you read the deposition testimony of these
23 experts?

24 A. I have.

25 Q. Have you read Meda's statement of facts submitted to

Wedner - direct

1 the Court for this case?

2 A. I have also.

3 Q. What are your opinions?

4 A. I have two opinions:

5 One, that Dymista is not unexpectedly superior
6 to the closest prior art, the closest prior art being the
7 combination of Flonase and Astelin in separate spray
8 bottles.

9 The second one is that Dymista has not satisfied
10 a long felt need but unmet need.

11 Q. What qualifies you to give these opinions or what do
12 you base your opinions on?

13 A. I base my opinions on the fact that I have been
14 training allergists and immunologists and practicing allergy
15 for over 40 years.

16 Q. So were you prescribing to patients before 2002?

17 A. I was.

18 Q. Do you continue to prescribe to patients today?

19 A. I do.

20 Q. Could you please describe a little bit what was your
21 prescribing practice in 2002 for patients presenting with
22 allergic rhinitis?

23 A. In 2002, the No. 1 drug for the treatment of allergic
24 rhinitis was an intranasal corticosteroid. The one that we
25 used most frequently was fluticasone or Flonase.

Wedner - direct

1 About a third of our patients, maybe 30 percent
2 needed an additional medication. The medication that we
3 used most commonly was Azelastine or Astelin. We used it
4 because it was more immediate and it gave the patients
5 complete relief for those patients who didn't have complete
6 relief with the corticosteroid.

7 Q. Let me slow you down a little bit, Dr. Wedner. So
8 you said there were a number of corticosteroids. Why did
9 you use Flonase?

10 A. Two reasons. Most importantly, Flonase worked. And
11 when a medication works, you tend to use it and you use it
12 over and over. It's a very good drug. It has a low
13 systemic absorption, so that is why we used it.

14 Q. Was your use of Flonase in your practice reflective
15 of the practices of other doctors and physicians with whom
16 you were familiar at the time?

17 A. Yes.

18 Q. When you told your patients to take Flonase, how did
19 you typically tell them to take it?

20 A. The initial starting dose was two sprays in each
21 nostril once a day. We may modify that, depending on the
22 patient's response to the therapy.

23 Q. And I think you said that about 30 percent of
24 patients were given another kind of drug. What was that
25 drug?

Wedner - direct

1 A. 30 percent of the patients needed something else, and
2 we gave them azelastine or Astelin.

3 Q. Is azelastine a different kind of drug from Flonase?

4 A. It is a much different drug. Flonase is a
5 corticosteroid and therefore it's a relatively slow-acting
6 drug because it has to get into cells in order to work.
7 Astelin is an H1 antihistamine and it binds to surface
8 receptors on cells and therefore is much more rapid in its
9 action.

10 Q. Is Azelastine or Astelin applied to the nose?

11 A. It is sprayed in the nose.

12 Q. Were there other -- can I call it a nasal
13 antihistamine?

14 A. You can call it a nasal antihistamine.

15 Q. Were there other nasal antihistamines available at
16 that time before 2002?

17 A. The only other one in 2002 was Levocabastine, and I
18 can honestly say I never used Levocabastine.

19 Q. When you prescribed Astelin to your patients, I think
20 you started getting into this, but why did you do so?

21 A. The first is it's a fast-acting drug, onset of some
22 of its actions is within 15 minutes; and the second is it
23 gave the patients more complete relief, so they liked it.

24 Q. And when you did prescribe Astelin to patients, how
25 did you tell them to take it?

Wedner - direct

1 A. We usually started with a conventional dose, which
2 was two sprays in each nostril twice a day. They were
3 allowed to modify that as necessary.

4 Q. And modify that how?

5 A. They could go from one spray in each nostril twice a
6 day, two sprays in each nostril once a day. It was a good
7 drug to use that way.

8 Q. And why could they only take it once a day?

9 A. Well, if you remember, people can wake up. They have
10 a stuffy nose, but when they go to bed, they don't like to
11 spray stuff in their nose, so they wouldn't like to take it
12 twice a day.

13 Q. Did you ever prescribe oral antihistamines?

14 A. We prescribed a lot of oral antihistamines.

15 Q. Why?

16 A. Well, if you recall, we talked about allergic
17 rhinitis, but allergic rhinitis is just part of what we call
18 the allergic diathesis. That's allergic rhinitis, allergic
19 conjunctivitis. You can have ear problems. Some patients
20 have atopic dermatitis. They have asthma. And so you need
21 the anti-histaminic not so much for the nose, but for the
22 rest of the patient.

23 Q. I see you list a number of other drugs here. Were
24 there other drug classes you could use in combination with
25 Flonase or other steroids?

Wedner - direct

1 A. Sure. There were a lot of them. I've listed there
2 anticholinergics. These are drugs that were used
3 specifically as drying agents. Patients who had profuse
4 rhinorrhea, that's a profound runny nose, or post-nasal
5 drip, we would add a Ipratropium bromide, which is an
6 intranasal cholinergic.

7 Mast cell stabilizers are actually quite
8 effective. The problem with them is that they have to be
9 used four times a day, and nobody uses a drug four times a
10 day, and they basically fall by the wayside.

11 Leukotriene receptor antagonists were
12 available prior to 2002. They don't add very much. In
13 clinical studies, they were only about eight percent more
14 effective than placebo and we only use them largely in
15 children. It's a pill rather than something that you put in
16 the nose, and then there are a whole series of decongestants
17 which can be both oral and intranasal.

18 Q. Can you say more about the decongestants? How would
19 you use those?

20 A. Sure. The number decongestant is pseudoephedrine is
21 a drug we basically do not like to use. It has a bad side
22 effect profile. It causes hypertension or it can accentuate
23 hypertension in patients who have it or have a family
24 history of it. It can cause twitching. It can cause heart
25 problems. And, more importantly, recently it can be

Wedner - direct

1 converted into other substances that people aren't supposed
2 to use.

3 Q. Sticking back to 2002, were there other decongestants
4 that you could use?

5 A. Sure. There were intranasal decongestants that were
6 available. They're still available. Oxymetazoline, which
7 is known as Afrin or Neo-Synephrine could be used. The
8 problem with alpha agonists is they have a rebound effect,
9 and so you can only use them for a very short period of
10 time. Otherwise you get a disease called rhinitis
11 medicamentosa.

12 Q. Can you describe for the Court the frequency with
13 which these other drugs were prescribed?

14 A. We didn't use them and still don't use them very
15 frequently. About ten percent of our patients will be on a
16 drug that's in the last list in that column.

17 Q. Doctor, were you here for opening argument this
18 morning?

19 A. I was.

20 Q. Do you see the plaintiffs' slide describing various
21 drug classes that they state were available in 2002?

22 A. That's correct.

23 Q. And that patients were still dissatisfied with those
24 treatments?

25 A. Yes.

Wedner - direct

1 Q. Did we just discuss decongestants, mast cell
2 stabilizers and anticholinergic --

3 A. We did.

4 Q. And do you see up there it says 24 antihistamine
5 options?

6 A. Yes.

7 Q. Do you see that plaintiffs said these options were
8 available?

9 A. Well --

10 Q. Do you see that?

11 A. Yes, I do.

12 Q. And do you agree with that?

13 A. No.

14 Q. Why not?

15 A. Well, some of them have, are not approved in the
16 United States, some of them have never been approved in the
17 United States for use in the nose. Others in that group are
18 sedating antihistaminics, and once the introduction of the
19 non-sedating antihistaminics came about, we never used them
20 for allergic rhinitis. So they were available, but they
21 weren't used.

22 Q. Of the 24 that they put up here as available, about
23 how many would you say were available?

24 A. Well, if you think about it, some of them were
25 available but not used. Triplennamine, which was available.

Wedner - direct

1 Diphenhydramine was available, but those are sedating
2 antihistaminics. The ones that were available that are
3 non-sedating were Cetirizine and loratadine and
4 fexofenadine, which is Allegra.

5 Q. Of these, how many were intranasal?

6 A. None of them were. The only one that was intranasal
7 was Azelastine.

8 Q. What about Levocabastine?

9 A. Levocabastine is there. As I say, we never used it,
10 so I can't comment on it.

11 Q. Doctor, was your prescribing practice recommended by
12 any guidelines available to physicians before 2002?

13 A. Yes, it was.

14 Q. What were those guidelines?

15 A. There are basically a number of them. There are two
16 which were available prior to 2002. One were the practice
17 parameters of the American College and the American Academy
18 of Allergy and Immunology. They were published in 1998,
19 often referred to as the Dykewicz Guidelines because the
20 first author was Mark Dykewicz.

21 And then there was another set of
22 guidelines called the ARIA Guidelines, which were published
23 in 2001. The lead author was Bousquet.

24 Q. Have you brought those with you today?

25 A. I have.

Wedner - direct

1 Q. Is this an excerpt from the ARIA Guidelines, which
2 are down below, DTX-81?

3 A. Yes.

4 Q. Could you actually state for the Court what ARIA
5 stands for?

6 A. ARIA stands for allergic rhinitis and its impact on
7 asthma.

8 Q. Can you please describe for the Court the excerpt
9 from the guidelines that you have pulled here on the slide?

10 A. This is taken from the use of topical
11 antihistaminics, which was discussed in the ARIA Guidelines.
12 These were the recommendations and they noted that topical
13 H1 have a rapid onset of action at low drug, at low drug
14 doses.

15 They act only on the target organ. They
16 usually require bi-daily administration and they may
17 therefore be recommended for mild organ limited disease as
18 an add-on medication in conjunction with a continuous one.
19 By that they meant add-on meant --

20 Q. Let me stop you there. Does it say add-on or on
21 demand?

22 A. I'm sorry. On demand. I got ahead of myself. I
23 meant add-on.

24 Q. Sir, before you do, you may have explained it
25 already, but what do you understand the continuous one to

Wedner - direct

1 mean?

2 A. The continuous one was the intranasal corticosteroids.
3 If you go back in the guidelines, they recommend that
4 intranasal corticosteroids should be used every day, and
5 that's how we used them in our patients.

6 Q. And so what do you understand the guidelines to say
7 by topical antihistamine may therefore be recommended as on
8 demand medication, in conjunction with that?

9 THE COURT: Doctor, it will help me and the
10 court reporter if you wait until the question is done before
11 answering it. Okay?

12 THE WITNESS: Sorry.

13 THE COURT: Go ahead.

14 BY MR. WURMAN:

15 Q. I will try to remind you.

16 A. All right.

17 Q. What do you understand the guidelines to mean topical
18 antihistamines can be used on demand in conjunction with a
19 continuous one?

20 A. On demand means that the patient is unhappy or isn't
21 completely cured by the intranasal corticosteroid. You can
22 add that on or as an add-on to the intranasal
23 corticosteroid.

24 Q. So will demand vary from patient to patient?

25 A. Certainly.

Wedner - direct

1 Q. And would that affect how much of the drug they end
2 up taking?

3 A. Yes.

4 Q. So what's the approved dosing for Azelastine?

5 A. The approved dosing for Azelastine is two sprays in
6 each nostril twice a day.

7 Q. Go ahead.

8 A. And you can vary the dose, and that's actually part
9 of the ARIA guidelines, which is in actually two pages
10 before what we've shown here.

11 Q. When you say "vary the dose," what do you mean?

12 A. What they mean is that you can use it two sprays in
13 each nostril twice a day, which is the recommended dose.
14 You can use it two sprays in each nostril once a day. You
15 can use it one spray in each nostril twice a day.

16 MR. WURMAN: Do we have that portion of the ARIA
17 guidelines? Could you blow up that right-hand column.

18 BY MR. WURMAN:

19 Q. Doctor, is this the portion of the guidelines to
20 which you were referring that called out Azelastine and
21 describes a bit?

22 A. Yes. This is the section dealing with Azelastine,
23 and if you go to the last bullet point, which is shown down
24 there, it talks a little bit about oral administration, but
25 it talks about administered intranasally. It doesn't induce

Wedner - direct

1 sedation and at doses used in Europe, which is
2 .56 milligrams, and that's actually the total dose.

3 Q. Total? Total dose in what sense?

4 A. Total dose means that one spray in each nostril twice
5 a day.

6 Q. So the total dosage over the course of a day?

7 A. Over the course of a day. And then the American
8 dose, which is two sprays in each nostril twice a day, is
9 actually just twice that.

10 Q. And, Dr. Wedner, if we could actually go back.
11 Before we move on, I might try to ask you to identify it,
12 but is the ARIA guidelines marked as DTX-81?

13 A. That it is.

14 Q. Did you bring another guidelines, the Dykewicz?

15 A. We brought the Dykewicz guidelines.

16 Q. Is this DTX-246 before I get ahead of myself?

17 A. Yes. This is DTX-246. On the left is the front page
18 of the article, and then on the right is the section which
19 deals with intranasal antihistamines.

20 Q. What does this date from?

21 A. This dates from 1998.

22 Q. And can you describe for the Court what you put up
23 here?

24 A. Again, this is the section dealing with intranasal
25 antihistamines. It notes that they are effective for the

Wedner - direct

1 treatment of allergic rhinitis. They are appropriate for
2 use occasionally as first line treatment or as part of
3 combination therapy with nasal corticosteroids.

4 Q. And I will stop you right there. Is that consistent
5 with your prescribing practices?

6 A. Absolutely.

7 Q. You threw in the word "occasionally" with first line
8 treatment. I don't see the word there. What did you mean
9 by that?

10 A. It means for some patients it may be a single dose
11 drug used as a first line therapy.

12 Q. And does it call out a particular antihistamine?

13 A. It talks about Azelastine or Astelin. And it notes
14 it's the first intranasal antihistaminic preparation
15 included for use in the U.S.

16 Q. I notice that it's not highlighted, but it actually
17 says that the recommended dosing is two sprays in each
18 nostril BID. Is that twice daily?

19 A. Correct.

20 Q. Is that consistent with your prescribing practice?

21 A. Correct. That's the standard dose. That's the 1.12
22 milligrams total dose per day.

23 Q. And what do you understand by the guidelines or the
24 label recommended such dosing?

25 A. Recommended means that's what we should start with

Wedner - direct

1 when we prescribe that drug.

2 Q. And afterwards can that vary?

3 A. Sure.

4 Q. Just below that it also says an onset of action has
5 been demonstrated within three hours.

6 Do you see that?

7 A. Yes.

8 Q. Is that consistent with what you saw earlier in the
9 ARIA guidelines?

10 A. Yes. Now, the ARIA guidelines actually said onset of
11 action could be as short as 15 minutes, but it's important
12 to remember there are many different symptoms of allergic
13 rhinitis. Sneezing is very quickly taken care of. Other of
14 the symptoms take longer. But all of these symptoms are
15 treated within the first three hours.

16 Q. And did you bring another page of the guidelines with
17 you?

18 A. Yes. This is the section that's two after the one I
19 showed you. It's on nasal corticosteroids. It lists the
20 seven nasal corticosteroids that were available. Of those,
21 the one that we used most frequently was Fluticasone or
22 Flonase. The one at the bottom, dexamethazone, we didn't
23 use and don't use. It's absorbed systemically.

24 Q. Does it give you any indication of the dosing of
25 Flonase?

Wedner - direct

1 A. Yes. The dosing of Flonase is two sprays per nostril
2 once a day or one spray per nostril twice a day.

3 Q. And is there any information on the efficacy of
4 corticosteroids in that excerpt?

5 A. If you look at the left-hand section, it notes that
6 nasally inhaled corticosteroids are the most effective
7 medication class in controlling symptoms of allergic
8 rhinitis.

9 Q. And is that consistent with your experience as a
10 prescribing physician?

11 A. It is.

12 Q. And, Dr. Wedner, are you familiar with a drug product
13 called Dymista?

14 A. I am.

15 Q. What are its active ingredients?

16 A. The two active ingredients are azelastine
17 hydrochloride and fluticasone propionate.

18 Q. Have you identified the closest prior art to the
19 Dymista product?

20 A. Yes. The closest prior art is simply the two drugs
21 given to the patient in two separate spray forms rather than
22 a single.

23 Q. I want to fast-forward to today. Have your
24 prescribing practices changed since 2002?

25 A. Not really. We still use the same drugs. We use the

Wedner - direct

1 same drugs in combination with allergic rhinitis.

2 Q. Has Dymista affected your prescribing practices at
3 all?

4 A. Not particularly.

5 Q. But has it in any --

6 A. We have used it, but it's important to remember that
7 most of the third party payers won't pay for it. It's very
8 expensive and you can get the same effect by using the two
9 drugs individually at significantly lower cost.

10 Q. Do you have an understanding as to why the
11 third-party payers don't provide coverage?

12 A. My understanding --

13 MR. EVENS: Objection, your Honor. I think it
14 calls for speculation here unless he can tie his
15 understanding into conversations based on documents.

16 THE COURT: Do you want to respond?

17 MR. WURMAN: Your Honor, I asked him about his
18 understanding. If he doesn't have an understanding, the
19 witness can answer like that, but he has been prescribing
20 medications with and without insurance coverage and he may
21 have an understanding.

22 THE COURT: I'm going to overrule the objection.
23 He can answer the question.

24 THE WITNESS: We deal a lot with insurance
25 companies, and insurance companies don't like to, or won't

Wedner - direct

1 pay the cost of over-the-counter medications. Fluticasone
2 propionate is now over the counter, so patients can simply
3 go and buy it without a prescription.

4 Azelastine is a generic drug. So the cost of
5 Fluticasone plus Azelastine is significantly less than the
6 cost of Dymista. If the patient wanted to pay for it, they
7 would have to pay for it out-of-pocket. Most of our
8 patients won't do that.

9 BY MR. WURMAN:

10 Q. That Flonase has gone over the counter, does that
11 affect the way you prescribe Flonase at all?

12 A. No. The only difference is we don't have to write a
13 prescription. What we do, we have a sheet of paper that
14 says here's the name of the drug, and we tell them where is
15 the cheapest place to get it.

16 Q. Dr. Wedner, have you tried Dymista yourself?

17 A. I have.

18 Q. Have you tried Azelastine?

19 A. I have.

20 Q. Have you tried Flonase?

21 A. Yes.

22 Q. Why do you try these drugs?

23 A. I'm going to try anything I spray in somebody's nose
24 or give them in liquid form.

25 Q. And why is that?

Wedner - direct

1 A. Well, I think it's not appropriate for a physician to
2 give somebody medication that may or may not taste bad and
3 not have tried it themselves so they can actually say, this
4 stuff really tastes bad or it doesn't taste at all.

5 Q. Dr. Wedner, in your experience treating patients, is
6 Dymista more effective than the combination of Flonase and
7 Astelin?

8 A. No.

9 Q. Why not?

10 A. Well, you're actually looking at the two same drugs
11 simply given sequentially or in conjunction. You give --
12 spray one in the nose. You spray the other in the nose.
13 And basically, that's the same as giving Dymista.

14 Q. Have you noticed any difference in improvement in
15 terms of efficacy for patients taking Dymista compared to
16 those taking the combination of Flonase and Astelin?

17 A. I have not.

18 Q. In your experience treating patients, is Dymista
19 faster than the combination -- does it work faster rather
20 than the combination of Flonase and Astelin?

21 A. No.

22 Q. Why not?

23 A. Well, the speed of Dymista is totally related to the
24 Azelastine component. So the speed of the combination will
25 also be totally related to the Azelastine component. So

Wedner - direct

1 they're both fast-acting and the long-term effects of
2 Fluticasone are the same as the long-term effects of the
3 Fluticasone in Dymista.

4 Q. All right. And in your experience treating patients,
5 does Dymista taste better than the combination of Flonase
6 and Astelin?

7 A. No.

8 Q. Why not?

9 A. It contains the drug which tastes bad, which is
10 Azelastine.

11 Q. Are there any proportion of patients in your practice
12 back in 2002 or to date that refuse to take Astelin because
13 of its bad taste?

14 A. Well, remember, there are people who taste Azelastine
15 and there are patients who don't taste it. I happen to be a
16 taster. Of those people who don't taste it, they're going
17 to take the drug because it doesn't taste bad to them. Of
18 the ones that do taste it, it's very effective, so only
19 about ten percent will refuse to take it.

20 Q. And what about the proportion of patients that refuse
21 to take Dymista because of its bitter taste?

22 A. It's about the same.

23 Q. Dr. Wedner, is there any advantage to Dymista over
24 the combination of Flonase and Astelin?

25 A. Sure. It's a much more convenient way, more

Wedner - direct

1 convenient to put the drug in one sprayer than to have to
2 hold two sprayers.

3 Q. Convenient for whom?

4 A. For the patient.

5 Q. Do patients prefer convenience?

6 A. Yes.

7 Q. Can there be a relationship between convenience for
8 patients and their compliance?

9 A. Certainly.

10 Q. Can you say more about that?

11 A. Sure. The difference is if a medicine works,
12 patients have a tendency to take it. If medicine doesn't
13 work, they are not going to take it. So the combination of
14 Azelastine and Fluticasone, whether it's in Dymista or
15 whether it's in the two different sprayers, are both -- is a
16 very good combination and patients do tend to take it.

17 Q. How about the impact of convenience on compliance?

18 Would there be a relationship between those?

19 A. Certainly. Convenience means better compliance, but
20 again as I say, if the drug, whether it's one sprayer or two
21 sprayers works very well, then patients are actually going
22 to use it.

23 Q. Dr. Wedner, do you have an opinion as to whether in
24 2002 it would have been obvious that a fixed dose
25 combination of Fluticasone and Azelastine would have been

Wedner - direct

1 more convenient for patients than taking Flonase combined
2 with Astelin?

3 A. Sure. It was obvious to put the two of them in a
4 single bottle.

5 Q. And for the reasons you just stated?

6 A. For convenience, of course.

7 THE COURT: Doctor, again, please wait until the
8 question is over before you answer.

9 Go ahead.

10 BY MR. WURMAN:

11 Q. Dr. Wedner, can you please summarize your expert
12 opinions in this case?

13 A. Basically two. Dymista has no unexpectedly superior
14 results compared to the closest prior art, which was Flonase
15 and Astelin as a single -- each in a single sprayer. And
16 the results of the two, whether it's Dymista or the two
17 drugs separately, it's comparable, and Dymista has not met a
18 long felt but unmet need. At most, Dymista is a convenient
19 way to administer two drugs in a single spritzer.

20 Q. Dr. Wedner, having considered Meda's purported
21 evidence of unmet need and unexpectedly superior results
22 which you read in their expert reports, do you have an
23 opinion as to whether in 2002 it was obvious to combine
24 Fluticasone and Azelastine in a single drug?

25 A. Sure. It was obvious.

Wedner - cross

1 Q. For the reasons?

2 A. For the reasons that I said. It's much better if you
3 have two drugs, put them in the same bottle and spray them
4 in the nose.

5 Q. Before I leave, actually, I would like to move into
6 evidence Exhibits DTX-292, 81 and 246.

7 THE COURT: Any objection?

8 MR. EVENS: No objection, your Honor.

9 THE COURT: Okay. Those are all admitted.

10 Cross-examination.

11 (Mr. Evens handed notebooks to the Court.)

12 CROSS-EXAMINATION

13 BY MR. EVENS:

14 Q. Hello again, Dr. Wedner.

15 A. Hello.

16 Q. Now, the first question Mr. Wurman asked you was your
17 prescribing practices; is that right?

18 A. Correct.

19 Q. And you responded that today, or in 2002, your
20 prescribing practice was to prescribe Flonase as a
21 corticosteroid and Astelin?

22 A. Correct.

23 Q. Okay. Do you remember we spent -- in fact, could you
24 put up slide 305.

25 Do you remember at your deposition we spent a

Wedner - cross

1 lot of time talking about your prescribing practices?

2 A. We did.

3 Q. We did. And I asked you about your prescribing
4 practices in like the mid-nineties up through the early
5 2000s and later.

6 Do you remember your answer to me? You may
7 not given your testimony, so let me kind of take you
8 through.

9 A. All right.

10 Q. When I asked you what your prescribing practices
11 were around that 1995 to just after 2000, and I think your
12 words were a little bit later, you said, an environmental
13 control.

14 Do you remember that?

15 A. Yes.

16 Q. And then you said a saline rinse.

17 A. Correct.

18 Q. Do you remember that?

19 A. Yes.

20 Q. And then you told me an intranasal corticosteroid.

21 Do you remember that?

22 A. That's also correct.

23 Q. And then you told me a non-sedating oral
24 antihistamine.

25 Do you remember that?

1 A. Also correct.

2 Q. Okay. But you didn't mention those other three
3 factors today when you responded to Mr. Wurman?

4 A. I did not.

5 Q. And then only later when a patient comes in would you
6 later prescribe something else which could include an
7 intranasal antihistamine and include Azelastine; is that
8 right?

9 A. That's correct.

10 Q. Okay. Now, I had asked you why you prescribed the
11 non-sedating oral antihistamine, and you responded there was
12 a method to your madness. You knew the patient would comply
13 with the pill.

14 THE COURT: Is there an objection? Hold on. Is
15 there an objection?

16 MR. WURMAN: He is not impeaching the witness,
17 just reading from the deposition.

18 THE COURT: Isn't that correct?

19 MR. EVENS: Your Honor, I don't think I'm -- I
20 do think I'm impeaching the witness. I'm saying that he
21 didn't give a full and complete answer to Mr. Wurman's
22 question.

23 MR. WURMAN: Your Honor, I would suggest that
24 Mr. Evens ask the witness a question, and if he thinks he
25 has contradicted himself, he can read the deposition.

Wedner - cross

1 THE COURT: Let's do it that way. Ask the
2 witness the question you want to ask him. If you think it's
3 inconsistent, you will impeach him.

4 MR. EVENS: Thank you.

5 BY MR. EVENS:

6 Q. You prescribed the non-sedating oral antihistamine
7 when the patient comes in as part of that first line
8 treatment because you're confident the patient will take
9 that pill every day?

10 A. Yes.

11 Q. It's a supplement to the corticosteroid?

12 A. I wouldn't call it a supplement. It's an overview.
13 In other words, we give the pill to treat the entire
14 allergic diathesis. We give the intranasal corticosteroid
15 to treat the nose.

16 Q. Okay. And then you view your treatment regimen as an
17 iterative process; right?

18 A. I do.

19 Q. Good. Why don't we go to 3.06.

20 MR. EVENS: I need paper, your Honor.

21 BY MR. EVENS:

22 Q. And Mr. Wurman took you through the ARIA guidelines.
23 Let me ask you a few questions about those.

24 Section 8-2-3-4, the title is
25 "Recommendations," is it not?

1 A. Yes.

2 Q. You are the author of what has been identified as the
3 ARIA guidelines with John B. Bousquet?

4 A. He was the lead author. There were a whole bunch of
5 them.

6 Q. You're friends with Mr. Bousquet, Dr. Bousquet?

7 A. Yes.

8 Q. You're colleagues?

9 A. We would be considered colleagues.

10 Q. All right. The guidelines are just guidelines.
11 They're not mandatory, are they?

12 A. No.

13 MR. EVENS: Can you pull up page 18 of the
14 guidelines, please? And could we focus on the last
15 paragraph.

16 BY MR. EVENS:

17 Q. All right. So in what has been described as the ARIA
18 guidelines, we learned that the paper is not intended to be
19 a standard of care document for individual countries; is
20 that right?

21 A. That's correct.

22 Q. It has not been adopted in the United States?

23 A. No guideline has actually been adopted in the United
24 States.

25 Q. Right. And then it actually goes further to tell us

Wedner - cross

1 that it is provided as a basis for physicians and
2 organizations involved in the treatment of allergic rhinitis
3 and asthma in various countries to develop relevant local
4 standard of care documents for their patients.

5 Is that right?

6 A. That's correct.

7 Q. Has St. Louis adopted a, such a treatment plan
8 relevant to the local standard of care in St. Louis?

9 A. I don't know that St. Louis has. Our training
10 program has a document which lists how you should treat
11 allergic rhinitis. So I don't think the St. Louis allergy
12 community has, but we have based upon the ARIA guidelines
13 and the Dykewicz guidelines.

14 Q. But do you know if that treatment plan was ever
15 produced to us?

16 A. You never asked for it, so I never produced it.

17 Q. And Apotex didn't deem it worth introducing into
18 evidence to show what the treatment plan adopted by --
19 and let me just interrupt my question. What do you mean by
20 "you"?

21 THE COURT: Sorry. That question was objected
22 to. That objection is sustained. But you're asking another
23 question. Go ahead.

24 BY MR. EVENS:

25 Q. When you say "we adopted"?

1 A. I'm talking about the training program. We are a
2 training program. We have six fellows and we have -- we
3 being the members of the faculty within the training program
4 have a written statement of what it is to treat allergic
5 rhinitis based upon the ARIA guidelines and the Dykewicz
6 guidelines.

7 Q. You never mentioned -- I take it you mean St. Louis
8 University?

9 A. No. I mean Washington University.

10 Q. I'm sorry. Washington University. You did not
11 include those guidelines in your expert report, did you?

12 A. I did not.

13 Q. Okay. Nor did you mention those guidelines in your
14 expert report when you were discussing ARIA or Dykewicz;
15 isn't that true?

16 A. That's true.

17 Q. Okay. Now, let's go back to slide 306, if we can.
18 And let's take the second sentence first.

19 You marked in yellow that the topical H1
20 antihistamines may be recommended for mild or limited
21 disease, and then you marked in yellow again as an on demand
22 medication in conjunction with a continuous one.

23 Do you see that?

24 A. I do.

25 Q. Okay. And then right after that, there's a notation

Wedner - cross

1 2088; is that correct?

2 A. That's correct.

3 Q. And that 2088 refers to the citation for the
4 statement that appears in that section?

5 A. That's correct.

6 Q. Okay. And I think just so I've got it in my mind,
7 you told us in response to Mr. Wurman that when ARIA
8 mentions a continuous one, that means a corticosteroid?

9 A. Correct.

10 Q. Okay. Now, have you reviewed the document that is
11 referenced as the only cite for this section, the 2088
12 document?

13 A. Specifically for this? No, I haven't.

14 Q. Okay.

15 MR. EVENS: Could you pull up that document for
16 us? I think it's PTX-329.

17 BY MR. EVENS:

18 Q. Dr. Wedner, looking at the title, does that refresh
19 your recollection? Is that the article to the best of your
20 knowledge?

21 A. Yes, I'm familiar with that article.

22 Q. Okay. And it is the article that appears, is
23 referenced in the section we were just looking at?

24 A. I will take your word for it.

25 Q. 2088.

Wedner - cross

1 So let's look at the methods section of that
2 article, if we could. If we could bring that up.

3 Now, this tells us what was studied by the
4 researchers?

5 A. Correct.

6 Q. And if we look, we see that the researchers tested
7 233 subjects with symptomatic allergic rhinitis; is that
8 correct, Dr. Wedner?

9 A. That's correct.

10 Q. And the researchers tell us that they tested those
11 subjects with Azelastine tablets?

12 A. Correct.

13 Q. Okay. And then it tells us further that each
14 received either an Azelastine nasal spray; is that right?

15 A. That's what it says, yes.

16 Q. Or a placebo nasal spray as adjunctive therapy; is
17 that right?

18 A. That is right.

19 Q. But there is no mention of a corticosteroid?

20 A. No.

21 Q. Okay. So the only -- if we could go back to 306.

22 The support for the conjunctive use with a
23 continuous one only refers to an azelastine nasal spray,
24 study that studied an azelastine nasal spray and an oral
25 azelastine.

Wedner - cross

1 A. I don't think so, no. In that study, there was no,
2 quote, "continuous" medicine. They gave one and then the
3 other. So assuming that that is the cite, it really doesn't
4 support what you said, but it is a continuous therapy. And
5 to me, the continuous therapy is an intranasal corticosteroid.

6 Q. I understand. That is not the question I asked. I
7 actually move to strike that.

8 If we go back to the document, it tells us the
9 researchers studied over seven days. That seems to be that
10 could be the "continuous" that they're referencing in the
11 recommendation, Dr. Wedner.

12 A. No, no. What they did is they gave them azelastine
13 for seven days, and then they gave them the nasal spray. To
14 me, that is not a continuous therapy.

15 Q. You may take that up with Dr. Bousquet the next time
16 you see him. It is still the only cite that supports the
17 statement in the area guideline recommendation.

18 A. I understand that.

19 Q. Okay.

20 MR. WURMAN: Objection. Is there a question?

21 THE COURT: Yes. Is that a question?

22 MR. EVENS: That was a question, Your Honor. He
23 answered it.

24 THE COURT: What was the answer?

25 THE WITNESS: I understand what he said. I

Wedner - cross

1 don't agree with it, but I understand.

2 BY MR. EVENS:

3 Q. Now, let's look at the first sentence. I'm sorry,
4 the first sentence back to the ARIA guidelines.

5 It says: Topical H1 antihistamines have a rapid
6 onset of action (less than 15 minutes) at low drug dosage,
7 but they act only on the treated organ.

8 Do you see that?

9 A. I do.

10 Q. And the cite again is to 2088, the 2088 reference;
11 correct?

12 A. I don't take it at 2088 has nothing to do with that,
13 with the 15 minute onset, as far as I know.

14 Q. You don't know what the basis for that statement is?

15 A. I do not. But there is a great basis for that in the
16 literature, so I assume these authors knew that and that is
17 why they put that in there.

18 Q. Well, since the authors of ARIA have the reference,
19 the only support in that, in that section to 2088, let's
20 just see what the researchers found. So if we could go back
21 to the first page.

22 And in the results section, the authors were
23 Porritt -- if we go to the third line. The third line.
24 There is a statistical significance -- I'll leave out the
25 math part -- versus placebo from the second through the

Wedner - cross

1 first ten hours after the initial dose.

2 So that is the author's report of onset of
3 action, statistically significant onset from the second
4 through the first ten hours; is that correct?

5 A. That is what they wrote.

6 Q. There is nothing else in ARIA. And there is nothing
7 in -- well, let's take it back. There is nothing in ARIA
8 that supports the less than 15 minutes. No cite that
9 supports less than 15 minutes as you stated; right?

10 THE COURT: Is there an objection?

11 MR. WURMAN: Objection, it calls for
12 speculation. The document is hundreds of pages long and he
13 is just showing one excerpt.

14 MR. EVENS: Fair enough.

15 BY MR. EVENS:

16 Q. You haven't pointed out any section in ARIA in your
17 testimony or in your expert report that pointed to a
18 15 minute onset of action, did you?

19 A. I did not.

20 Q. Okay. So the only cite you gave us today was this
21 cite from the recommendation; correct?

22 A. Correct.

23 Q. And then I guess we can just disagree on whether the
24 2088 cite, which is the only cite in that section, applies
25 to the 15 minute reference or not.

Wedner - cross

1 A. Well, there is in the literature significant evidence
2 --

3 Q. I'm not asking --

4 THE COURT: Hold on. Hold on. If you are going
5 to ask a question, you have got to take the answer.

6 MR. EVENS: Fair enough.

7 THE COURT: So was that a question?

8 MR. EVENS: I'm sorry.

9 THE COURT: Was that a question or was that not
10 a question?

11 MR. EVENS: I don't think that -- it was not the
12 question I asked, but I have now forgotten my question so I
13 can move on.

14 THE COURT: All right. Let's move on then.

15 BY MR. EVENS:

16 Q. Why don't we try this. Are you familiar with the
17 azelastine label?

18 A. Am I familiar with the azelastine label? Yes.

19 Q. Yes. And you do know that the Astelin label requires
20 that the onset of action is three hours?

21 A. It says within --

22 Q. Within three hours. That is certainly part greater
23 than the 15 minutes you are suggesting for us; correct?

24 A. No.

25 Q. No?

1 A. Remember, that allergic rhinitis has many different
2 symptoms. It has sneezing, it has itchy nose, it has
3 rhinorrhea, it has postnasal drip, and the data that is in
4 the literature is that one of those, sneezing, actually has
5 a 15 minute onset of action. That is well documented in the
6 literature.

7 Q. That is rhinorrhea; right?

8 A. That is sneezing. All of them are controlled within
9 that three hour period. So if you take the disease as a
10 whole, the onset of action is within three hours. That
11 doesn't mean that there isn't a part which is controlled in
12 15 minutes. It simply means that if you take the whole
13 symptom complex, it's controlled within three hours. And
14 within three hours means three hours or less.

15 Q. You have not provided us today with any cite,
16 supported cite to a 15 minute onsite of action, with
17 azelastine?

18 A. I have.

19 Q. Doctor, you brought up in your talk -- it wasn't in
20 your slides but 8-2-2-4-3 from the ARIA guidelines. Do you
21 recall that?

22 A. That is correct.

23 Q. And I think you made a point that the dosage that is
24 reported there is non-sedating?

25 A. I'd have to look at it to see the exact language.

Wedner - cross

1 MR. EVENS: Could we pull that up? I don't
2 think we have it. Let's move on.

3 Let's go to 309.

4 Let me ask you this: You recall that ARIA talks
5 about azelastine as formulated in Europe, right?

6 A. ARIA talks about two different, different doses not
7 formulations. ARIA says that the European dose is half of
8 the American dose. It has nothing to do with the
9 formulation of how many sprays you put in the nose.

10 Q. But in the U.S. dose, as dosed, there is a sedation
11 effect; correct?

12 A. There can be.

13 Q. Can be. Let's go to 309.

14 In your view, the only difference of Dymista and
15 the sequential administration of azelastine and fluticasone
16 is the choice between convenience and flexibility; is that
17 right.

18 A. No. I don't think it's a choice at all.

19 Q. I think --

20 MR. EVENS: Let's pull up 35 from his expert
21 report.

22 Never mind. Let's go to 310.

23 Ah, let's go to 26. I'm sorry. 26 of the
24 report.

25 BY MR. EVENS:

1 Q. So you talk about -- you see for the former group, we
2 have patients who have failed conventional histamines and
3 steroids; correct?

4 A. Yes.

5 Q. Okay, and for the former group, you have an
6 intranasal antihistamine to the steroids and offer them the
7 choice of a combination in a single spray, Dymista, or the
8 use of two sprays. Right?

9 A. Correct.

10 Q. And you explain the benefits of both, convenience
11 versus flexibility?

12 A. Correct.

13 Q. So you do offer them that choice?

14 A. But it doesn't mean that only convenience for one and
15 flexibility for the other.

16 Actually adding Dymista increases flexibility
17 because if you pick a dose and that dose is the same one
18 that is in Dymista, it gives you the option of actually
19 using Dymista. So it's both convenience and flexibility.

20 Q. I see. So let me ask you this: Drug companies pay
21 you to speak on behalf of their products; correct?

22 A. They do.

23 Q. At your deposition, you identified a number of drug
24 companies that pay you to speak; correct?

25 A. That's correct.

1 Q. And you speak on behalf of their products. And when
2 the doctors speak about a particular drug, when you speak
3 about a particular drug, the sponsoring company gives you a
4 slide deck, do they not?

5 A. They do.

6 Q. And you use that PowerPoint; correct?

7 A. I do.

8 Q. And you don't vary the PowerPoint from what is given
9 to you by the drug company?

10 A. If it is what we call a branded talk; in other words,
11 we're talking about a specific brand of medication; we don't
12 deviate. If it's an unbranded talk, then we can deviate as
13 much as we want.

14 Q. But for the branded company, you don't deviate from
15 the PowerPoint?

16 A. That's correct.

17 Q. Okay. And in any event, you received the deck that
18 is prepared by the brand and you have some understanding
19 that deck has been submitted to FDA for review?

20 A. That is correct.

21 Q. Okay. So to avoid any FDA compliance problems, you
22 don't deviate from that deck from the brand?

23 A. That is correct.

24 Q. Okay. And you present everything in the deck because
25 you don't -- so you don't deviate from the deck, you present

1 everything in the deck?

2 A. In general, yes.

3 Q. Okay. Once -- now, when I talked to you earlier, you
4 identified the drug companies, you did not identify Meda,
5 did you?

6 A. I did not.

7 Q. But you were retained by Meda or were part of the
8 Meda Speakers Bureau for Dymista?

9 A. At one point, yes. I don't think I ever actually
10 spoke for them.

11 Q. Do you recall speaking for Meda?

12 A. I do not.

13 Q. Let me try to refresh your recollection, if I could,
14 okay?

15 A. Sure.

16 MR. EVENS: Okay. So can we pull up Tab 1,
17 please?

18 (Pause.)

19 BY MR. EVENS:

20 Q. Now, this is something we pulled off the Internet,
21 Doctor, called dollars for Doctors. And it has a reference.
22 If we go to the next page.

23 At the top, you are being paid \$2,925 for
24 Dymista for education purposes. Do you recall that?

25 A. I actually don't, but I can't deny it.

Wedner - cross

1 Q. Okay. Do you recall -- let me try it this way. Do
2 you recall on December 16th, 2013 at a Missouri Coalition of
3 Nurses in Advanced Practice giving a talk about the benefits
4 of Dymista?

5 A. No.

6 (Counsel confer.)

7 BY MR. EVENS:

8 Q. Here is an invite that went out. Do you see that?
9 The title is Dymista (Azelastine Hydrochloride and
10 Fluticasone Propionate) Nasal Spray. It has the date, and
11 the form, it has the topic, and it has the speaker, H.
12 James Wedner and Julie Riebow. Do you know Julie Riebow?

13 A. I do not.

14 Q. Do you remember corresponding with her?

15 A. No.

16 Q. Do your remember working with her on the slide deck?

17 A. No.

18 Q. Do you remember correcting the slide deck?

19 A. I may have corrected some of the slide deck but I do
20 a lot of slide decks.

21 Q. So you may have received a slide deck from Meda on
22 Dymista?

23 A. Yes.

24 Q. But according to this document, you are the speaker
25 for Dymista. You don't recall that?

Wedner - cross

1 A. I do not.

2 Q. Look at Tab 3. Why don't we pull the collage.

3 MR. WURMAN: Your Honor?

4 THE COURT: Yes.

5 MR. WURMAN: May I have a copy of this document?

6 THE COURT: Yes. But you want the one previous,
7 correct?

8 MR. WURMAN: Yes.

9 MR. EVENS: Give him all of them.

10 BY MR. EVENS:

11 Q. So, Dr. Wedner, here we see the billing I guess for
12 the talk, Washington University, School of Medicine. You,
13 the slide deck with your name on it?

14 A. I see it. I honestly do not remember it, and I don't
15 remember that person in the picture.

16 Q. Maybe if we flip through the slide deck itself, you
17 might remember presenting at this association.

18 So here is the slide deck. It's not the one
19 identified in the picture because it doesn't have your name
20 on it, but let me just take you through a couple pages to
21 see if this refreshes your recollection, okay?

22 A. Sure.

23 MR. WURMAN: Your Honor, objection. There is no
24 reason for us to know if he has ever seen this document
25 before. There is no foundation. We don't know what year

Wedner - cross

1 this deck is from. There is no foundation for him to see it
2 at all.

3 MR. EVENS: Your Honor, we're trying to refresh
4 his recollection, but the picture did show a slide deck with
5 his name and the date, which is December of 2013, which is
6 when he gave apparently gave the talk, although the witness
7 says he can't remember it. I'm simply trying to refresh his
8 recollection.

9 MR. WURMAN: Your Honor, I don't have the slide
10 deck he just showed, but they look like different slide
11 decks, at least on my first impression.

12 THE COURT: Well, it looks as if the cover at
13 least is similar. I don't know how common this picture is.
14 Can you enlighten me? Does that narrow it down or does it
15 not?

16 MR. WURMAN: I withdraw my objection for the
17 moment, Your Honor.

18 THE COURT: All right.

19 MR. EVENS: Thank you, Your Honor.

20 THE COURT: You can continue questioning.

21 MR. EVENS: Thank you.

22 And you can see at the bottom, we did produce
23 the document during discovery, too.

24 So with that said, Dr. Wedner, why don't we flip
25 to page three, if we could.

Wedner - cross

1 MR. WURMAN: Your Honor.

2 THE COURT: Yes.

3 MR. WURMAN: It appears that there actually was
4 also a similar graphic that appeared in their opening slide
5 for a completely different purpose for a marketing document.
6 So I still don't know that there is any foundation for this
7 witness to have ever seen this.

8 MR. EVENS: I don't think --

9 THE COURT: Hold on. To the extent that is an
10 objection, I'm overruling the objection. I'm going to allow
11 the examination on this document. I do think we need to
12 identify for the record, though, at least what the Bates
13 number is of the page you are showing.

14 MR. EVENS: Thank you, Your Honor. The Bates
15 number at the bottom is MEDA _APTX02465640.

16 Thank you.

17 BY MR. EVENS:

18 Q. Do you see the title on page 3 of the deck, Dr.
19 Wedner?

20 A. I do.

21 Q. For the record, it is MEDA_ APTX302465640. It says
22 Unmet Needs in Allergic Rhinitis.

23 A. Correct.

24 Q. Does that refresh your recollection of the talk you
25 gave to the nurses association in St. Louis in December of

1 2013?

2 A. No.

3 Q. Why don't we flip to page 5. I'm sorry. Let's go to
4 Page 4 first.

5 On Page 4, which is MEDA_APTX 02465641, we talk
6 about the significant burden of allergic rhinitis. Are you
7 familiar at least with those statistics, Dr. Wedner?

8 A. I'm familiar with the statistics.

9 THE COURT: Hold on, Doctor. Is there an
10 objection?

11 MR. WURMAN: I withdraw the objection.

12 THE COURT: All right. Sorry, Doctor. You can
13 answer.

14 THE WITNESS: I just did.

15 THE COURT: If you already did, that's great.
16 Go ahead.

17 MR. EVENS: Thank you, Your Honor.

18 BY MR. EVENS:

19 Q. Let's go to page 5, which talks out how AR is
20 frequently underestimated and inadequately treated. And it
21 says, 44 percent of the patients are not fully satisfied
22 with the current prescription allergy medication and believe
23 their allergy medication does not provide symptom relief
24 quickly enough.

25 Do you recall, does that help refresh your

1 recollection?

2 A. Again, I agree with the statement. I think it is a
3 little less, but I don't recall this slide deck. I don't
4 recall ever having used it. So I can't say I saw it or not.

5 Q. Just a few last questions to sum up. You said
6 Dymista was no more effective in treating your patients. Is
7 that what I heard you say?

8 A. No more effective than the combination.

9 Q. Than the combination. But you haven't done any
10 research on that, have you?

11 A. I have not.

12 Q. And you did not provide us any of your patient
13 treatment records, did you?

14 A. I did not.

15 Q. Okay. And you said there are no difference in the
16 effects of Dymista I guess, between that and the two
17 monotherapies individually but, again, you have conducted no
18 research?

19 A. I have not done research, no.

20 Q. Okay. And you didn't point to any research that you
21 had read?

22 A. I did not.

23 Q. Okay. And you said the long term effects are the
24 same but, again, you haven't conducted any research on that,
25 have you?

1 A. I have not.

2 Q. And you have not reported, pointed to any research
3 that you read to support that statement?

4 A. I did not.

5 Q. So let me get this. To sum up, you did not review
6 your patient records to prepare for your expert report or
7 testify today, did you?

8 A. No.

9 Q. You did not conduct research to prepare your expert
10 report or testify today, did you?

11 A. That's correct.

12 Q. Okay. You didn't provide us with any written records
13 to support, that you have kept on treatment patterns to
14 support your expert report for your testimony today?

15 A. Well, as we discussed in my deposition, prior to
16 2002, we had paper records. We destroyed most of the paper
17 records when we went to her, so it would have been
18 impossible for me to do so.

19 Q. Well, you did have records though; right?

20 A. We had records after 2002, but not before 2002.

21 Q. Well, I remember -- and, I'm sorry. Had you
22 finished? I didn't mean to cut you off.

23 A. I'm finished.

24 Q. I remember you telling me for your longer term
25 patients, you did have those records?

Wedner - cross

1 A. We could have found records, yes?

2 Q. But you didn't search?

3 A. We did not.

4 Q. Okay. And you have not published on the use of
5 Azelastine in corticosteroids. Right, Doctor?

6 A. I have not.

7 Q. Okay. And I think Mr. Wurman at the beginning took
8 you through your impressive resume' with over 140 articles?

9 A. Approximately, yes.

10 Q. And he pointed to two from 1984.

11 A. Correct.

12 Q. And those didn't deal with combination therapy or
13 using the drugs we're discussing today?

14 A. They did not.

15 Q. Okay. And subsequent -- and, of course, you couldn't
16 have, because Azelastine and Fluticasone didn't come out
17 until the mid-nineties?

18 A. That's right.

19 Q. But since then you have not published articles on
20 using those drugs conjunctively, have you?

21 A. I have not.

22 Q. All right. So I want to go back to kind of when we
23 were talking. You went through your rules of how you keep
24 your records.

25 Do you remember that?

1 A. Yes.

2 Q. And you said in your records, you do write down the
3 drugs you prescribe?

4 A. All of them, yes.

5 Q. We don't have those, and you wrote down the effects
6 of those drugs; is that correct?

7 A. Yes.

8 Q. But you don't have those.

9 And then do you recall telling me that you
10 give a patient, if you give a patient a drug and the patient
11 gets better --

12 MR. WURMAN: Your Honor, objection.

13 THE COURT: Are you summarizing his prior
14 testimony?

15 MR. EVENS: I am. I'm just asking him if he
16 said it, if he recalled saying it.

17 THE COURT: I'm going to sustain the objection.
18 Just ask him what you want to ask him. He might tell you
19 what you want to hear.

20 MR. EVENS: Your Honor, we're finished.

21 THE COURT: You're finished?

22 MR. EVENS: Yes.

23 THE COURT: Fine.

24 Redirect?

25 MR. EVENS: Your Honor, with that, we would like

Wedner - redirect

1 to introduce Plaintiffs' 326 and Plaintiffs' 329 and the
2 impeachment documents.

3 THE COURT: I'm sorry. Are there numbers on the
4 other documents?

5 MR. EVENS: They are not. They are not marked.

6 THE COURT: You'll have to mark those. You can
7 do that and present them tomorrow if you wish.

8 MR. EVENS: Okay, your Honor.

9 THE COURT: But 328 and 329 you're offering?

10 MR. EVENS: Yes, your Honor.

11 THE COURT: Any objection to those?

12 MR. WURMAN: Your Honor, I didn't quite catch
13 all of the exhibits he wanted to admit into evidence, but to
14 the extent they were stamped as exhibits for this trial, we
15 have no objection to these.

16 (Pause while counsel conferred.)

17 THE COURT: Give me an update tomorrow on where
18 we are on these exhibits. I won't admit any of them that
19 were just used in cross for now subject to further discussion.

20 Any redirect?

21 MR. WURMAN: Yes, your Honor.

22 Could we put up 3.07 I think, that excerpt from
23 the ARIA guidelines.

24 REDIRECT EXAMINATION

25 BY MR. WURMAN:

Wedner - redirect

1 Q. Doctor, do you recall Mr. Evens asking you about this
2 excerpt from the ARIA Guidelines?

3 A. Yes.

4 Q. And do you recall the discussion about the onset of
5 action of topical antihistamines?

6 A. Yes.

7 Q. Do you recall telling Mr. Evens that you were
8 familiar with the literature generally of Azelastine?

9 A. Yes.

10 Q. And that that literature supports the set of
11 statements?

12 A. Yes, I do.

13 MR. WURMAN: Could you put up Defendants'
14 Exhibit 43. Could we blow up the top portion just so we
15 could get a sense of what it is.

16 BY MR. WURMAN:

17 Q. Dr. Wedner, are you familiar with this article?

18 A. I am.

19 Q. Can we find the date on it? Is it from the
20 publication called "Drugs" from 1998?

21 A. Yes, it is.

22 Q. And is its title "Intranasal Azelastine, a review of
23 its efficacy in the management of allergic rhinitis"?

24 A. Yes.

25 Q. And you said you're generally familiar with this

Wedner - redirect

1 article?

2 A. Yes.

3 MR. EVENS: Excuse me, your Honor.

4 THE COURT: Yes?

5 MR. EVENS: I don't think we have a copy of
6 this. I also think it's outside my cross-examination.

7 THE COURT: All right. Is there a copy for
8 them?

9 MR. WURMAN: Your Honor, he can certainly have
10 my copy.

11 THE COURT: Okay. And is it outside the scope
12 of the cross?

13 MR. WURMAN: It is not, your Honor. It goes
14 directly to the question of whether there is, in fact, other
15 support for that proposition in the ARIA guidelines, which
16 Dr. Wedner was familiar.

17 It was not --

18 THE COURT: Okay. Did you want to respond to
19 that?

20 MR. EVENS: Well, there was no noun in there.
21 He said for a -- I don't know what proposition.

22 THE COURT: All right. Tell us which
23 proposition?

24 MR. WURMAN: For the proposition that topical
25 antihistamines have an onset of action within 15 to

Wedner - redirect

1 30 minutes, or approximately 15 minutes.

2 THE COURT: All right. Do you still have an
3 issue on that?

4 MR. EVENS: Well, I do have an objection, your
5 Honor, that the witness never in his expert report had any
6 statement about onset of action. Not in his deposition.

7 THE COURT: All right.

8 MR. EVENS: And I don't believe -- I think the
9 cite, he chose the ARIA Guidelines, pulled up the cite, and
10 the cite doesn't support the 15 minutes.

11 THE COURT: All right.

12 MR. EVENS: And let me just finish.

13 While the witness says that he knows of other
14 literature, he's not -- he never pointed to any of that
15 other literature in any report.

16 THE COURT: Are you still arguing that use of
17 this document is outside the scope of the cross?

18 MR. EVENS: I am, your Honor.

19 THE COURT: All right. Are you also arguing
20 that this is beyond the scope of his expert report?

21 MR. EVENS: I think it is, your Honor.

22 THE COURT: All right. If you want to respond?

23 MR. WURMAN: Yes, your Honor. He opined as to
24 onset of action in his expert report. If you give me a
25 moment?

Wedner - redirect

1 THE COURT: Sure. Do I have a copy here in my
2 binder?

3 MR. WURMAN: Of his expert report?

4 THE COURT: Yes. If I don't, you'll have to
5 pass it up unless you persuade counsel it is in there.

6 MR. WURMAN: Of course, your Honor. And for the
7 record, it's paragraph 38 of his opening report. May I
8 approach?

9 THE COURT: You may.

10 (Mr. Wurman handed documents to the Court.)

11 MR. WURMAN: It's a marked-up copy. May I
12 approach? I have a clean copy.

13 THE COURT: Sure. If you have a clean copy,
14 we'll trade this one back to you.

15 All right. Mr. Evens, do you still object to
16 this testimony being outside the scope of his testimony of
17 what was disclosed in his report?

18 MR. EVENS: No, your Honor, but I would point
19 out there's a total lack of support there and they never put
20 us on notice what the support was.

21 THE COURT: I'm sorry. That is or is not an
22 objection that it's outside the scope?

23 MR. EVENS: It's not an objection as to outside
24 the scope. There was a mention in the expert report that's
25 unsupported.

Wedner - redirect

1 THE COURT: Okay. I'm going to overrule the
2 objection, so you can ask your question.

3 BY MR. WURMAN:

4 Q. Can we please go to page 102 of the exhibit? I'm
5 sorry. 102 of the article. If you can find it.

6 And at the very bottom of the left column and
7 continuing into the top right column, can we blow those
8 up?

9 Dr. Wedner, does this article appear to be
10 reporting a study in which 84 percent of 103 patients
11 reported an onset of action within 30 minutes of
12 administering the drug intranasally, the mean onset of
13 action in this study was 17 minutes?

14 A. Yes.

15 Q. And does it refer to Azelastine in this excerpt?

16 A. It does.

17 Q. And does that support your proposition in your
18 testimony?

19 A. Yes.

20 Q. That antihistamines act within 15 minutes?

21 A. Yes, it does.

22 MR. WURMAN: I have no further questions for
23 this witness, but I move DTX-43 be entered into evidence.

24 THE COURT: All right. Is there any objection?

25 MR. EVENS: No, your Honor, but we would request

Wedner - redirect

1 a brief period to just -- before we do a redirect, or see if
2 there is a redirect, at least have the opportunity to read
3 this article.

4 THE COURT: I'm sorry. It would be a recross.
5 Correct?

6 MR. EVENS: Recross. I'm sorry, your Honor.

7 THE COURT: I generally don't permit recross. I
8 don't see a basis to do so here.

9 MR. EVENS: All right, your Honor.

10 THE COURT: So the document is admitted.

11 (DTX-43 was admitted into evidence.)

12 THE COURT: And you can step down, Doctor.

13 THE WITNESS: Thank you.

14 THE COURT: Thank you.

15 (Witness excused.)

16 THE COURT: All right. We're going to go
17 probably to about 7:00 o'clock, so defendants can call
18 another witness if they wish.

19 MR. HAUER: Good afternoon, your Honor. I'm
20 Ryan Hauer from Winston & Strawn. I represent Apotex.

21 We'd like to introduce testimony by deposition
22 designations at this time. The parties agreed to the
23 versions of the pretrial order on designations and
24 counter-designations, which we'll play by video.

25 The first video is from the deposition of

Fuge - designations

1 Mr. Dennis Fuge, which took place on April 14th, 2016.

2 Mr. Fuge is the Vice President of Technical
3 Operations at Meda. He was noticed personally and he was
4 noticed as a 30(b)(6) witness on numerous topics. The total
5 time of the video is ten minutes and 13 seconds with eight
6 minutes and 52 seconds allocated to defendants and one
7 minute and 22 seconds allocated to plaintiffs.

8 I will note that the Fuge Deposition Exhibits 12
9 and 13, which are mentioned in the video, correlate to
10 DTX-300 and is mentioned in the deposition.

11 We have binders of the designated testimony and
12 that exhibit. If we may approach?

13 THE COURT: You may approach.

14 We'll need you to give us, instead of the
15 minutes and seconds, we'll need it by percentage time if the
16 clock is running the whole time you're speaking and we'll
17 just apply that percentage for tomorrow.

18 Thank you. And you may pass those up.

19 THE COURT: Play the deposition when you are
20 ready.

21 (The videotaped deposition of Dennis Fuge was
22 played as follows.)

23 "Question: Good morning.

24 "Answer: Good morning.

25 "Question: Would you please state your name for

Fuge - designations

1 the record?

2 "Answer: Dennis Brian Fuge.

3 "Question: And who do you currently work for?

4 "Answer: Meda Pharmaceuticals.

5 "Question: And what is your title there?

6 "Answer: My current title is VP of technical
7 operations.

8 "Question: Do you know" --

9 THE COURT: Is it possible to turn up the
10 volume? Thank you.

11 (Videotape stopped.)

12 (Pause.)

13 MR. HAUER: Would it be helpful to go back.

14 THE COURT: We can pick it up from there.

15 "Question: Do you know why Meda was trying to
16 develop a product comprising Azelastine and Fluticasone as a
17 nasal spray?

18 THE WITNESS: Yes. Meda was really good at
19 listening to consumers and listening to physicians and
20 trying to find unmet needs in the marketplace, so we had a
21 very active program with the Azelastine molecule to address
22 those needs.

23 "Question: So did I hear correctly that -- to
24 your recollection, Meda was trying to develop a Fluticasone/
25 Azelastine nasal spray product since approximately 2002?

Fuge - designations

1 THE WITNESS: Yes. The time frame -- I cannot
2 recall the exact time frame, but the answer is yes, we were
3 actively trying to develop such a product.

4 "Question: Okay.

5 "And that was -- and to your recollection, it's
6 just prior to 2003; you just don't know exactly what time
7 period that was?

8 "Answer: Yes.

9 "Question: Okay.

10 "And to your recollection, the reason why Meda
11 started doing this was because of feedback from the
12 consumers that Meda was receiving?

13 "THE WITNESS: Yes, we had a very active program
14 of listening to consumers and physicians and trying to find
15 unmet needs in the marketplace.

16 "Question: Was Meda aware when you received
17 this request around 2003 that patients and Drs. Were using
18 Azelastine product and Fluticasone product separately as a
19 nasal spray for a single patient?

20 THE WITNESS: No, that's better answered by the
21 marketing team at the time because they would have been
22 listening to the consumers and the physicians.

23 "Question: Okay.

24 "But were you aware?

25 "THE WITNESS: Some time during that period I

Fuge - designations

1 would become aware that there was any anecdotal evidence of
2 physicians using the two sprays.

3 "Question: So Exhibit 12 is an e-mail attaching
4 a report from your meetings on August 3rd and 4, 2006, in
5 which you visited the Cipla Goa facility and meeting with
6 Mr. Lulla, Ms. Malhotra and Patsy; is that right?

7 "Answer: (Reviewing) I believe this is the
8 report on the visit to the Goa facility.

9 (Reviewing.)

10 "Question: Well, if you look at Exhibit 13
11 goes, on top it states, Cipla, August 3rd and 4, 2006.

12 "Do you see that?

13 "Answer: I do.

14 "Question: But what I'm asking you is, did this
15 e-mail get sent after your meeting at Mumbai?

16 "Answer: I do not know.

17 "Question: Okay.

18 "The attachment's title is August 3rd and 4th.

19 "Do you see that?

20 "Answer: I do.

21 "Question: So isn't it fair to believe that
22 this is describing the events at August 3rd and 4th at
23 Cipla?

24 "Answer: No, because the report doesn't include
25 anything about the negotiation piece that happened in

Fuge - designations

1 Mumbai, so that's why I cannot -- I cannot confirm that.

2 "Question: So Mr. Fishman was with you during
3 your meeting at India; is that right?

4 "Answer: Correct.

5 "Question: Okay.

6 "So if he was present with you, why did you
7 create this report for him?

8 "Answer: Because after every trip I created a
9 trip report to document the actions that we took or the
10 findings that we made.

11 "Question: Now, your meeting with Mr. Lulla,
12 Ms. Malhotra and Patsy, that was an important meeting, was
13 it not, for Meda?

14 "Answer: Yes.

15 "Question: Did you create a report after that
16 meeting?

17 "Answer: I do not recall.

18 "Question: But you created Exhibit 13?

19 "Answer: Yes.

20 "Question: And as far as we know, this is the
21 only report that was created after your visit to India?

22 THE WITNESS: (Reviewing.) I cannot recall if
23 there was another report after this one.

24 "Question: Okay.

25 "You don't know if there is another report other

Fuge - designations

1 than this one; is that right?

2 "Answer: I cannot -- I cannot recall.

3 "Question: Now, when you are sending a report
4 to your boss, Mr. Fishman, do you try to make it as
5 accurate -- accurate as possible?

6 "Answer: Yes.

7 "Question: Okay.

8 And this was a potentially important development
9 for Meda, licensing these patents, was it not?

10 "Answer: Yes.

11 "Question: So when you drafted this report, did
12 you review it for accuracy?

13 "Answer: (Reviewing.) Yes.

14 "Question: Let's take a look at the summary
15 report that you provided. Take a look at the executive
16 summary.

17 "Answer: Mm-hmm.

18 "Question: Just read that to yourself.

19 "Answer: (Reviewing.) All right.

20 "Question: Okay.

21 "Second paragraph.

22 "Answer: Mm-hmm.

23 "Question: The first sentence reads: 'They are
24 about to launch Astelin in the USA with one of their
25 partners, most likely Watson's. They are expecting patent

Fuge - designations

1 clearance in early 2007 for this formulation.

2 "Do you see that?

3 "Answer: I do.

4 "Question: Now, you go on to say, 'They
5 selected the Azelastine/Fluticasone combo because it was
6 obvious.'

7 Do you see that?

8 "Answer: I do.

9 "Question: And by they, you are referring to
10 Cipla, correct?

11 "Answer: Yes.

12 "Question: And by the Azelastine/Fluticasone
13 combo, you are referring to the Duonase product that Cipla
14 was selling at the time; is that right?

15 "Answer: That is my understanding from this
16 report.

17 "Question: Now, when you say they selected the
18 Azelastine/Fluticasone combo, you are referring to the fact
19 that Cipla chose to develop a combination nasal spray
20 formulation with the active ingredient Azelastine and
21 Fluticasone; is that right?

22 "Answer: Yes.

23 "Question: And you are saying here that
24 according to Cipla, they did this because it was obvious,
25 correct?

Fuge - designations

1 "Answer: No, that is not what I am implying.

2 "Question: I just read you a quote. 'They
3 selected the Azelastine/Fluticasone combo because it was
4 obvious.'

5 "Do you see that?

6 "Answer: I do.

7 "Question: And that's the sentence that you
8 wrote, right?

9 "Answer: Yes.

10 "Question: Okay.

11 But you are not -- but you are saying that --
12 that it's not correct that according to Cipla, they
13 developed the Azelastine/Fluticasone combo because 'It was
14 obvious.'

15 "That's an incorrect understanding; is that what
16 you are saying?

17 "Answer: That is my interpretation of why they
18 selected those two.

19 "Question: You stated that it is your
20 interpretation of why they selected those two, meaning
21 Azelastine and Fluticasone, because it was obvious.

22 "What did you mean by that?

23 "Answer: My interpretation was that Fluticasone
24 was the then best selling steroid, and Azelastine was the
25 best antihistamine.

Fuge - designations

1 "Question: The time period that we are talking
2 about is when they, meaning Cipla, developed this
3 formulation, right?

4 "Answer: You know, that is my understanding, is
5 that they selected those two compounds, because they were
6 the best two compounds.

7 "Question: And did that rationale make sense to
8 you, that somebody would select the two best selling nasal
9 spray formulations to combine together?

10 THE WITNESS: No, because MedPointe had also
11 selected those two compounds as the best two compounds to
12 utilize.

13 "Question: And your rationale is that MedPointe
14 did not ultimately develop that product?

15 "Answer: No, but it was obvious to us that
16 those were the two best compounds to use for any product we
17 did develop.

18 "Question: So what you are saying is that it
19 was obvious to think of combining those two ingredients
20 together but not necessarily obvious to have carried out the
21 formulation; is that what you are saying?

22 "THE WITNESS: It is my understanding that those
23 two compounds were the best choices for a formulation.

24 "Question: And why was that?

25 THE WITNESS: My understanding is Azelastine was

Fuge - designations

1 the best antihistamine on the market in a nasal spray form,
2 and Fluticasone propionate was the best steroid on the
3 market for seasonal allergic rhinitis.

4 "That is why I would have made that conclusion.

5 "Question: The conclusion that the combination
6 was obvious?

7 "Answer: That those two compounds were the best
8 to choose -- the obvious two compounds to choose for a
9 formulation.

10 "Question: For a combination formulation?

11 "Answer: Whether it was a dual-chamber device
12 or what type of formulation, I didn't speculate on.

13 (End of videotaped deposition.)

14 MR. HAUER: Your Honor, at this time Apotex
15 would like to enter into evidence DTX-300, which was
16 referenced in the designated testimony 6789.

17 THE COURT: Any objection?

18 MR. VARUGHESE: No objection, your Honor.

19 THE COURT: All right. It's admitted.

20 (DTX-300 was admitted into evidence.)

21 MR. KLEIN: Your Honor, at this time we'd call
22 Dr. Robert Schleimer.

23 THE COURT: Okay.

24 ... ROBERT P. SCHLEIMER, having been duly sworn
25 as a witness, was examined and testified as follows ...

Schleimer - direct

1 THE COURT: Good evening, Dr. Schleimer.

2 Welcome. You may approach.

3 (Mr. Hauer handed notebooks to the witness.)

4 MR. WURMAN: May I approach?

5 (Mr. Wurman handed notebooks to the Court.)

6 THE COURT: You may proceed when you are ready.

7 MR. KLEIN: Thank you, your Honor.

8 DIRECT EXAMINATION

9 BY MR. KLEIN:

10 Q. Good afternoon, Dr. Schleimer. What's your full
11 name?

12 A. Robert Paul Schleimer.

13 Q. Where do you work?

14 A. Northwestern University, Feinberg School of Medicine.

15 Q. Did Apotex retain you as an expert in this case?

16 A. Yes.

17 Q. What's your area or areas of expertise?

18 A. I'm interested in the cellular and molecular
19 mechanisms of allergic disease as well as the use and
20 mechanisms of drugs that are effective in treating allergic
21 disease.

22 Q. And do you have a slide deck to supplement your
23 testimony today?

24 A. Yes, I do.

25 Q. On the screen is a snapshot from DTX-294. Is that a

Schleimer - direct

1 copy of your C.V.?

2 A. Yes.

3 Q. What is your position at Northwestern?

4 A. I'm the Roy and Elaine Patterson Professor, and the
5 Chief of the Division of Allergy-Immunology as well as a
6 professor of medicine.

7 Q. Please summarize your responsibilities in that
8 position.

9 A. I'm responsible for the administration, strategic
10 development, recruitment, et cetera, and running of the
11 Division of Allergy-Immunology.

12 Q. And does your division have a clinical practice?

13 A. Yes. Our division, which consists of just under 100
14 people total and over 20 faculty, has a very active clinical
15 practice for which I'm ultimately responsible for, and also
16 has a very active research program with people in the
17 laboratory as well as doing clinical research.

18 Q. And how does that clinical practice compare to
19 clinical practice, clinical allergy practices at other
20 organizations?

21 A. I think that ours is one of the biggest in the
22 country.

23 Q. So do you oversee clinicians and scientists in your
24 role as the chief of division of allergy-immunology?

25 A. I do. I'm responsible for overseeing the research in

Schleimer - direct

1 the laboratory and in the clinic, and I'm also the principal
2 investigator of the training grant that pays for the
3 salaries of clinical fellows who are learning to do allergy
4 as well as research in the field of allergy. And finally,
5 as I mentioned, I'm responsible for overseeing the clinic.
6 We have a clinical practice director also.

7 Q. When did you start serving in this role?

8 A. In 2004.

9 Q. Do you have an MD?

10 A. I do not.

11 Q. Do you have a Ph.D.?

12 A. Yes.

13 Q. And what is that degree in?

14 A. My Ph.D., I received from the University of
15 California at Davis in pharmacology and toxicology. But I
16 worked with a world renowned immunologist. So I have
17 interest in drug action in immunology and more recently
18 allergy.

19 Q. And when did you graduate? I'm sorry. When did you
20 get your Ph.D.?

21 A. In 1979.

22 Q. So you mentioned pharmacology and toxicology. Can
23 you explain what those are?

24 A. It's the study of the development and the mechanisms
25 of action, toxicities, and effects of drugs and toxic

Schleimer - direct

1 agents.

2 Q. Do you consider yourself to be a pharmacologist?

3 A. I consider myself to be an immunopharmacologist but
4 also do a lot of clinical research in allergic diseases.

5 Q. Now, this is probably an obvious question, but as a
6 pharmacologist do you prescribe medications?

7 A. I do not.

8 Q. But are you familiar with the treatments of allergic
9 rhinitis?

10 A. Yes. I've been attending the clinical allergy
11 conferences and rounds while I was at Johns Hopkins for
12 25 years and in the last 12 years at Northwestern.

13 Q. Have you taught medical students?

14 A. Yes.

15 Q. And what about medical MD fellows who were training
16 to be allergists? Have you taught them?

17 A. Yes. One of our major goals is to train residents to
18 learn allergy and become board certified allergists, and I
19 played an active role in that training program both the
20 development of it and teaching.

21 Q. Do you belong to any professional societies?

22 A. Yes. This lists a number of societies. Probably the
23 most relevant to this case is I'm a fellow of the American
24 Academy of Allergy, Asthma and Immunology, which is a
25 leading academy arguably in the world but certainly in the

1 U.S.

2 Q. Have you served on any editorial boards?

3 A. Yes. As shown here, a number of editorial boards.
4 Again, most relevant is the Journal of Allergy and Clinical
5 Immunology on which I was a senior associate edit or and.

6 Q. And that was from 1993 to 1998. Did I have that
7 right?

8 A. Yes.

9 Q. Have you edited any books relevant to this case?

10 A. I have. These three books are on the subject of
11 antiinflammatory steroids or glucocorticoids. We have been
12 referring to them so far in the case as steroids, and I'll
13 continue to do so.

14 They are all books related to the use of inhaled
15 or intranasal steroids for the allergic diseases of the
16 lungs or upper airways.

17 Q. About how many articles have you published?

18 A. I think it's over 350.

19 Q. Have you authored any publications related to the
20 treatment of allergic rhinitis in particular?

21 A. I have. This is one article as an example. The
22 Middleton textbook is widely considered to be the leading
23 Text book in allergic diseases, and this particular chapter
24 on steroids was written by me for many additions of this
25 textbook, and it deals both with mechanisms of action as

Schleimer - direct

1 well as the use of these important drugs and allergic
2 disease.

3 Q. Now, Dr. Schleimer, do you, as a pharmacologist,
4 participate in drug development activities?

5 A. Yes. Perhaps because I'm an immunopharmacologist who
6 has interest in disease, my expertise has been of interest
7 to a number of pharmaceutical companies and a list is shown
8 here.

9 Q. Have you consulted for both brand and generic
10 companies?

11 A. Mostly brand, but on occasion generic.

12 Q. Have you provided consulting advice related to
13 allergic rhinitis?

14 A. I have.

15 Q. And is the list that we see on the screen which is
16 DDX-4.08, is that an exclusive list?

17 A. No, most of these are recent ones. I would say the
18 full list is probably more than double this.

19 Q. And how long have you been consulting for
20 pharmaceutical companies?

21 A. Well, the first project I was working on as a
22 graduate student, we actually interacted with and
23 collaborated with a pharmaceutical company, and that was in
24 the 70s.

25 Q. Are you listed as an inventor on any patents?

Schleimer - direct

1 A. Yes, I hold nine patents, and most of them have been
2 licensed from Johns Hopkins. Some of them for Allakos,
3 which is the first listed company here, which I am the
4 founder of and presently has three clinical trials ongoing.

5 Q. Are you generally familiar with the process for
6 obtaining patents?

7 A. Yes.

8 Q. And are you generally familiar with the process for
9 obtaining FDA approval of a drug?

10 A. Yes. Over the years, on many occasions I have
11 assisted companies as they prepare packages for submission
12 to the FDA for approval.

13 MR. KLEIN: Your Honor, at this time, Apotex
14 tenders Dr. Schleimer as an expert in the areas of allergy,
15 immunology, pharmacology and drug development.

16 THE COURT: Any objection?

17 MR. VARUGHESE: No objection, Your Honor.

18 THE COURT: Okay. He is so recognized.

19 BY MR. KLEIN:

20 Q. Dr. Schleimer, can you summarize the opinions you
21 intend to present today?

22 A. Yes. As bulleted on this slide, I think that by June
23 2002, it was obvious to co-formulate fluticasone propionate
24 with azelastine hydrochloride to treat allergic rhinitis.

25 I think that doctors combined these two drugs

Schleimer - direct

1 because they had complementary mechanisms of action, as
2 we've heard. Flonase is the best antiinflammatory drug
3 available for this disease but it works slowly and Astelin
4 works quickly, and that gives them great complementary.

5 In addition, two pharmaceutical companies
6 disclosed co-formulating these two drugs for nasal
7 administration.

8 Q. Now, there are a couple of the bullets are shaded
9 out. If appropriate, do you plan to address those issues
10 during the rebuttal case?

11 A. Yes.

12 Q. Okay. And for convenience, can we refer to the two
13 drugs as simply fluticasone and azelastine?

14 A. Yes, please.

15 Q. How have you organized your testimony?

16 A. Well, first I'd like to briefly mention allergic
17 rhinitis in the background section.

18 Q. We've obviously heard a little bit about allergic
19 rhinitis so far. But can you explain a little bit, give us
20 a little bit more background about that disease?

21 A. Yes. As briefly touched on by Mr. Lombardi, it is
22 commonly known as hayfever, and it is caused when a person
23 becomes sensitive to an inhaled substance which we call an
24 allergen, something that causes allergic reactions.

25 A couple of examples here are pollen or dust

1 mites.

2 These allergens, when they go into the nose, as
3 you can see, there are sensitized mass cells. It is a type
4 of inflammatory cell that releases mediators such as
5 histamine and others that cause the symptoms of the disease
6 including sneezing, wheezing, nasal obstruction, runny nose,
7 et cetera.

8 Q. Can you explain what happens to an allergic person
9 when he or she is exposed to an allergy?

10 A. Yes. If an asymptomatic allergic person is exposed
11 to allergen, there is usually a biphasic response. There is
12 an immediate or early phase response that occurs within
13 minutes of the exposure, and then that results usually
14 around an hour or so, and then there is a later phase
15 response which can evolve four to ten hours or even longer
16 after that. And that is more of an inflammatory response
17 rather than an acute neurophysiological response.

18 Q. And is there a particular reference that you cite as
19 an example for this phenomenon?

20 A. Yes. Drouin is one selected from many possible.

21 Q. Which is PTX-333?

22 A. Yes.

23 Q. So what happens in the early phase?

24 A. In the early phase, as I mentioned the mass cells
25 release their inflammatory mediators which include

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1 histamine, but as you can see, underlined on the excerpt
2 from Galant, leukotrienes are also released; and I mention
3 that only because they will come up later as we review the
4 Cramer patent. These mediators then cause the symptoms very
5 rapidly.

6 Q. You are now referring to DTX-34?

7 A. Yes.

8 Q. What happens in the late phase?

9 A. Well, the late phase is more of a chronic
10 inflammatory-type response. Inflammatory cells come from
11 the blood into the tissue and they release some of the same
12 and some different mediators and cause this inflammatory
13 response that can be prolonged. And we use Galant as one of
14 many possible examples of this.

15 Q. Again, this is DTX-34?

16 A. Yes.

17 Q. As we'll explain in a moment, I'd like to focus on
18 the early to mid-June -- early to mid-2002 time period.
19 What would be the top treatments for the late phase of
20 allergic rhinitis at that time?

21 A. Well, it has been known for many decades and it is
22 still the case that the single most effective drugs in
23 inhibiting the late phase response are steroids. And shown
24 on this slide are four examples of steroids given
25 intranasally. You can see from left to right, there is

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1 Flonase, Beconase, Nasacort, and Nasonex.

2 And the active ingredients are listed
3 underneath: fluticasone propionate, beclomethasone
4 dipropionate, triamcinolone acetonide, mometasone furoate.

5 And as we briefly discuss, the ARIA guidelines
6 are guidelines prepared by international experts to help
7 allergists make their treatment choices, and they listed
8 intranasal steroids as first line treatment or drug of first
9 choice for patients suffering from this disease. But --

10 Q. And -- I'm sorry. I didn't mean to interrupt.

11 A. But it's important to note, as you see the reference
12 at the bottom, which is from a review that I wrote in 1998,
13 that these drugs, if used long enough, say a week or longer,
14 can begin to inhibit the early phase. So this is an issue
15 with the use of these drugs because they have a deficiency,
16 if you want to call that, that patients don't perceive that
17 they're working well, sometimes for days, and that's an
18 important aspect of these drugs in this case.

19 Q. Why is that important?

20 A. It's important because before the priority date, it
21 was already clear that these were the best drugs to manage
22 this disease, but there is this problem that they don't work
23 very quickly. So many people, and we are just discussing a
24 few in the case, it occurred to them to combine these drugs
25 with something that worked quickly in order to compensate

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1 for that, that lack of rapidity of the steroids.

2 Q. And for the record, the ARIA guidelines are PTX-326;
3 is that right?

4 A. I believe so.

5 Q. And the ARIA reference is DTX-78. And you also have
6 a "see also" to the Galant reference. Are you relying on
7 that as well?

8 A. Yes.

9 Q. And that is DTX-34?

10 A. Yes.

11 Q. Were any of the nasal steroids at the time known to
12 be the most potent? Again, focusing on mid-2002.

13 A. Yes. This slide actually shows two studies that
14 compare the potency of most of the presently available
15 intranasal steroid. One is from my lab, Stellato in 1999
16 and the other was from Malcolm Johnson's lab at
17 GlaxoSmithKline.

18 And together, the studies use seven different
19 assays of potency, and the uniform conclusion was that
20 fluticasone propionate was the most potent, with mometasone
21 furoate slightly behind it, and the others were considerably
22 less potent.

23 Q. And Stellato is PTX-325 and Johnson is DTX-39, right?

24 A. Yes.

25 Q. Now, in 2002, or by 2002, what were the top

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1 treatments for the early phase of allergic rhinitis?

2 A. Well, certainly the most popular class of drug, one
3 of the most popular classes of drug was the antihistamine
4 class. And that is true to this day. And this slide shows
5 four of many, as we saw earlier, antihistamines that were
6 available.

7 On the right you have Claritin and Zyrtec which
8 are oral antihistamines with the active ingredients of
9 loratadine and cetirizine.

10 On the left, you see the only two intranasal
11 antihistamines, azelastine levocabastine which have been
12 discussed already.

13 And in general, antihistamines are effective
14 against many of the symptoms of seasonal allergic rhinitis
15 such as sneezing, itching, rhinorrhea, but they're not
16 particularly effective in relieving nasal blockade,
17 blockage.

18 Q. Are you relying on the Drouin reference, PTX-333, for
19 that proposition?

20 A. Yes.

21 Q. By the way, you see it says H1 receptor antagonist.
22 Is that another name for antihistamines?

23 A. Yes, that is the important histamine receptor
24 involved in allergic disease and antagonist means an
25 inhibitor. So these are antihistamine H1 receptor

1 antagonists.

2 Q. How do oral and intranasal antihistamines compare in
3 terms of side effects?

4 A. Well, as has already been discussed in this case, the
5 use of an intranasal drug allows the physician to get high
6 local concentrations of the drug without high systemic
7 concentrations. And that means that systemic side effects
8 are avoided or greatly minimized. And that, that is a major
9 advantage of both classes of these drugs using them locally.
10 They're safer.

11 Q. And what do you mean by systemic side effects?

12 A. Well, with antihistamines, an important systemic side
13 effect is drowsiness, for example, and that is when the
14 histamine goes into the brain and by keeping it locally in
15 the nose, the concentration in the blood is very, very low.
16 So the amount going to the brain is minimal.

17 Q. So, in other words, the intranasal antihistamines are
18 more or less sleep inducing than the oral?

19 A. Much less. They're very safe drugs.

20 Q. And so we're looking at the ARIA guidelines here
21 which is PTX-326, right?

22 A. Yes.

23 Q. And it says topical antihistamines. Is there a
24 difference between topical and intranasal?

25 A. Topical refers to putting it on the surface and

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1 intranasal is the one nose topical application, so in this
2 case they're synonymous.

3 Q. Are there relevant differences between the effects
4 the oral and intranasal antihistamines?

5 A. Yes. It turns out that with selected antihistamines,
6 not all of them but selected ones, they also had
7 antiinflammatory effects, effects that were mediated
8 independent of their ability to block the H1 receptor. They
9 could inhibit the release of inflammatory mediators or
10 inflammatory cells.

11 And this is an effect that is for the most part
12 not associated with oral antihistamines because the
13 concentrations in the nose when you take it orally are not
14 quite high enough to exert these effects.

15 Q. Now, are you saying that a topical antihistamine can
16 treat the late phase inflammatory symptoms of allergic
17 rhinitis?

18 A. There is some evidence that they serve
19 antiinflammatory effects and can partially inhibit the late
20 phase.

21 Q. How do those effects compare to the effects of using
22 intranasal steroid?

23 A. As I mentioned, intranasal steroids are the most
24 effective effects.

25 Q. Are you referring to Berger, DTX-26?

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1 A. Yes.

2 THE COURT: Are you done with that slide?

3 MR. KLEIN: Yes.

4 THE COURT: We will have to stop there for
5 tonight.

6 So tomorrow, definitely we will be together by
7 3:30 so be prepared for 3:30. If we think we can start
8 sooner, as I said, based on how the other trial is going,
9 we'll get notice to you as soon as possible. And if you can
10 make it sooner, we'll start sooner. All right?

11 Have a good evening. We'll see you tomorrow.

12 (Proceedings adjourn at 7:00 p.m.)

13

14 I hereby certify the foregoing is a true and accurate
15 transcript from my stenographic notes in the proceeding.

16 /s/ Brian P. Gaffigan
17 Official Court Reporter
18 U.S. District Court
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