

MEDA PHARMACEUTICALS, INC. and
 CIPLA LTD.

 Plaintiffs,

 v.

 APOTEX, INC. and APOTEX CORP.

 Defendants.

Argentum Pharmaceuticals LLC v. Cipla Ltd.
CIP2013
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 also submitted a rebuttal report on July 29, 2016. I have been asked to respond to the report of Dr. Michael Kaliner submitted by plaintiffs on July 29, 2016, in rebuttal to my opening report. I do so below, and incorporate the contents of my previous reports here, as if set forth verbatim.

3. 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.

4. 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.

5. My professional background and the bases for my opinions are set forth in my previous reports.

I. SUMMARY OF OPINIONS

6. In paragraph 31 of his report, Dr. Kaliner succinctly states the basis for his disagreements with my opinion that it would have been obvious to a POSA to combine intranasal azelastine and intranasal fluticasone. He offers six grounds for disagreement. He alleges: (1) there were dozens of available allergic rhinitis treatments, yielding hundreds of possible two-

drug pairings; (2) many of these drugs had activity in both the early and late phases of the allergic response, and thus a POSA would not have sought to combine an early-phase drug with a late-phase drug; (3) studies of antihistamine/steroid pairings showed no benefit over steroids alone; (4) experts at the time concluded from these studies that there is no benefit to combining an antihistamine and a steroid; (5) a clinician would have been discouraged from combining the two drugs to minimize patients' drug exposure; and (6) a POSA would have been discouraged by FDA's combination rule requiring superior results over either monotherapy, in light of the antihistamine/steroid studies suggesting no improvement over steroids. Points (3), (4), and (6) all generally rely on the combination studies to which Dr. Kaliner refers and may be treated together. None of these points are correct or cause me to change my opinions.

7. To the first point, it is not true that a POSA would have had to wade through hundreds of possible pairings in 2002 in coming to an obvious decision about what drugs to combine into a single product. As explained in my opening report, my rebuttal report, and in the rebuttal report of Dr. James Wedner, there were only a handful of treatments that doctors routinely used for the treatment of allergic rhinitis. Dr. Kaliner himself admits that intranasal steroids were the most common treatment. Of these, fluticasone propionate was one of only five FDA-approved steroids in 2002 and was a best-selling drug product (known as Flonase®). Antihistamines were the other most common treatment, and although oral antihistamines were and continue to be prescribed, *intranasal* antihistamines were nonetheless a widely used option and were known to be more effective than oral antihistamines. At the time, there were only *two* available intranasal antihistamines—azelastine and levocabastine. Of these, azelastine was shown to be more safe and effective *and* it was far more commonly prescribed (as Astelin®) than levocabastine. What's more, doctors routinely prescribed both Flonase® and Astelin® to patients

who did not respond sufficiently to Flonase[®] (and occasionally Astelin[®]) alone.

8. Addressing the second point, it is true that some drugs have effects on both the early-phase allergic response as well as the late phase. I stated no differently in my report. Intranasal steroids have an impact on *all* symptoms, but they have their *strongest*, and more importantly *most timely*, impact on the late phase. Intranasal azelastine, moreover, was known to be effective in part because it also had an effect on late-phase inflammation. But like other antihistamines, its predominant effect was on the early-phase response. It would have been obvious to combine the two, as doctors routinely did by prescribing both Flonase[®] and Astelin[®], for patients with cases of more severe or persistent allergic rhinitis. The fact that they have some overlapping effects does not make it inventive to combine the two, particularly when there is no dispute that they achieve those effects through different mechanisms of action.

9. To the third, fourth, and sixth points, Dr. Kaliner interprets selected studies showing that oral antihistamines combined with intranasal corticosteroids are no better than corticosteroids alone as indicating that any combination of these drugs would have no benefit above that of the steroid monotherapy. I strongly disagree with this interpretation. Even if these studies would be interpreted as Dr. Kaliner says (a proposition with which I disagree), they are of relatively little importance to a POSA's decision in 2002 whether to combine intranasal azelastine and intranasal fluticasone. As discussed in some detail in my opening report, in my rebuttal report, and in the rebuttal report of Dr. McCulloch, these studies were all of *oral* antihistamines combined with intranasal steroids—none studied a combination of an *intranasal* antihistamine with an intranasal steroid. As explained repeatedly, intranasal antihistamines were known to be significantly more effective than oral antihistamines. Additionally, all but one of these studies reported results only after at least a week of treatment—a time point at which the

delayed effects of the corticosteroids would have taken effect, masking any immediate benefit of the antihistamines in the first days of treatment. As also discussed in these earlier reports, the true value of adding the topical antihistamine to the intranasal steroid is primarily realized during that first week while the steroid effects are not yet fully apparent. But moreover, these combination studies *did* show improved results for a combination treatment for two symptoms that are critical to allergic rhinitis patients—itching and sneezing.

10. Finally, as to the fifth point that addresses Dr. Kaliner’s concerns about minimizing drug exposure, a combination product would not impact the clinician’s consideration at all. The clinician would know that a combination product was suitable for the more severe and persistence cases of allergic rhinitis—for those patients for whom Flonase[®] (or Astelin[®]) was insufficiently effective on its own. But once a patient’s symptoms were under control, reverting to a monotherapy prescription would still be an option. Thus, a POSA would not be discouraged by the desire to minimize drug exposure. Such a desire is always present and does not discourage the development of more effective drugs. And to the extent a POSA would have viewed this concern as a material one, it is not addressed by the claimed invention or Dymista[®].

11. I discuss these views in more detail below and in my earlier reports. If I do not directly respond to any particular statement of Dr. Kaliner’s, I do not intend to convey that I agree with that statement.

II. PERSON OF ORDINARY SKILL IN THE ART

12. Dr. Kaliner challenges my definition of a person of ordinary skill in the art (a “POSA”). He disagrees that a POSA would have a Ph.D. or a Pharm.D., “because these individuals are not qualified to diagnose patients, treat patients, or prescribe drugs to patients.”

¶ 17. “Critically,” Dr. Kaliner writes, “the majority of the asserted claims are directed to methods of *using* claimed compositions to treat allergic rhinitis.” *Id.* But doctors are usually *not*

involved in the discovery of new drug products. Rather, although some researchers are clinicians and some clinicians are researchers, it is typically researchers who are the ones that develop, discover, and invent new drugs that practicing clinicians can then use.

13. Dr. Kaliner’s own opinion demonstrates why merely being a clinician—without any experience researching the science behind allergic rhinitis treatments—is insufficient. He explains “that the POSA clinician in 2002 would have focused on actually treating patients’ symptoms; he would not have been concerned with the underlying mechanisms.” ¶ 57. However, *all* inventors have to have some understanding of *how* something works in order to make progress in the field. That is particularly true here. Dr. Kaliner’s POSA would have no such knowledge, and would know nothing about the vast literature describing the mechanisms of allergic rhinitis drugs that would have been known to a clinician researcher or to a Ph.D. or Pharm.D. This definition excuses Dr. Kaliner’s POSA from being aware of the well-developed literature showing that intranasal azelastine, and some other intranasal antihistamines, have anti-inflammatory properties that are not shared by the oral versions of the same drugs or by oral antihistamines as a class. This literature was widely available to and diffused across the relevant academic and industry communities. A POSA actually involved in the research and development of new drugs or drug formulations would undoubtedly have been aware of it.

III. ANALYSIS

A. Dr. Kaliner’s main arguments are unconvincing.

- i. **Combining an intranasal antihistamine and intranasal steroid would have been an obvious choice, and combining intranasal azelastine and intranasal fluticasone would have been obvious in particular.**

14. Dr. Kaliner opines that it would not have been obvious to combine intranasal azelastine and intranasal fluticasone because of the “many available possible treatments documented in the art” (¶ 67), including “twenty-four antihistamines, nine decongestants, four

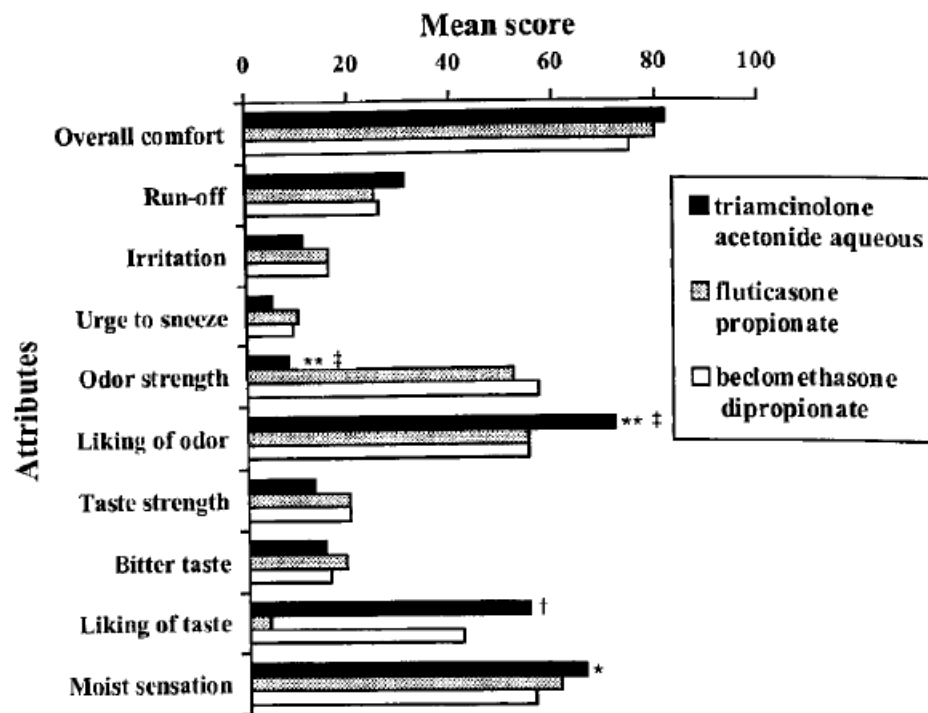
anticholinergics, three leukotriene receptor antagonists, two mast cell stabilizers, and eight corticosteroids” (¶ 72). *See also* ¶¶ 73, 75, 76.

15. Dr. Kaliner’s point is not persuasive. First, as he explains in his report, “the use of corticosteroids supplanted antihistamines as the most effective treatment option for allergic rhinitis; by 2002, corticosteroids were recognized as the most potent treatment option.” ¶ 36. He thus agrees that a POSA would have looked to a corticosteroid above all else—and further agrees that potency was one of the most important concerns. As I stated in my opening report, fluticasone propionate is among the most potent of the steroids—meaning a smaller concentration achieves the same efficacy as other steroids with higher concentrations. Opening Report ¶ 66; *see also* Stellato et al. (1999) (showing fluticasone propionate is more potent *in vitro* than mometasone furoate, budesonide, and beclomethasone dipropionate). That may help explain why Flonase[®] was one of the best-selling drugs prior to 2002 and continues to be a best-selling drug today.

16. Dr. Kaliner’s point that intranasal steroids are largely indistinguishable in clinical effect is irrelevant. ¶ 83. Dr. Kaliner, or a general practitioner that he refers to as a POSA, may be unfamiliar with the difference between efficacy and potency, but a POSA as I have defined them, i.e. a researcher developing drugs, would know the difference.

17. Dr. Kaliner also opines that fluticasone “was associated with a strange smell and taste that many patients found undesirable,” and thus other options “were far preferable to fluticasone.” ¶ 83. The sales and marketing numbers, however, belie this claim. As reported in the report of plaintiffs’ commercial success expert, fluticasone propionate had 42 *million* prescriptions in 2015—far outstripping all other nasal spray treatments (branded Nasonex was second with about 4.6 million prescriptions). *See* Jarosz Opening Report Tab 3.

18. Patients do not, and did not prior to June 2002, have a problem with the odor and taste of fluticasone. Dr. Kaliner’s source for the claim that “many patients found undesirable” the taste and smell of fluticasone—Blais 2001—reports the results of two studies of an experimental design intended to test the sensory attributes of the various intranasal corticosteroids, in which only 94 and 95 patients participated respectively. A POSA would not draw firm conclusions from such an isolated study of so few patients. Besides the very modest effect, the data do not indicate that the patients actually reported *disliking* the odor or taste of fluticasone; rather, they reported *liking* the taste and odor of triamcinolone more:



Triamcinolone is significantly better than beclomethasone; * $P \leq .01$, ** $P \leq .001$.
 Triamcinolone is significantly better than fluticasone; † $P \leq .04$, ‡ $P \leq .001$.

Figure 1. Results immediately after administration.¹⁰

Blais 2001, at S8. Regardless, the author explains in the conclusion: “Now, the challenge is to develop a reliable, consistent instrument and method of assessment for these patient preference

studies, which will allow us to include patient preference as a standard assessment tool in all of our intranasal steroid clinical studies.” *Id.* at S10. In short, the studies reported in Blaiss 2001 were isolated, experimental, admittedly unreliable, included extremely small sample sizes, and do not even stand for the proposition that Dr. Kaliner claims they do. Considering this, as well as the tens of millions of patients taking this drug, there is simply no convincing evidence that fluticasone propionate is or ever has been offensive to patients. There is simply no evidence that any patient has ever refused to use fluticasone because of its smell or taste.

19. Next, although Dr. Kaliner writes that there were 24 “available” antihistamines, he stated in his opening report that there were 24 “known” antihistamines (Kaliner Opening Report ¶ 47)—only five of which were commercially available or FDA-approved in oral form in 2002, and only two of which were available for intranasal administration. Wedner Opening Report ¶¶ 19, 24; Schleimer Opening Report ¶ 91. 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. Because of these high local concentrations, they have anti-inflammatory effects that oral versions of the same drugs do not have. These facts would have motivated a POSA toward the antihistamines that had strong intranasal activity and that exerted these anti-inflammatory effects locally in the nose. That was an obvious thing to do. Opening Report ¶¶ 74, 83. Only azelastine and levocabastine were available for intranasal use, and azelastine was by far the more commonly prescribed. Oddly, Dr. Kaliner cites the fact that there were only two available intranasal antihistamines as evidence that a POSA would *not* have sought to combine an intranasal antihistamine with a steroid. ¶ 77. But that is exactly why a POSA *would* have been led to azelastine—because it was the only available best-selling intranasal antihistamine and was known to be more effective than oral

antihistamines.

20. Dr. Kaliner adds that I ignored the intranasal antihistamine “antazoline although it was known to be associated with ‘almost no side effects.’” ¶ 82 (citing ARIA at S253). This is misleading. The ARIA guidelines actually state: “The use of intranasal antihistamines like levocabastine, azelastine and antazoline has the benefit of almost no side effects.” ARIA at S253. That is, *all* of these antihistamines have no side effects, not merely antazoline. More importantly, as already explained, *only* levocabastine and azelastine were FDA-approved as of June 2002, and only azelastine was widely used (in the form of Astelin[®]). There is no compelling reason a POSA would have thought the use of antazoline was a more obvious choice than azelastine for a useful, nasally administered antihistamine.

21. Thus, Dr. Kaliner overstates the number of treatment options available for the great majority of allergic rhinitis patients.

22. Dr. Kaliner claims that my citing Falser as evidence that azelastine would be viewed by a POSA as being clinically superior to levocabastine is incorrect, and that I have misread the key study by Falser comparing these drugs (specifically stating that the error bars in the study showed overlap). Dr. Kaliner also states that Falser acknowledged the frequently reported bitter taste of azelastine. As far as bitter taste is concerned, Falser states: “Surprisingly enough not a single case of taste disturbance was reported....” i.e., of the 90 patients receiving azelastine, not one complained about bitter taste. Falser at 392. Regarding the more important point about efficacy of the two drugs, a POSA, even as narrowly defined by Dr. Kaliner, would not have misunderstood the findings and conclusions of Falser et al. In the abstract summarizing the entire study they finish with the statement: “Azelastine, however, was statistically superior in efficacy as well as in safety....” *Id.* at 387. The basis for this strong conclusion is that this study

of 180 patients demonstrated that the superiority of azelastine to levocabastine spanned three of the five criteria evaluated, including evening total symptom score, evening nasal symptom score and, importantly, global judgment of efficacy by the investigator. Even the patients themselves judged azelastine effects to be “very good” or “good” 92% of the time while levocabastine received a “very good” or “good” score only 76% of the time. In all of these cases, the superiority of azelastine was statistically significant. Thus, azelastine was determined to be superior by patients, by the clinicians carrying out the study, by the statisticians analyzing the data, and by the investigators performing and writing up the study.

23. But moreover, a POSA would not have had to wade through hundreds of possible combinations because doctors already routinely prescribed both Astelin[®] and Flonase[®] to the same patient at the same time. Opening Report ¶ 79; Schleimer Rebuttal Report ¶ 25; Accetta Tr., at 22:16-23:5; 55:16-56:13; Wedner Rebuttal Report ¶¶ 12, 25, 26. This combination was known—and it was known to be effective.

24. Dr. Kaliner challenges the probative value of Dr. Accetta’s testimony, arguing that “[t]he small number of records over the course of thousands of patients shows that the use of azelastine and fluticasone together was not obvious” and that “Dr. Accetta’s stepwise prescriptions teach away from the combination of the two drugs in a single formulation.” ¶ 68. This is beside the point, however, because no one disputes that a combination of azelastine and fluticasone is only appropriate for patients with persistent and severe allergic rhinitis. Dr. Accetta’s stepwise prescription method is fully consistent with the relevant guidelines, as Dr. Kaliner himself recognizes. ¶¶ 19, 57. And it is also completely consistent with prescribing azelastine and fluticasone together—or to combine them in one drug—to those patients at the more severe end of the stepwise treatment paradigm. Such a combination for these patients was

obvious to and used by Dr. Accetta, Dr. Wedner, and other clinicians and researchers well before June 2002.

25. Part of the reason this combination was expected to be effective, as explained, was that the 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). Moreover, azelastine was particularly effective because it *also* treated the late-phase response through its anti-inflammatory properties. *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).

26. Dr. Kaliner argues, however, that a POSA would not have sought to combine an early-phase drug with a late-phase drug because many AR drugs affect both phases (¶¶ 50-55, 85, 88, 119), and because “[t]he POSA clinician at the time of invention did not have a complete understanding of the mechanisms of allergic rhinitis, and as such, would not have relied on the early- and late-phase dichotomy to treat his patients” (¶ 70). These arguments are wrong. First, as explained above, antihistamines were known to treat *predominantly* the early-phase response, and corticosteroids were known to treat *predominantly* the late-phase response. Thus, antihistamines would have been obvious to combine with corticosteroids—and doctors regularly did combine them. But moreover, and as repeatedly explained, a POSA would have been particularly motivated to combine *intranasal azelastine* with a corticosteroid because of its

additional beneficial effect in the late-phase response as well. Indeed, Dr. Kaliner recognizes in his statement respecting my research that *intranasal* corticosteroids have some effects in in the early-phase response as well as the late-phase response, whereas research shows systemic (oral) corticosteroids have no effect on the early phase. ¶ 53.

27. Indeed, it is noteworthy that in the introduction of Falser et al., which was published in 2001, the investigators state: “Azelastine (CAS 58581-89-8) being an antiallergic agent has potent activity at a number of sites associated with the allergic reaction: these include potent and selective H1 receptor antagonism (ref 1), blockade of histamine release from mast cells (ref 2) and antagonism of leukotriene and platelet activating factor (ref 3).” It is my opinion that even a POSA defined by Dr. Kaliner’s weak terms, i.e. a clinician seeing patients in this field and not involved in drug discovery, would have been aware of this study and therefore informed about the non-canonical anti-inflammatory effects that distinguish intranasal azelastine from oral antihistamines, including inhibition of mast cells and suppression of leukotrienes. That is, even Dr. Kaliner’s POSA should have been aware that intranasal azelastine was a particularly effective antihistamine because of its effect in both phases.

28. Thus, I do not and have never disputed that some drugs have effects in both phases. Azelastine was a particularly obvious choice for treatment because it was known to rapidly relieve symptoms otherwise controlled too slowly by the steroid component as well as to have effects in *both* phases. The contention that these drugs may have effects in both phases is in no way contrary to my opinions.

29. As for Dr. Kaliner’s point that the mechanisms of allergic rhinitis were not completely understood, his argument is partly overstated and partly irrelevant. To be sure, if Dr. Kaliner’s clinician POSA did not understand the mechanisms of allergic rhinitis very well, it

would support very well my contention that a POSA interested in creating new drugs would be a researcher in industry or in the academy steeped in the widely available literature on such mechanisms and who actually has experience developing new drug products. Regardless, that the mechanisms of allergic rhinitis were not *fully* understood—and still are not fully understood—does not undermine the fact that a POSA would have had significant knowledge of these mechanisms that can well inform the development process.

ii. The combination studies of oral antihistamines and intranasal steroids relied upon by Dr. Kaliner would not have deterred a POSA from combining, and did not deter doctors from prescribing together, azelastine and fluticasone.

30. Dr. Kaliner’s third, fourth, and sixth argument are really the same argument: a POSA would not have had an expectation of success because the four studies Dr. Kaliner cites allegedly show no improvement with a combination of antihistamine and corticosteroid. For example, he writes that a POSA would have been discouraged from combining intranasal azelastine and intranasal fluticasone because of FDA’s combination rule requiring superiority over each monotherapy, because “[a]s I said, it was widely accepted in the art at the time of invention that the co-administration of an antihistamine and a corticosteroid conferred no benefit over the corticosteroid alone.” ¶¶ 62-64. *See also, e.g.*, ¶¶ 34-49, 86-87, 89. He summarizes with the conclusions of Akerlund 2005 that adding an oral antihistamine to a corticosteroid “is not supported by clinical trials.” ¶ 46.¹

31. But Akerlund’s conclusion—which was written in 2005 and would not have been available to a POSA—is only as good as the literature on which he and Dr. Kaliner rely: Juniper (1989), Benincasa (1994), Simpson (1994), and Ratner (1998). *See* Akerlund (2005) at S476. The same is true of the other summary review articles such as Howarth and Nielsen. ¶¶ 45-49.

¹ He also notes Barnes 2006 concluded that such a combination is “inappropriate” (¶ 47), but Barnes did not base his conclusion on any pre-2002 knowledge and must be discounted because it is not prior art.

And as explained in my opening report (§§ 80-83) and my rebuttal report (§§ 42-47), the literature to which Dr. Kaliner refers studied only oral antihistamines with corticosteroids. There was already a well-developed literature, not discussed by Dr. Kaliner, 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.”); *see also* 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).

32. Additionally, as I explain in my opening report, the four combination studies involving oral antihistamines would not have deterred a POSA from combining azelastine and fluticasone—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, by the time the data were collected, 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. More critically, by the end of the first week the steroids would be in full effect and thus mask the additional benefit of the antihistamines that had been apparent in the early days of treatment.

33. As explained in my rebuttal report, Simpson (1994), the only of the above studies to report daily results, shows that with an oral antihistamine there was more improvement on day one for patients taking the antihistamine or combination than those taking the steroid alone. 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, especially of acute phase symptoms, whereas steroids provide slowly-developing relief, especially of late-phase symptoms.

34. Moreover, Dr. McCulloch noted in his report that two of the four studies did not have proper experimental parameters—Juniper et al. did not have a placebo group and Benincasa et al.—which studied fluticasone propionate—did not have a placebo group *or* an antihistamine monotherapy group. McCulloch Report ¶¶ 22, 28. Indeed, Dr. Kaliner, in his discussion of the Ratner 2008 study of the sequential administration of Astelin[®] and Flonase[®], states the following:

Clinical studies of two drugs, used either in conjunction or combination, should include four treatment arms: (1) the combination group (here, azelastine and fluticasone); two individual groups, here (2) fluticasone and (3) azelastine; and (4) a placebo (control) group. Each group is critical for different reasons. The first will, ostensibly, test the benefit (or lack thereof) of conjunctive or combination therapy in a given patient population. The second and third serve as checks to ensure that the patient population *is adequately responding to each monotherapy*. The fourth serves to ensure that the data from groups (1)-(3) are not tainted by false positives as a result of the placebo effect.

¶ 137 (emphasis added). I agree with Dr. Kaliner. Applying Dr. Kaliner’s observation here to Juniper and Benincasa, I conclude—and so should he—that these studies would have been of limited utility to a POSA.

35. Indeed, Dr. Kaliner claims that Benincasa is “particularly relevant here” because it studied fluticasone in combination with an antihistamine. ¶ 40. But Benincasa lacked both a placebo group and an antihistamine monotherapy group. Not only did Benincasa therefore not account for possible placebo effects, but just as Dr. McCulloch stated, it is impossible to know whether the patient population was adequately responding to each monotherapy. Ratner 1998—the other study Dr. Kaliner explains is “particularly relevant here” because it studied fluticasone in combination with an antihistamine—showed no statistically significant difference between the placebo group and the antihistamine monotherapy group. Thus, as Dr. Kaliner himself would observe, this proves that the patient population was not adequately responding to each monotherapy. A patient population or experimental protocol must first be identified in which the antihistamine is effective—otherwise, of course, a combination would likely show no improvement over the steroid alone.

36. Also, as I have repeated before, several prior art studies 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.). And as explained by Dr. McCulloch, even the four studies on which Dr. Kaliner relies *do* reveal some important benefits to a combination. McCulloch Rebuttal Report ¶ 23 (Juniper shows additive benefit to eye symptoms), ¶ 26 (Ratner 1998 shows

additive benefit to runny nose and sneezing); ¶ 29 (Simpson shows additive benefit in first days of treatment).

37. Dr. Kaliner’s criticism of the combination studies Drouin 1995 and Brooks 1996 is that they “only show that conjunctive use of loratadine [an antihistamine] and beclomethasone dipropionate [a corticosteroid] might improve itching or sneezing symptoms to a statistically significant degree, [and] neither study shows that the improvement is clinically relevant.” ¶ 44; *see also* ¶¶ 41-43. “At bottom,” Dr. Kaliner adds, “improving a patient’s symptoms would have been the POSA clinician’s primary objective, and neither Drouin 1995 nor Brooks 1996 demonstrate that any patient’s clinical outcome meaningfully changed. At most, these references would have suggested to the POSA clinician that loratadine might be a beneficial on-demand adjunct to beclomethasone dipropionate in patients with severe itching or sneezing symptoms.” ¶ 44.

38. Dr. Kaliner’s criticism is unpersuasive. First, it is unclear what he means by “improving a patient’s symptoms would have been” the “primary objective,” and these studies do not demonstrate a “meaningful[] change[]” in clinical outcome. I do not dispute that improving symptoms is the objective. (Elsewhere Dr. Kaliner writes that “[t]he POSA clinician would have been interested in treating symptoms, not mechanisms,” ¶ 50, but this is a strange criticism given that the different mechanisms lead to different symptoms, as I explained in my opening report.) But Drouin 1995 and Brooks 1996 demonstrate that the combination of an antihistamine and topical steroid does just that—it treats symptoms. Dr. Kaliner does not explain his understanding of “meaningfully changed.” The studies show statistically significant improvements in itching and sneezing—two hallmark symptoms of allergic rhinitis that greatly and adversely affect patient quality of life. The addition of an oral antihistamine—actually

practiced then and today by many doctors—is justified by these studies as well as by Juniper, Ratner, and Simpson’s conclusions respecting improved results for eye symptoms, runny nose, and sneezing. Perhaps that is why Akerlund (2005) notes that for “highly allergic patients . . . international consensus reports now recommend the combined use of an intranasal corticosteroid and an oral antihistamine.” Akerlund (2005) at S476.

39. Second, to the extent Dr. Kaliner opines that the utility of the Brooks and Drouin references is reduced because they only cover a specific antihistamine and a specific corticosteroid, I agree that a POSA would also reasonably want to know whether there was literature that *other* antihistamines or other steroids were better at treating patients. Indeed, as explained in my opening report and as I have repeated here, there was significant evidence that an intranasal antihistamine, and intranasal azelastine in particular, would be far more effective than even loratadine. That is why doctors prescribed Astelin[®] together with Flonase[®] for patients with the most severe and persistent cases, and it would likewise have been obvious to a POSA to combine them.

40. I also note that Dr. Kaliner’s report is internally inconsistent and confused on this issue of oral antihistamines. As just described, he spends significant effort in his report suggesting that a POSA would have been discouraged from combining an antihistamine with a steroid because four existing combination studies of oral antihistamines and steroids purportedly showed no benefit to the combination. Yet in the very same report he argues that because intranasal azelastine was associated with a bitter taste and compliance was important, the POSA clinician “would have instead looked to one of the blockbuster oral antihistamines, whose market shares (and my clinical experience) suggest were subject to high compliance.” ¶ 30. He later states that combining azelastine and fluticasone would not lead to increased convenience because

of “patient preference for oral dosage forms.” ¶ 112. Dr. Kaliner wants to have it both ways: a POSA would have been **discouraged** from an azelastine/fluticasone combination because of the oral combination studies showing no improved results over the steroid alone; and a POSA would have been **encouraged** to combine an oral antihistamine, rather than intranasal azelastine, with another drug.

41. This contradiction arises from his own mischaracterization of the evidence and literature available to a POSA. Regardless of a patient preference for oral medications, intranasal steroids—as Dr. Kaliner himself observed—were the most widely used allergic rhinitis drugs because of their superior effect. Thus, tens of millions of patients were using Flonase[®] irrespective of any preference for oral tablets. And combining intranasal azelastine, which many patients also already used alongside Flonase[®], into a single product would have undoubtedly been convenient for those patients already taking Flonase[®] and/or Astelin[®], especially if they disliked nasal sprays.

42. At a minimum, Dr. Kaliner recognizes that there would have been no reason not to try a combination product. As he explains, “the POSA clinician would have understood that the combinations of azelastine, fluticasone, and excipients recited in the asserted claims would be at least as effective as azelastine, but no more effective than fluticasone, in treating patients.”

¶ 5. In other words, there would have been no reason not to try a combination product, which would have still been effective in the treatment of allergic rhinitis.

iii. The need to reduce drug exposure to patients needing less exposure is not relevant to the question whether a combination would be effective for patients needing more serious treatment.

43. That leaves Dr. Kaliner’s remaining point: he argues that a clinician POSA “would have been motivated to reduce his patient’s drug exposure by titrating down to the lowest effective dosage. This means that the POSA clinician may initially have prescribed two or more

drugs to gain control over his patient's symptoms. But as soon as the patient's symptoms were controlled, the POSA clinician would also reduce the prescription to a single drug capable of maintaining control." ¶ 59.

44. Dr. Kaliner misses the point that a combination product does not eliminate the possibility of downward titration at all. A combination product, as previously explained, would have been used for the more persistent and severe cases. As soon as those cases became less severe, a doctor could prescribe either Astelin[®] alone, Flonase[®] alone, or something else entirely. Nothing about the existence of a combination product would change that possibility.

45. Dr. Kaliner makes the similar argument that the Astelin[®] and Flonase[®] dose recommendations could not both be met if the same concentrations of azelastine and fluticasone were combined into a single spray, and thus a POSA would not have been motivated to combine azelastine and fluticasone. ¶ 111. Here, Dr. Kaliner fails to recognize or admit that the given concentration of either ingredient was effective, and thus a combination product with those concentrations would also be expected to be effective. It is true that at the doses in the combination a patient can take more doses of azelastine per day than fluticasone per day without exceeding recommendations. That does not change the fact, however, that a POSA would have been motivated to combine the two ingredients because patients with severe and persistent AR were routinely using both Astelin[®] and Flonase[®] together and a combination was known to be effective. I agree with the discussion in the Reply Report of Maureen Donovan, in which she explains quite correctly that the literature demonstrated that one dose of azelastine was effective, but it could be used more often as needed. Donovan Reply Report ¶¶ 38-40.

B. Dr. Kaliner's other arguments are equally unconvincing.

i. Dr. Kaliner's discussion of failure of others and FDA skepticism is unconvincing.

46. Dr. Kaliner’s rebuttal contains a section arguing that “[r]eal-world evidence contradicts” my obviousness opinions. ¶¶ 126-132. He argues that “aside from Cipla, Meda, and the copycats I described in my Opening Report, I am not aware of anyone else who has successfully developed a fixed-dose combination product for the treatment of allergic rhinitis before Dymista®.” ¶ 126. This is not surprising, however, because Cipla and Meda *owned the intellectual property* for such a combination product. When MedPointe discovered Cipla’s patent application in 2006, it ceased attempting to formulate a combination product. Donovan Rebuttal Report ¶ 33; Declaration of Alexander D’Addio ¶¶ 26-28. And Meda owned the patent—not expiring until 2011—for the use of azelastine in a nasal spray for the treatment of allergic rhinitis. Schleimer Rebuttal Report ¶ 11.

47. Dr. Kaliner argues that MedPointe’s failure to formulate a combination product in 2006 is also evidence that doing so would not be obvious. ¶¶ 129-130. Dr. Donovan’s rebuttal report, with which I independently agree, sufficiently dispenses with this argument. MedPointe’s “attempt” at formulation was one short-lived experiment in which they conducted no tests to determine if they had actually succeeded in their objective. They did not even attempt to complete the experiment because they discovered Cipla’s patent application and decided to license the intellectual property from them. *See* Donovan Rebuttal Report *passim*.

48. Dr. Kaliner also insists that FDA was skeptical of a combination product. ¶¶ 62, 131. As discussed in Dr. McCulloch’s report, with which I fully agree, FDA was merely skeptical that Meda had created clinical studies with appropriate experimental parameters. Indeed, FDA appears to have assumed that a combination *would* be effective for the correct patient population. McCulloch Rebuttal Report ¶¶ 45-51. But even if FDA was skeptical that a combination product would provide any clinical benefit, Dr. Kaliner’s further proposition that a

“POSA clinician also would have been aware that experts at the FDA were skeptical” (§ 62) is entirely unbelievable. His POSA clinician, after all, is merely a general practitioner with a few years’ experience treating allergic rhinitis patients. Such a POSA clinician would know nothing about drug development and the FDA approval process, not to mention the fact that FDA communications with applicants are confidential.

49. And if it is true that getting a combination drug FDA approved is costly (§ 62), this is true of *all* combination drugs. More still, the inventors in this case were in India, and they never had to contend with FDA approval.

ii. Dr. Kaliner misreads the prior art references and reads them in isolation.

50. Dr. Kaliner argues that the prior art references I cite do not make a combination product obvious. §§ 90-98. But Dr. Kaliner only refers to any given reference *in isolation*, as if a POSA would have only known of one reference or article. And he misreads them. For example, he argues that Galant & Wilkinson 2001 recommended an antihistamine as an “add-on” but does not identify azelastine as one of the recommended antihistamines, citing to pages 461-62 of Galant & Wilkinson where they make their conclusions and recommendations. § 90. But Galant & Wilkinson recommended the addition of a second-generation antihistamine, and in the section of their article dealing with those antihistamines they discuss azelastine thoroughly. Galant & Wilkinson at 455-58.

51. Similarly, Dr. Kaliner argues that Advair Diskus[®] is “wholly irrelevant here” because asthma treatment is different from allergic rhinitis treatment. § 95. The point, however, was to show that it was common in related fields to combine fast-acting agents with slower-acting agents that acted on different mechanisms. More still, the product contained fluticasone propionate. This reference would have been well known to a POSA in the field of allergic rhinitis treatments because asthma and allergic rhinitis are related, as Dr. Kaliner himself admits.

Id. And a POSA would not read this reference in isolation.

52. As for Dr. Kaliner’s assessment of ARIA and Berger as requiring a stepwise approach, ¶¶ 91-94 & 97, that has no bearing whatsoever on whether it would be obvious to try a combination product for the more severe and persistent cases. And, although Lieberman does discuss nonallergic rhinitis (¶ 96), a POSA would know that the available drugs generally treated both allergic and nonallergic rhinitis.

iii. Ratner 2008 demonstrates that a sequential administration of Astelin[®] and Flonase[®] had similar results to a combination product, and thus plaintiffs have not met their burden to produce evidence showing that Dymista[®] was superior to this closest prior art.

53. In my opening report, I explained that the closest prior art to a combination product—and one of the primary reasons it would be obvious for a POSA to try a combination product—was the sequential administration of Astelin[®] and Flonase[®].² I then explained that studies of this sequential administration have since shown that Dymista[®] is not superior to the closest prior art. Thus, my opinion is that Dymista[®] was and is not *unexpectedly superior* to the closest prior art.

54. Dr. Kaliner argues that Ratner 2008—the study of the sequential administration of Astelin[®] and Flonase[®]—is not prior art and “would not have entered into the POSA clinician’s understanding as of 2002.” ¶ 135. Dr. Kaliner misses the point. Ratner 2008 is not prior art nor evidence of prior art. Rather, I noted that doctors *actually prescribed* both Astelin[®] and Flonase[®] to single patients prior to 2002. *That* is the knowledge that would have been available to a POSA. Ratner 2008 merely supports the argument respecting the “secondary consideration” of unexpected results: it demonstrates that Dymista[®] does not appear to have unexpectedly superior results to this prior art.

² Cramer and Segal also disclosed combination products, but my understanding is that they were never reduced to practice.

55. Dr. Kaliner is correct that an ideal study would test the efficacy of a sequential administration versus a combination in the same patient population. But I understand that *plaintiffs* carry the burden of producing evidence that Dymista[®] has unexpectedly superior results to this closest prior art. Thus far, in my opinion, they have failed to provide any evidence that Dymista[®] is unexpectedly superior to a sequential administration of Astelin[®] and Flonase[®].

C. The patents are not sufficiently described or enabled *if* the plaintiffs are right about obviousness.

56. Dr. Kaliner argues that my “enablement/written description opinions are contradictory to [my] obviousness opinions” (¶ 147) presumably because if combining azelastine and fluticasone were obvious, then a POSA would not need any additional information provided by the patents-in-suit in order to enable them or understand them. I have never opined, however, that the patents-in-suit are not enabled or lack a written description; rather, I argued in my opening report that *if* plaintiffs are right that a combination product was non-obvious, *then* the patents are insufficiently enabled or described because a POSA would not have learned anything from them. *See* Opening Report ¶ 132 (“But if [plaintiffs] are correct, then my opinion based on the relevant standards as I understand them is that the asserted claims are neither adequately described nor enabled by the specifications of the patents-in-suit.”).

57. Moreover, Dr. Kaliner’s key opinion on the merits is that “the non-obviousness of the subject matter of the ’620, ’723 and ’428 patents does not depend on the claimed azelastine/fluticasone fixed combination being ‘surprisingly useful.’” ¶ 149. This opinion contradicts Dr. Kaliner’s entire opinion, which is precisely that—that a combination product was *unexpectedly* (i.e., *surprisingly*) *useful* in light of the combination studies of oral antihistamines and intranasal steroids that existed prior to 2002. *See, e.g.*, ¶ 4 (“...the art provided no expectation of success; and Dymista[®] exhibits objective indicia of non-obviousness, including

unexpected results”); ¶ 23 (“(1) the POSA clinician would not have been motivated to co-administer the classes of antihistamines and corticosteroids, which had been shown not to have any clinically relevant benefit; (2) the POSA clinician would not have selected azelastine and fluticasone . . . because fluticasone, in particular, had repeatedly been shown to exhibit no benefit in combination with other antihistamines”); ¶ 24 (“The wisdom of the time, as reflected in Dr. Schleimer’s cited references, was that the conjunctive use of antihistamines and corticosteroids provided no benefit over available corticosteroid monotherapies.”); ¶ 25, (“showed no benefit”); ¶ 26 (“the combination rule would have guided the POSA clinician to one of the beneficial pairings—not to antihistamines and corticosteroids”); ¶ 31 (“the pairing of antihistamines and corticosteroids . . . consistently showed no benefit over steroids alone”); *see also, e.g.*, ¶¶ 34-49, 56, 62-64, 65, 67, 74, 86-98, 120-25.

58. Dr. Kaliner also argues that I have “failed to identify any mammal for which treatment is not enabled,” but the specifications teaches nothing at all about the clinical effects of the invention on any mammal whatsoever, and thus it is only enabled if my conclusion about what the prior art teaches is correct. Similarly, Dr. Kaliner argues that a POSA would know what amounts of antihistamine and/or corticosteroid to give for different indications in light of the prior art “*with [the] information*” in the specifications of the patents-in-suit. ¶ 157 (emphasis in original). My whole point, however, is that these specifications tell a POSA nothing at all—as I stated in my opening report, the specifications contain no experimental data showing that the combination nasal drug products covered by the claims actually have any effect whatsoever in humans, animals, or even any *in vitro* tests. Thus, that is consistent with my views on obviousness—a POSA was well aware of the uses of azelastine hydrochloride and fluticasone propionate before 2002, and would not have been surprised at all to know that combining the two

drugs would have an additive effect or, at the very least, would not have lower efficacy than the sequential administration of each drug as a monotherapy.

IV. CONCLUSION

59. In conclusion, I do not find Dr. Kaliner's rebuttal convincing. A POSA seeking to make an improved allergic rhinitis treatment would know to start with an intranasal steroid, which Dr. Kaliner recognizes was the most potent, effective, and widely used allergic rhinitis treatment then and now. Of these, fluticasone was the most potent, and it was one of the best-selling allergic rhinitis treatments at the time. A POSA would also know that, because it predominantly treats a different mechanism of action and has effects in a different phase, an intranasal antihistamine would be the best addition for a combination product—indeed, doctors had been prescribing oral antihistamines with intranasal steroids for years. Finally, a POSA would know that an intranasal antihistamine, and particularly azelastine, had particularly strong effects because of its localized application and also had anti-inflammatory effects normally unseen with oral antihistamines because of this localized application. A POSA would know that both azelastine and fluticasone were widely available and used by doctors as Astelin[®] and Flonase[®] and that many doctors prescribed the two together to patients. It would take no special insight or inventiveness for a POSA to settle on combining Astelin[®] and Flonase[®]. Such a combination was obvious.

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: August 19, 2016

By: 

Robert Schleimer, Ph.D.

Materials Considered for the Reply Expert Report of Robert Schleimer

Description	Begin Bates	End Bates
Akerlund, Anders, et al., "Clinical trial design, nasal allergen challenge models, and considerations of relevance to pediatrics, nasal polyposis, and different classes of medication," J. Allergy Clin. Immunol., Mar. 2005, vol. 115, No. 3, pp. S460-S482	APOTEX_AZFL 0059261	APOTEX_AZFL 0059283
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Expert Report of James Wedner (June 30, 2016)	N/A	N/A
Expert Report of John Jarosz (June 30, 2016)	N/A	N/A
Expert Report of Robert Schleimer, Ph.D. (June 30, 2016)	N/A	N/A
Expert Report of Michael Kaliner, Ph.D. (June 30, 2016)	N/A	N/A

Description	Begin Bates	End Bates
Declaration of Alexander D'Addio (June 30, 2016)	N/A	N/A
Rebuttal Expert Report of Charles McCulloch, Ph.D. (July 29, 2016)	N/A	N/A
Rebuttal Expert Report of James Wedner (July 29, 2016)	N/A	N/A
Rebuttal Expert Report of Michael Kaliner, Ph.D. (July 29, 2016)	N/A	N/A
Rebuttal Expert Report of Robert Schleimer, Ph.D. (July 29, 2016)	N/A	N/A
All documents cited in my rebuttal expert report	N/A	N/A