

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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Argentum Pharmaceuticals LLC v. Cipla Ltd.
CIP2012
IPR2017-00807

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1. I, Robert P. Schleimer, have been retained by Defendants Apotex, Inc., and Apotex Corp. as an expert to analyze certain claims of U.S. Patent Nos. 8,163,723 (“the ’723 patent”); 8,168,620 (“the ’620 patent”); and 9,259,428 (“the ’428 patent”), in connection with this lawsuit.

2. I submitted an opening expert report on June 30, 2016, opining that the asserted claims of the patents-in-suit are obvious. I reserve the right to reply to any expert report submitted by plaintiffs in response to my opening expert report.

3. I have been asked in addition to respond to the expert reports of Dr. Warner Carr and Dr. Michael Kaliner, submitted by plaintiffs on June 30, 2016, to the extent they opine that Dymista[®] met a long felt but unmet need, or had unexpected superior results.

4. I reserve the right to amend or supplement my opinions in light of evidence presented by or on behalf of the plaintiffs, or in connection with additional information that may later be made available to me. At trial, I may use demonstrative exhibits if useful for explaining and understanding the opinions in this report, and I may testify about background scientific concepts related to pharmacology to explain as necessary the context of the claims.

5. I am being compensated for my time on this matter at a rate of \$400/hour for consulting and \$600/hour for testimony. Those are my standard consulting rates. My compensation is in no way dependent on the outcome of this case.

6. My professional background and the bases for my opinions are set forth in my opening expert report.

I. SUMMARY OF OPINIONS

7. First, it is my opinion that Dymista[®], what Meda says is a commercial embodiment of the patents-in-suit, does not meet any long-felt but unmet need in the field of treatments for allergic rhinitis.

8. I understand from counsel that this “secondary consideration of non-obviousness” looks to whether demand existed for the patented invention, and that others tried but failed to satisfy that demand.

9. Here, Dymista[®] did not satisfy any long-felt and unmet need. As explained in my opening report, combination antihistamine/steroid therapies were known and practiced for the treatment of allergic rhinitis in the art before June 2002. Indeed, doctors prescribed both Astelin[®] (azelastine hydrochloride) and Flonase[®] (fluticasone propionate) to the same patient at the same time before that date. Opening Report ¶ 79; Accetta Tr., at 22:16-23:5; 55:16-56:13. Additionally, I have reviewed the expert report of Dr. James Wedner, MD, and note that he, too, prescribed both drugs and observed other doctors doing so. Report of H. James Wedner ¶¶ 12, 25, 26.

10. Thus, the only “need” Dymista could have satisfied was a desire by doctors or patients to combine the active ingredients of Astelin[®] and Flonase[®] into a single formulation for patient convenience. Yet, Drs. Carr and Kaliner have not shown that there was any particular long-felt or unmet need for such convenience.

11. I further understand from counsel that there was a so-called “blocking patent,” which would have provided a strong disincentive for a person of ordinary skill in the art (a “POSA”) to develop a combination azelastine hydrochloride and fluticasone propionate product. *See* Hettche, U.S. Patent No. 5,164,194 (covering “a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used in the form of . . . a spray (preferably a nasal spray)”) (expiring May 2011); *see also* Phillips, U.S. Patent No. 4,335,121 (covering intranasal corticosteroids) (expiring May 2004). In my opinion, the fact that others did not co-formulate azelastine and fluticasone before June 2002 relates to patent protection and not issues

of obviousness.

12. Second, it is my opinion that Dymista[®] does not exhibit any unexpected or surprising results in light of the closest prior art.

13. Here, the closest prior art is the sequential administration of an azelastine HCl drug (Astelin[®]) and a fluticasone propionate drug (Flonase[®]), which were prescribed together by doctors before June 2002. In my opinion, Dymista[®] produced the same results as azelastine HCl and fluticasone propionate, delivered together in two separate sprays. In fact, Drs. Kaliner and Carr have discussed no study comparing the results of Dymista[®] to this closest prior art. The only study comparing this prior art to azelastine monotherapy and fluticasone monotherapy suggests that the magnitude of improvement is at least the same as the magnitude of improvement with Dymista[®]. Moreover, as also explained, to the extent the monotherapies are the correct prior art comparison, the superiority of Dymista[®] is not unexpected at all, for the numerous reasons stated in my opening report.

14. Thus, and as also explained in my opening report, the only attributes Dymista[®] provides over the prior art are conveniences resulting from using a single nasal spray. But in my opinion a more convenient dosing form was obvious at the time, such increased convenience does not provide a meaningful advance in clinical care, this convenience did not meet any previously unfilled need of any patient population, and the results of the co-formulation were expected.

15. Lastly, as I also explain in my opening report, the handful of studies on combinations of oral antihistamines and a steroid on which Plaintiffs rely would not have deterred a POSA from combining an intranasal azelastine and intranasal fluticasone for a number of reasons—and the superior results from such a combination would be fully expected.

II. LEGAL STANDARDS

16. I have been informed that the following four factors are considered when determining whether a patent claim is obvious: (a) the level of ordinary skill in the art; (b) the scope and content of the prior art; (c) the differences between the prior art and the claim; and (d) secondary considerations tending to prove obviousness or nonobviousness. These secondary considerations may include: (i) long-felt need, (ii) unexpected results, (iii) skepticism of the invention, (iv) teaching away from the invention, (v) commercial success, (vi) praise by others for the invention, and (vii) copying by other companies. I have also been informed that there must be a nexus (a connection) between the evidence that is the basis for the secondary factor and the scope of the invention claimed in the patent.

17. I have also been informed that, to support a finding of unexpected results, a patentee must show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected compared to the closest prior art. Further, in order to assert unexpected results, a patentee must present evidence that the results claimed to be unexpected actually occurred. Speculation or unproven hypotheses about what might become an unexpected result are simply not enough. I have also been informed that, to be an unexpected result, the difference between the claimed invention and the prior art must be a difference in kind, and not merely a difference in degree.

18. In my opening report, I explained that I have been informed that a patent claim is invalid as obvious if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time that the invention was made to a person of ordinary skill in the art (a “POSA”). I defined a POSA for the clinical aspect of this field as having “an M.D., Ph.D. or Pharm.D. in the field of allergy/immunology and/or pharmacology (or the equivalent), and at least three additional years

of experience in the treatment, or research for treatments, of allergic rhinitis, including with nasally administered steroids and antihistamines.” Opening Report ¶ 27. Drs. Smyth, Kaliner, and Carr, in contrast, opine that the relevant POSA would have an M.D. degree and 2-4 years of experience as a general practitioner. Smyth ¶ 23; Kaliner ¶ 28; Carr ¶ 15. I agree that a POSA could have an M.D., but I disagree that only 2-4 years of general practice would suffice. A POSA would have to have “at least three additional years of experience in the treatment, or research for treatments, of allergic rhinitis, including with nasally administered steroids and antihistamines.” Opening Report ¶ 27. Additionally, such a POSA need not have an M.D., but could also have a Ph.D. or Pharm.D. in the field of allergy/immunology and/or pharmacology (or the equivalent).

III. THE STATE OF THE PRIOR ART

A. Azelastine was a preferred antihistamine.

19. In their expert reports, Drs. Kaliner and Carr list 24 antihistamines under sections titled “treatment options.” Kaliner ¶ 47; Carr ¶ 36. Azelastine is buried in the middle of their lists without explanation. However, Drs. Kaliner and Carr omit or ignore several important distinctions among antihistamines. In the first place, most of these antihistamines were not available for intranasal administration—a critical issue. As I explain in my opening report, intranasal (topical) antihistamines have much more rapid onsets of action than oral antihistamines and a higher concentration can be delivered without adverse effects. Opening Report ¶¶ 74, 83. *See also, e.g.,* ARIA (2001) at S230 (“Topical H1-antihistamines have a rapid onset of action (less than 15 minutes) at low drug dosage, but they act only on the treated organ.”); Nielsen et al. (2001), at 1565 (azelastine has “a faster onset of action than oral antihistamines and act[s] within 15 to 30 minutes.”).

20. What’s more, only two of the 24 antihistamines listed in Dr. Kaliner and Dr.

Carr’s list were available for intranasal administration—azelastine and levocabastine. Opening Report ¶ 91. Of these, azelastine was known to be both safer and more effective. *Id.*; *see also* Falser et al. (2001). Additionally, numerous prior art publications specifically recommended azelastine. *See, e.g.*, Lieberman (2001), at 201 (“Only two classes of medication have received Federal Drug Administration approval for use in chronic rhinitis. Included are first-generation oral antihistamines, topical corticosteroids and the topical second-generation antihistamine azelastine.”).

21. Additionally, Drs. Kaliner and Carr make no mention in their reports that azelastine was known to have anti-inflammatory effects that treated the late-phase allergic response as well as the early-phase response, thus making it a unique and preferred antihistamine. *See* Opening Report ¶¶ 48-52; Fields et al. (1984); Fischer & Schmutzler (1981); Katayama et al. (1987); Church & Gradidge (1980); Lytinas et al. (2002); Kusters et al. at (2002); Hide et al. (1997); Honda et al. (1982); Togias et al. (1989); Ciprandi et al. (1996); Wang et al. (1997); Mosges & Klimek (1998); Jacobi et al. (1999).

22. Thus, Drs. Kaliner and Carr overstate the treatment options available for the general AR patient population. To determine whether the claims of the patents-in-suit are obvious—and to determine whether Dymista[®] meets a previously unmet need—a POSA and/or practitioner would compare the drug to previously available treatments suitable for these same patient populations (thus, for example, one would not compare Dymista[®] to injectable drugs). Of these treatment options, intranasal azelastine was a preferred antihistamine.

B. Fluticasone propionate was a preferred steroid.

23. In both of their reports, Drs. Kaliner and Carr list eight steroids as available treatment options. Kaliner ¶ 52; Carr ¶ 48. It is true that many of these steroids would be

suitable for nasal administration. Drs. Kaliner and Carr neglect to mention, however, that only two of these steroids—mometasone furoate and fluticasone propionate—featured in best-selling, FDA-approved products (Nasonex[®] and Flonase[®], respectively). Additionally, fluticasone propionate was the most potent of the steroids. Opening Report ¶ 66. Thus, Drs. Kaliner and Carr again overstate the number of treatment options available for Dymista[®]'s patient population. Only a few of the steroids they list were commercially available, and fluticasone was a preferred steroid.

C. Combinations of azelastine and fluticasone were actually practiced in the prior art.

24. In his report, Dr. Kaliner states: “In short, the clinical POSA would attempt to treat his patient by prescribing the appropriate drug or combination of drugs based on symptoms and severity. Due to significant patient-to-patient variability in response to treatment options, the clinical POSA would likely try one drug or combination and, if that regimen did not work, the POSA would cycle through other drugs until he found the best treatment for his patient.” Kaliner ¶ 73. I agree with this statement to the extent it suggests that clinicians combined various medications with different mechanisms of action because they knew that different drugs targeted different components of the mechanisms that caused AR and that targeting two mechanisms could yield better results than targeting a single mechanism. For example, as explained in my opening report, antihistamines specifically treated the early phase reaction and corticosteroids treated more successfully the late phase reaction. Opening Report ¶¶ 44-47 (antihistamines); 54-58 (steroids). It thus would have been obvious to a POSA and a prescriber to combine both an antihistamine and a steroid, and azelastine and fluticasone in particular, which were preferred drugs and available in the FDA-approved products Astelin[®] and Flonase[®].

25. Indeed, doctors routinely prescribed both drugs to the same patient at the same

time. Opening Report ¶ 79; Accetta Tr., at 22:16-23:5; 55:16-56:13. Additionally, I have reviewed the expert report of Dr. James Wedner, MD, and note that he, too, routinely prescribed both drugs and observed other doctors doing so. Report of Dr. H. James Wedner ¶¶ 12, 25, 26. Indeed, it is telling that Drs. Kaliner and Carr do not dispute that doctors regularly prescribed these drugs together before the priority date of the patents-in-suit.

IV. SECONDARY CONSIDERATIONS

A. The primary need Dymista[®] meets is for a convenient single-dose spray.

26. I disagree with the conclusions of Drs. Kaliner and Carr that Dymista[®] meets a long-felt but unmet need for an improvement in treatment. Dr. Kaliner opines that “the steady growth in prevalence of allergic rhinitis demonstrates a long-felt need for improved treatment.” Kaliner ¶ 84. Dr. Carr similarly opines that the “steadily growing incidence of allergic rhinitis demonstrates a long-felt need for improved treatment.” Carr ¶ 91. While it is true that the prevalence of allergic rhinitis and some other allergic diseases, such as asthma, has increased over the last several decades, this fact is irrelevant with respect to the choice of medications and the role of any particular drug. Whether the medications at issue (antihistamines and corticosteroids) successfully treat the symptoms of allergic rhinitis will have no impact upon the prevalence of the condition itself. Dymista[®] has not been demonstrated to, nor is it expected to, have any effect on prevalence of disease. It is not curative in any patients, and it is not used to prevent incidence of disease.

27. Dr. Kaliner further opines that patients “were often left with incomplete symptom relief,” noting that “[e]ven intranasal corticosteroids, widely accepted as the best option at the time of invention, took days to reach full effect.” Kaliner ¶ 85. He concludes: “Patients needed immediate and complete relief, and no available drug consistently offered both.” *Id.* Dr. Carr similarly opines that “[n]ot only was complete symptom relief unavailable at the time of the

invention, but relief was too slow.” Carr ¶ 96. He adds, “it is important that . . . patients experience quick relief to ensure that they stay on their prescribed treatment[.]” *Id.* ¶ 101.

28. I agree with both of their assessments that corticosteroids take days to reach full effect and that it was important for patients to experience quick relief. But that is why doctors prescribed antihistamines in combination with steroids before the priority date of the patents-in-suit. And that is why doctors, such as Dr. Accetta, prescribed azelastine and fluticasone in particular—because azelastine was available for intranasal administration and was known to be the most effective and fastest-acting antihistamine. Accetta Tr., at 22:16-23:5; 55:16-56:13.

29. Dr. Kaliner also offers the following opinion:

Where patients take two or more nasal sprays, the sheer volume of fluid in the nasal passage has at least two negative effects: (1) the drug may not appropriately deposit on the location needed to provide a benefit; and (2) much of the fluid—including some of the active dose—either passes from the nasal passages into the stomach or drips out the front of the nose, decreasing the efficacy of the dose.

Kaliner ¶ 88. I agree with Dr. Kaliner that, before June 2002, it would have been known that excess volume in the nasal passage *may* lead to a decrease in effectiveness due to leakage and similar issues. Thus I noted in my Opening Report:

[P]roviding a combination of a known antihistamine and a known steroid in a single administration ensured that the dosing and administration of each drug was optimal. For example, it was known that excessive administration of liquids into the nasal cavities might be less effective due to drainage, and this might happen with sequential administration. *See, e.g., Harris et al. (1986).* Thus, a POSA would have been motivated to combine active ingredients in a single formulation to ensure maximal absorption.

See Opening Report ¶ 88. The primary need in the prior art that Dymista[®] might fill was simply the convenience of one nasal spray. But even with regard to this need, it would have been obvious that combining azelastine and fluticasone in one nasal spray would meet this need.

30. Moreover, it is not entirely clear whether a single spray actually solves the alleged

problem of excess fluid in the nasal passage due to two sprays, or if such a problem actually existed. As I explain in my opening report, a study comparing the efficacy of administering two separate sprays together showed a magnitude of improvement over both monotherapies comparable to the improvement of Dymista[®] over these monotherapies. Opening Report ¶¶ 127-28. This confirms my opinion that there was no compelling need for a single combination spray. In my opinion, to the extent the patented combination did incrementally improve AR treatment, it did so only based on readily predictable attributes of the two drugs in combination. In short, my opinion is that neither Dr. Kaliner nor Dr. Carr established that the claimed combination, embodied in Dymista[®], satisfied a long-felt but unmet need.

31. For this reason, too, the Rajan Declaration referred to in Kaliner (¶ 91) is unpersuasive. Dr. Rajan, a consultant for Cipla, submitted a declaration during the prosecution of the patents-in-suit purporting to describe previously unmet needs met by Dymista[®]'s counterpart in India, Duonase. In that declaration, he states that shortcomings of previously available treatments included the misuse of decongestants; the slow onset of action for intranasal steroids; and the sedative and other side effects of oral antihistamines. MEDA_DYM_00001436. For all the reasons discussed here and in my opening report, all of these shortcomings would have been resolved by the use of either intranasal azelastine—which Dr. Rajan omits from his discussion—or a combination of intranasal azelastine with an intranasal steroid. I would note in addition that Dr. Rajan, in his deposition, admitted that he did not know whether a combination of intranasal azelastine and an intranasal steroid would have met those needs (it would have). Rajan Dep. 140:7–144:1.

32. Finally, Drs. Kaliner and Carr opine that Dymista[®] has a less bitter taste than Astelin[®], stating that only 4% of patients experience bitterness with Dymista[®] whereas nearly

20% of patients experience bitterness with Astelin[®]. Kaliner ¶ 100; Carr ¶ 84. For this proposition, they cite the Dymista[®] 2015 label for the 4% figure, and the FDA approval letter for Astelin[®] from fifteen years earlier for the 20% figure. However, many factors might contribute to how patients experience the bitter taste of azelastine, and one must compare the patient response in a single trial with similar conditions. Indeed, the Dymista[®] label reports that only 5% of patients experienced bitterness (dysgeusia) for azelastine monotherapy—that is only one percent more than those who experienced bitterness with Dymista[®]:

Table 1. Adverse Reactions with $\geq 2\%$ Incidence and More Frequently than Placebo in Placebo-Controlled Trials of 2 Weeks Duration with DYMISTA in Adult and Adolescent Patients with Seasonal Allergic Rhinitis

	1 spray per nostril twice daily			
	DYMISTA (N=853)*	Azelastine Hydrochloride Nasal Spray [†] (N=851)	Fluticasone Propionate Nasal Spray [†] (N=846)	Vehicle Placebo (N=861)
Dysgeusia	30(4%)	44(5%)	4(1%)	2(<1%)
Headache	18(2%)	20(2%)	20(2%)	10(1%)
Epistaxis	16(2%)	14(2%)	14(2%)	15(2%)

*Safety population N=853, intent-to-treat population N=848

[†] Not commercially marketed

MEDA_APTX02180635. Dymista[®] does not satisfy any unmet need in this respect.

B. Dymista[®] does not exhibit unexpectedly superior results.

i. Dymista[®] does not have superior efficacy over the closest prior art (the sequential administration of azelastine and fluticasone).

33. As explained in my opening report, Dymista[®] does not exhibit unexpectedly superior results. The closest prior art is the combined administration of a fluticasone propionate spray and an azelastine hydrochloride spray, and studies showed a magnitude of improvement over either monotherapy for this combined administration similar to that shown for Dymista[®]. As I explain in my opening report, the Dymista[®] study in Hampel et al. (2010) showed an improvement over fluticasone propionate of just over 39%, whereas the sequential administration

study in Ratner et al. (2008) showed an improvement just under 40%—essentially identical.¹ Thus, the superiority of Dymista[®] over the closest prior art has not been demonstrated. Opening Report ¶¶ 126-29.

34. Although Drs. Kaliner and Carr do not cite Hampel, they cite Meltzer et al. (2012) which reports a Dymista[®] study from one year after the Hampel et al. study. Meltzer et al. reported the exact same improvement with Dymista[®] over fluticasone propionate—39%. Meltzer et al. (2012) at 327 (“As shown in Fig. 2, MP29-02 [Dymista[®]] provided a 39% improvement in the rTNSS beyond the contribution of FP [fluticasone propionate].”). Taken as true, therefore, this study does not change my analysis from before.

35. Finally, Drs. Kaliner and Carr also refer to Carr et al. (2012), which compares the efficacy of Dymista[®] compared to fluticasone propionate and azelastine hydrochloride using formulations with the exact same excipients as in the Dymista[®] formulation. This study demonstrates an improvement over fluticasone propionate of only 11.8%.² This is lower than reported in either Hampel or Meltzer, and is far lower than the improvement reported for sequential administration of fluticasone and azelastine in Ratner (2008). This continues to confirm my opinion that the superior efficacy of Dymista[®] over the closest prior art of separate administration of the monotherapies has not been demonstrated, even though the drug does contain obvious clinical benefits over either azelastine or fluticasone *alone*.

¹ I have also refined the calculations using better figures from both Hampel et al. and Ratner et al. The improvement over fluticasone for Dymista[®] was more accurately just over 38%, and the improvement over fluticasone for a sequential administration was just over 42%. Previously, I had compared the percentage improvements for each monotherapy to the percentage improvement for the combination product or the sequential administration. Because the subjective nature of the rTNSS scoring, this will sufficiently approximate differences in improvement for the various treatments. If one actually calculates based on the mean rTNSS scores, which are available in Figure 1 of Hampel and Figure 1 and Table 2 of Ratner, the improvement differences over fluticasone are $[(5.31-3.84)/3.84] \times 100 = 38.3\%$ for the combined product and $[(7.4-5.2)/5.2] \times 100 = 42.3\%$ for sequential administration of the monotherapies. Because of the subjective nature of the scores, either this or my previous figures are sufficient approximations. Using the actual rTNSS scores merely further highlights that Dymista[®] has not been proven to be an improvement over a sequential administration.

² This is calculated from the mean change in rTNSS from the baseline as follows: $[(5.7-5.1)/5.1] \times 100 = 11.8\%$.

36. To my knowledge, there is no evidence available showing the superiority of the combination over the administration of both drugs separately but concurrently. Dymista®'s improved efficacy over those monotherapies would be not at all unexpected for all the reasons laid out in my opening report. *Id.* ¶ 130.

ii. Dymista® does not have a faster onset of action than azelastine, or the sequential administration of azelastine and fluticasone.

37. Drs. Kaliner and Carr both opine that Dymista® had a fast onset of action (as little as 30 minutes) and that this would have been unexpected from the prior art. Dr. Carr states: “Dymista® achieves a statistically superior reduction in symptoms in as little as 30 minutes when compared to placebo. This accelerated onset of action would have been unexpected to a POSA at the time of invention. As I previously explained, corticosteroids have a slow onset of action on the order of days, and azelastine had an onset of three hours. The POSA would not have expected Dymista® to take effect in thirty minutes.” Carr ¶ 87. Dr. Kaliner states similarly: “Dymista® achieves a statistically superior reduction in symptoms in as little as 30 minutes when compared to placebo. This accelerated onset of action would have been unexpected to a POSA at the time of invention, who would not have expected Dymista® to take effect in thirty minutes. As I previously explained, corticosteroids have a slow onset of action on the order of days, and azelastine had an onset of one to three hours.” Kaliner ¶ 99. Both rely on prescribing information for Astelin® (azelastine hydrochloride) as indicating it takes effect in three hours. Carr ¶ 86; Kaliner ¶ 98.

38. This conclusion is wrong. The Astelin® label on which Kaliner and Carr both rely states: “In dose-ranging trials, Astelin® Nasal Spray administration resulted in a decrease in symptoms, which reached statistical significant from saline placebo *within* 3 hours after initial dosing and persisted over the 12-hour dosing interval.” Astelin® Label [APOTEX_AZFL

0059088] (emphasis added). The label does not specify that azelastine did not have effect *until* 3 hours had passed.

39. Indeed, the opinion that the speed of onset was unexpectedly rapid fails to acknowledge a clear literature showing that azelastine gives measurable benefits within minutes. This literature—which would have been known to a POSA and to many prescribing doctors—taught that azelastine took effect in 15 to 30 minutes. Nielsen et al. (2001), at 1565 (azelastine has “a faster onset of action than oral antihistamines and act[s] within 15 to 30 minutes.”); ARIA (2001) at S230 (“Topical H1-antihistamines have a rapid onset of action (less than 15 minutes) at low drug dosage, but they act only on the treated organ.”).

40. One of the most powerful studies on rapidity was done by Greiff et al., which evaluated the rapidity of azelastine’s ability to inhibit both sneezing and vascular leak (a component of nasal secretions) caused by histamine. This study found that azelastine inhibited both parameters profoundly within one hour of treatment, suggesting an impact within minutes. Figure 2D, reproduced below, illustrates the effects on α -2 macroglobulin, a measure of blood vessel leakage, one hour after administration of azelastine. The histamine-induced leak is completely blocked using a low doses of histamine in the challenge (40 μ g/ml) and nearly completely blocked using the higher dose of histamine to cause the response (400 μ g/ml):

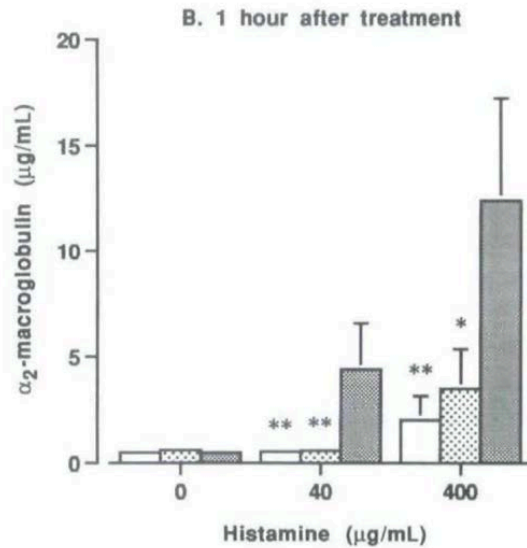


Fig 2. Effects of topical azelastine, oral cetirizine and placebo on histamine challenge-induced mucosal exudation of bulk plasma (α_2 -macroglobulin). Treatments were given at time point zero and challenges with control saline histamine (40 and 400 $\mu\text{g/mL}$) were given 1 h before treatment and 1–24 h after each treatment. (Comparisons between each treatment and placebo, $*P < 0.05$, $**P < 0.01$). \square = azelastine; \checkmark = cetirizine; \blacksquare = placebo.

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This graph shows that both cetirizine (middle bar) and azelastine (left bar) reduced the presence of α_2 macroglobulin created by a histamine challenge. Not only did azelastine reduce the presence of α_2 macroglobulin more than did cetirizine, it almost completely eliminated the presence of α_2 macroglobulin within one hour. This demonstrates that azelastine acts within minutes, not hours. Grieff et al (1997).

41. Therefore, the conclusion of Drs. Carr and Kaliner that a POSA would find it to be “unexpected” for Dymista[®] to act within 30 minutes is simply incorrect. The *azelastine* in Dymista[®] is the ingredient that acts within 30 minutes, not the fluticasone. And azelastine was known to act within 15 to 30 minutes.

iii. The oral combination studies relied upon by Drs. Kaliner and Carr would not have deterred a POSA from combining, or doctors from prescribing together, azelastine and fluticasone, and the efficacy of such a combination would not have been unexpected.

42. Both Drs. Kaliner and Carr opine that “[t]he weight of literature available at the time of invention taught that combined antihistamine/corticosteroid treatments were unlikely to provide any benefit over the steroid alone.” Kaliner ¶ 86; *see also* Carr ¶ 88 (similar). Both cite four studies: Juniper (1989), Benincasa (1994), Simpson (1994), and Ratner (1998). (Although both also cite Nielsen (2001), Nielsen is a review article and does not report any data beyond the four studies previously listed.) They conclude on this basis that there was both a need that the commercial embodiment of the patents-in-suit satisfied, and that this embodiment had unexpectedly superior results.

43. I disagree with Drs. Kaliner’s and Carr’s statements, as they refer only to the literature using combined oral antihistamines with corticosteroids. There was already a well-developed literature, not discussed by either Dr. Kaliner or Dr. Carr, showing that topical azelastine provided anti-inflammatory effects not observed with oral antihistamines. Thus, a POSA and any clinician would still have been motivated to combine or prescribe an *intranasal* antihistamine with an intranasal steroid, knowing that localized application permitted higher concentrations with better, faster, and safer effects. Opening Report ¶ 83; Nielsen et al. (2001), at 1565 (azelastine has “a faster onset of action than oral antihistamines and act[s] within 15 to 30 minutes.”); ARIA (2001) at S230 (“Topical H1-antihistamines have a rapid onset of action (less than 15 minutes) at low drug dosage, but they act only on the treated organ.”).

44. Additionally, as I explain in my opening report, these studies would not have deterred a POSA from combining azelastine HCl and fluticasone propionate—and they would not (and did not) deter a doctor from prescribing them together—because all but one of these

studies report the effects of the steroid or the steroid combined with oral antihistamine after a number of weeks of administration. Thus, the steroids would be at their full effect. *See* Juniper (1989) (reporting after week one); Benincasa (1994) (reporting only after week three); Ratner (1998) (reporting after week one). However, patients outside of clinical trials routinely failed to adhere to intranasal steroid treatment for this long because of its delayed onset of action. *See* Opening Report ¶¶ 59-62, 65, 81; Spector (1999) at S387; Nielsen (2001) at 1567; Flonase® Label at 2, *ll.* 44-47. Thus, doctors knew to prescribe a fast-acting antihistamine in addition to the slower-acting steroid to increase effectiveness.

45. Indeed, Simpson (1994), the only of the above studies to report daily results, shows that there was more improvement on day one for patients taking the antihistamine or combination than those taking the steroid alone:

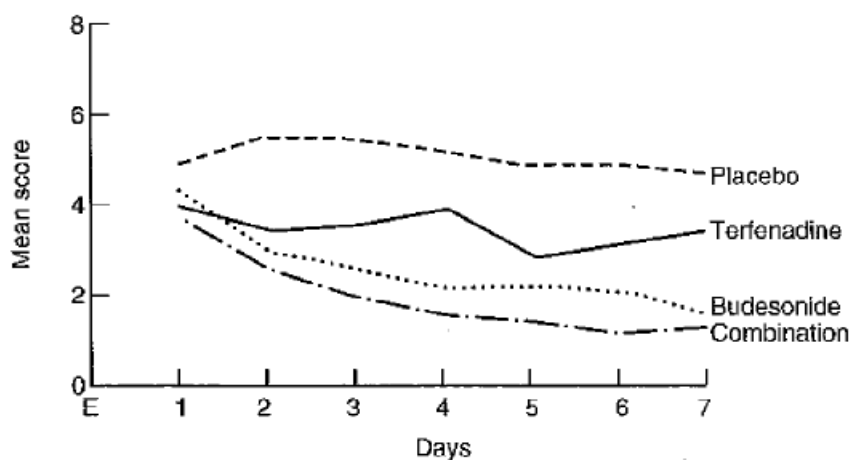


Figure 3. Changes in mean total nasal symptom scores in each treatment group during the first week of treatment.

Simpson (1994) at 500. This confirms the benefit of prescribing both a steroid and an antihistamine that would be fully expected from the literature: antihistamines provide fast-acting relief, whereas steroids provide relief of late-phase symptoms.

46. Additionally, several studies and prior art did describe additive benefits for

patients taking both an oral antihistamine and an intranasal steroid over those patients taking only intranasal steroids, and the medical literature continued to recommend that such a combination be practiced. *See* Opening Report ¶ 82; Drouin (1995); Berger (1999); Spector (1999); Lieberman (2001); Galant & Wilkinson (2001); ARIA (2001); Nielsen et al. (2001) (citing Brooks et al.).

47. Drs. Kaliner and Carr both conclude on this point, which in my opinion is not supported.³ As discussed at length in my first report as well as in this rebuttal, there was an ample literature showing that topical azelastine had local anti-inflammatory effects that were beneficial in patients and were not exerted by oral antihistamines. Once one accepts this fact, it would no longer be surprising that the combination therapy would also benefit from these topical anti-inflammatory effects. While some doctors may not have known about the sizable published literature respecting the effectiveness of topical azelastine, I understand that a POSA is presumed to have known of this literature.

iv. The inventor's testimony reveals that the results of Dymista® were not unexpected.

48. Finally, the inventor's own testimony reveals that she did not believe any of Dymista®'s results would be unexpected. As I mentioned in my opening report, she testified at deposition that no clinical trials were conducted before the date that the application for the patents was filed. *See* Malhotra Deposition Tr. at 18-20, 208-09. She further testified that her and her co-inventor's selection of azelastine and fluticasone "was based on the knowledge of what we knew of steroids and antihistamines." *Id.* at 209:7-9. In my opinion, this testimony strongly suggests that superior efficacy was fully expected.

³ *See* Kaliner ¶ 123 ("Critically, Dymista® went against the prevailing science by combining two products that, at the time of invention, were believed not to have any cumulative effect on allergic rhinitis."); Carr ¶ 102 ("This product showed for the first time an efficacy greater than that of an intranasal corticosteroid.").

C. The few instances of industry praise are unpersuasive.

49. Both Drs. Kaliner and Carr refer to the opinions of a select number of other authors. Dr. Carr writes that “one author explicitly stated that Dymista® ‘responds to the call of AR sufferers for new therapies that achieve a faster and more substantial relief of symptoms.’” Carr ¶ 98 (citing E. Ridolo (2015)). Dr. Kaliner refers to this author as well. Kaliner ¶ 112. Dr. Kaliner adds that the editors of the Journal of Allergy and Clinical Immunology declared Dymista® to be “the drug of choice for the treatment of AR” after reviewing the clinical studies discussed above. Kaliner ¶ 110 (citing D.Y.M. Leung et al.). He also cites another author as concluding that Dymista® “represented a breakthrough in AR management.” Kaliner ¶ 111 (citing J. Bernstein (2013)).

50. This praise is not unusual in the wave of hyperbole that often follows the typical launch of a new drug product, especially considering that Drs. Carr and Bernstein had been consultants for some time for the pharmaceutical companies involved and were directly involved in the development of this particular drug.⁴

51. Second, the editors of the Journal of Allergy and Clinical Immunology did *not* praise Dymista® as “the drug of choice for the treatment of AR.” The source cited by Dr. Kaliner for that proposition is in fact nothing more than a summary, most likely written by the authors themselves, reporting the conclusions of *Dr. Carr* in his clinical studies presented in the same volume of the journal. See MEDA_APTX02845997. The editors of the journal are merely passing along Dr. Carr’s view that: “Given these findings, MP29-02 can be considered the drug of choice for the treatment of AR.” Indeed, it is clear from the testimony of Dr. Accetta and the report of Dr. Wedner that Dymista® is not considered the drug of choice for most doctors and patients.

⁴ See Meltzer et al. (2012) at 324, Carr et al. (2012) at 1, and Bernstein (2013) at 11.

52. Third, as for the E. Ridolo article, that article simply reported the results of the Meltzer and Carr clinical trials. It is important to note, moreover, that the manuscript was sent to Meda Pharmaceuticals for review before it was published. MEDA_APTX01864083.

V. CONCLUSION

53. In conclusion, it is my opinion that Dymista[®] does not meet a long-felt but unmet need for improved allergic rhinitis treatment, and it does not demonstrate unexpectedly superior results. To the extent that Dymista[®] incrementally improved AR treatments, it did so based on known elements of the two individual drug agents.⁵

⁵ Inasmuch as plaintiffs' commercial success expert adopts the opinions of Drs. Carr and Kaliner in paragraph 70 in his report, I disagree with his opinion as well.

DECLARATION

I declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true.

Date: July 29, 2016

By:



Robert P. Schleimer, Ph.D.

Materials Considered for the Rebuttal Expert Report of Robert Schleimer

Description	Begin Bates	End Bates
ARIA Guidelines (2001)	APOTEX_AZFL 0132361	APOTEX_AZFL 0132548
Astelin [®] Label	APOTEX_AZFL 0059081	APOTEX_AZFL 0059097
Benincasa, C., et al., Evaluation of Fluticasone Propionate Aqueous Nasal Spray Taken Alone and in Combination with Cetirizine in the Prophylactic Treatment of Seasonal Allergic Rhinitis	MEDA_APTX03227075	MEDA_APTX03227083
Berger, W., et al., Double-blind Trials of Azelastine Nasal Spray Monotherapy Versus Combination Therapy with Loratadine Tablets and Beclomethasone Nasal Spray in Patients with Seasonal Allergic Rhinitis, Vol. 82 (June 1999)	APOTEX_AZFL 0059688	APOTEX_AZFL 0059694
Church, M., et al., Inhibition of Histamine release from Human Lung in vitro by Antihistamines and Related Drugs, Br. J. Pharmac. Vol. 69, pp. 663-667 (1980)	APOTEX_AZFL 0131999	APOTEX_AZFL 0132003
Ciprandi, G., et al., Topical Azelastine Reduces Eosinophil Activation and Intercellular Adhesion Molecule-1 Expression on Nasal Epithelial Cells: An Antiallergy Activity, J. Allergy Clin. Immunol. Volume 98, Number 6, Part 1, pp. 1088-1096	APOTEX_AZFL 0132004	APOTEX_AZFL 0132012
Declaration of Dr. Sujeet Rajan (Aug. 16, 2011)	MED_DYM_00001434	MED_DYM_00001453
Drouin, M., et al., Adding Loratadine to Topical Nasal Steroid Therapy Improves Moderately Severe Seasonal Allergic Rhinoconjunctivitis, Advances in Therapy Vol. 12, No. 6, pp. 340-349 (November/December 1995)	APOTEX_AZFL 0060084	APOTEX_AZFL 0060093
Dymista Prescribing Information (2015)	MEDA_APTX02180630	MEDA_APTX02180666
Falser, N., et al., Comparative Efficacy and Safety of Azelastine and Levocabastine Nasal Sprays in Patients with Seasonal Allergic Rhinitis, Arzneim-Forsch./Drug Res. 51(I), pp. 387-393 (2001)	APOTEX_AZFL 0133042	APOTEX_AZFL 0133048
Fields, D., et al., Inhibition by Azelastine of nonallergic Histamine Release from Rat Peritoneal Mast Cells, J. Allergy Clin. Immunol., Vol. 73, No. 3 (March 1984)	APOTEX_AZFL 0132030	APOTEX_AZFL 0132033
Fischer, B., et al., Inhibition by Azelastine of the Immunologically	APOTEX_AZFL 0132580	APOTEX_AZFL 0132583

Description	Begin Bates	End Bates
Induced Histamine Release from Isolated Guinea Pig Mast Cells, Arzneimittelforschung, Dru. Res. 8/1981, pp. 1193-1195		
Flonase [®] Label	APOTEX_AZFL 0060185	APOTEX_AZFL 0060207
Galant, S., et al., Clinical Prescribing of Allergic Rhinitis Medication in the Preschool and Young School-Age Child, 15(7) BioDrugs (2001)	APOTEX_AZFL 0060307	APOTEX_AZFL 0060317
Deposition Transcript of Sujeet Rajan (April 7, 2016)	N/A	N/A
Deposition Transcript of Geena Malhotra (April 25, 2016)	N/A	N/A
Deposition Transcript of Donald Accetta (May 6, 2016)	N/A	N/A
Greiff et al, Topical azelastine has a 12-hour duration of action as assessed by histamine challenge-induced exudation of α 2-macroglobulin into human nasal airways, Volume 27, Issue 4, April 1997	APOTEX_AZFL 0133061	APOTEX_AZFL 0133068
Hampel, F., et al., Double-blind, Placebo-Controlled Study of Azelastine and Fluticasone in a Single Nasal Spray Delivery Device Annals of Allergy, Asthma, & Immunology, Vol. 105 pp. 168-173 (August 2010)	MEDA_APTX02308986	MEDA_APTX02308991
Hide, I., et al., Suppression of TNF- α Secretion by Azelastine in a Rat Mast (RBL-2H3) Cell Line, Evidence for Differential Regulation of TNF- α Release, Transcription, and Degranulation, The Journal of Immunology, Vol. 159, No. 6, (September 15, 1997)	APOTEX_AZFL 0132082	APOTEX_AZFL 0132092
Honda, M. et al., Effect of Azelastine Hydrochloride on Macrophage Chemotaxis and Phagocytosis in Vitro, Allergy, Vol. 37, pp. 41-47 (1982)	APOTEX_AZFL 0132093	APOTEX_AZFL 0132099
Jacobi, H., et al., Histamine and Tryptase in Nasal Lavage Fluid After Allergen Challenge: effect of 1 week of Pretreatment with Intranasal Azelastine of Systemic Cetirizine, J. Allergy Clin. Immunol., Vol. 103, No. 5, Part 1 (May 1999)	APOTEX_AZFL 0132100	APOTEX_AZFL 0132104
Juniper, E F., et al., "Comparison of beclomethasone dipropionate aqueous nasal spray, astemizone, and the combination in the prophylactic treatment of ragweed pollen-induced	APOTEX_AZFL 0060456	APOTEX_AZFL 0060462

Description	Begin Bates	End Bates
rhinoconjunctivitis,” Journal of Allergy and Clinical Immunology, Vol. 83, No. 3, Cover page, Publications page, pp. 627-633 (Mar. 1989)		
Katayama, S. et al., Effect of Azelastine on the Release and Action of Leukotriene C4 and D4, Int. Archs Allergy Appl. Immun. Vol. 83 pp. 284-289 (1987)	APOTEX_AZFL 0132692	APOTEX_AZFL 0132699
Kusters, S., et al. at, Effects of Antihistamines on Leukotriene and Cykotine Release from Dispersed Nasal Polyp Cells, ArzneimForsh DrugRes, 2/2002, Vol. 52, No. 2, pp. 73-144 (2002)	APOTEX_AZFL 0132700	APOTEX_AZFL 0132707
Lieberman, P., Treatment Update: Nonallergic Rhinitis, Allergy and Asthma Procedure Vol. 22, No. 4, pp. 199-202 (July-August 2001)	APOTEX_AZFL 0060544	APOTEX_AZFL 0060547
Lytinas, M., et al., Azelastine's Inhibition of Histamine and Tryptase Release from Human Umbilical Cord Blood-Derived Cultured Mast Cells as well as Rat Mast Cell-Induced Vascular Permeability: Comparison with Olopatadine, Abstract, Allergy and Asthma Proc.	APOTEX_AZFL 0132105	APOTEX_AZFL 0132105
Meltzer, et al., MP29-02 (a novel intranasal formulation of azelastine hyrdochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: A randomized, double-blind, placebo-controlled trial of efficacy and safety, Allergy and Asthma Proceedings, pg. 324-332, Vol. 33, No. 4 (July-August 2012)	MEDA_APTX02429157	MEDA_APTX02429165
Mosges, R., et al., Azelastine Reduces Mediators of Inflammation in Patients with Nasal Polyps, Allergy and Asthma Proc., Vol. 19, No. 6, pp. 379-383 (November-December 1998)	APOTEX_AZFL 0132142	APOTEX_AZFL 0132146
MP29-02: A Breakthrough for the treatment of Allergic Rhinitis, Expert Opinion Pharmacotherapy, 14(15) (2013)	MEDA_APTX01675508	MEDA_APTX01675521
MP29-02: A Major Advancement in the Treatment of Allergic Rhinitis, The Journal of Allergy and Clinical Immunology, Volume 129, Number 5	MEDA_APTX02845997	MEDA_APTX02845998
Nielsen, et al., “Intranasal corticosteroids for allergic rhinitis: superior relief?” Drugs, 2001, vol. 61, No. 11, pp. 1535-1691	MEDA_APTX01676267	MEDA_APTX01676284
Ratner, P., et al., “A Comparison of the Efficacy of Fluticasone	MED_DYM_00001355	MED_DYM_00001364

Description	Begin Bates	End Bates
Propionate Aqueous Nasal Spray and Loratadine, Alone and in Combination, for the Treatment of Seasonal Allergic Rhinitis,” The Journal of Family Practice, Vol. 47, No. 2, pp. 118-125 (Aug. 1998)		
Ratner, P., et al., Combination Therapy with Azelastine Hydrochloride Nasal Spray and Fluticasone Propionate Nasal Spray in the Treatment of Patients with Seasonal Allergic Rhinitis, Annals of Allergy, Asthma, & Immunology, Vol. 100 pp. 74-81 (January 2008)	MEDA_APTX01608673	MEDA_APTX01608680
Ridolo, E., A Role for the Intranasal Formulation of Azelastine Hydrochloride/Fluticasone Propionate in the Treatment of Allergic Rhinitis, Therapeutic Delivery	MEDA_APTX01864079	MEDA_APTX01864085
Simpson, R., Budesonide and terfenadine, separately and in combination, in the treatment of hay fever, Annals of Allergy, Vol. 73 pp. 497-502 (Dec. 1994)	APOTEX_AZFL 0061723	APOTEX_AZFL 0061728
Spector, S., Ideal Pharmacotherapy for Allergic Rhinitis, Journal of Allergy Clinical Immunology, Vol. 103, Number 3, Part 2	APOTEX_AZFL 0061786	APOTEX_AZFL 0061787
Togias, A., et al., In vivo and in vitro Effects of Antihistamines on Mast Cell Mediator Release: A Potentially Important Property in the Treatment of Allergic Disease	APOTEX_AZFL 0132326	APOTEX_AZFL 0132332
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U.S. Patent No. 5,164,194 (Hettche)	APOTEX_AZFL 0054360	APOTEX_AZFL 0054365
U.S. Patent No. 8,163,723	CIP_DYM 0054179	CIP_DYM 0054192
U.S. Patent No. 8,168,620	CIP_DYM 0054193	CIP_DYM 0054206
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Wang, D., et al., Effect of Topical Applications of Budesonide and Azelastine of Nasal Symptoms, Eosinophil Count and Mediator Release in Atopic Patients after Nasal Allergen Challenge during the Pollen Season, Int. Arch Allergy Immunol. Vol. 114 pp. 1185-1192 (1997)	APOTEX_AZFL 0132733	APOTEX_AZFL 0132742
Expert Report of Warner Carr (June 30, 2016)	N/A	N/A
Expert Report of Michael Kaliner (June 30, 2016)	N/A	N/A

Description	Begin Bates	End Bates
Rebuttal Expert Report of H. James Wedner (July 29, 2016)	N/A	N/A
All documents cited in my rebuttal expert report	N/A	N/A