

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC

Petitioner

v.

CIPLA LIMITED

Patent Owner

Case No. IPR2017-00807

U.S. Patent No. 8,168,620

SECOND DECLARATION OF WARNER CARR, M.D.

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I, Warner Carr, do declare as follows:

I. Introduction

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. Patent Owner Cipla Ltd. (“Cipla”) has retained me as an expert witness in the *inter partes* review matter referenced above concerning U.S. Patent No. 8,168,620 (“the ’620 patent”) (EX1001). I understand that this petition for *inter partes* review was filed by Argentum Pharmaceuticals LLC (“Argentum”).

3. I am being compensated for my time in connection with this matter at my customary rate of \$800 per hour, and my compensation does not depend upon the ultimate outcome of this case. I will also be compensated for any reasonable expenses that arise in connection with this matter, including travel costs incurred while conducting activities associated with this *inter partes* review.

4. I have been asked by Cipla to review and respond to Argentum’s petition and the supporting declaration submitted by Dr. Robert Schleimer.

II. Professional and Educational Background

5. I am currently a Partner and Vice-President of Allergy and Asthma Associates of Southern California and I am the Co-Medical Director of Southern California Research. I have served in both positions since 2009 after joining the practice in 2007.

6. Prior to joining Allergy and Asthma Associates of Southern California, I was an Investigator for the Division of Experimental Therapeutics at Walter Reed Army Institute of Research from 2004 until 2007. My responsibilities at Walter Reed included clinical work treating patients, bench top research, reviewing clinical programs for investigational drug products, and conducting clinical trials for new drugs.

7. While at Walter Reed, I served for a year as a Medical Officer in the FDA Center for Drug Evaluation and Research (CDER) in the Division of Pulmonary and Allergy Drug Products. While assigned to the FDA, I worked directly under Badrul Chowdhury, the Director of the Division of Pulmonary and Allergy Products (DPAP). My responsibilities at DPAP included reviewing submissions to the FDA under the Prescription Drug User Fee Act (PDUFA). I reviewed all aspects of clinical development from phase 1 to phase 4, including Investigational New Drug Applications (INDs) and New Drug Applications (NDAs). These responsibilities required me to interact directly with sponsors for new drug products.

8. I left the FDA to serve as the Chief of Medicine for the 21st Combat Support Hospital in Iraq from March to October of 2006, after which I returned to Walter Reed Army Institute of Research.

9. I received my medical degree from the University of Washington School of Medicine in 1996 and my bachelor's degree in Biology from Boise State University in 1991. After receiving my medical degree, I completed an internship and residency at Brooke Army Medical Center for Internal Medicine in 1999. From 1999 to 2002, I was a core member of the teaching faculty in the internal medicine residency program at William Beaumont Army Medical Center. I then completed a fellowship in Allergy & Immunology at Walter Reed Army Medical Center in Washington, DC from 2002 to 2004.

10. I am licensed to practice medicine in two states. I have been licensed in Maryland since 2004 and in California since 2007. I am certified in Allergy and Immunology by the American Board of Allergy and Immunology and in Internal Medicine by the American Board of Internal Medicine.

11. I am a Fellow at the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma and Immunology ("ACAAI"), and the American College of Physicians. I was an ACAAI National Fellow-in-Training Representative from November 2002 to November 2004. From November 2011 to November 2014, I was a member of the ACAAI Board of Regents. I served as the president of the California Society of Allergy, Asthma and Immunology. I am also currently on the Board of Directors for the Western Society of Allergy, Asthma, and Immunology.

12. I have published and lectured extensively on the topic of treating allergic rhinitis (“AR”), which is the subject of this *inter partes* review. My publications can be found in my CV, which is attached as CIP2002.

13. I was previously a witness for Cipla and Meda Pharmaceuticals, Inc. (“Meda”), the exclusive licensee of the ’620 patent, during the patent infringement trial against Apotex Inc. and Apotex Corp. (“Apotex”).

III. Basis for my opinions

14. I have considered the following documents in arriving at the opinions I express below. The product labels and journal articles are generally derived from reliable authorities in the AR field, and book excerpts are from compilations generally relied on by physicians.

<i>Cipla’s Exhibit #¹</i>	<i>Description</i>
2002	Warner Carr, M.D. <i>Curriculum Vitae</i>
2019	Bench Trial Transcript, Volume B, December 14, 2016, <i>Meda Pharmaceuticals Inc. and Cipla Ltd., v. Apotex Inc. and Apotex Corp.</i> , Case No. 1:14-cv-01453-LPS (D. Del.)
2021	Bench Trial Transcript, Volume D, December 16, 2016, <i>Meda Pharmaceuticals Inc. and Cipla Ltd., v. Apotex Inc. and Apotex Corp.</i> , Case No. 1:14-cv-01453-LPS (D. Del.)
2022	Plaintiffs' Proposed Findings of Fact, January 10, 2017, <i>Meda Pharmaceuticals Inc. and Cipla Ltd., v. Apotex Inc. and Apotex</i>

¹ I refer to each exhibit as EX____ or CIP____, followed by the appropriate page, paragraph, or column and line.

<i>Cipla's Exhibit #¹</i>	<i>Description</i>
	<i>Corp.</i> , Case No. 1:14-cv-01453-LPS (D. Del.) (D.I. 155)
2031	Duonase Imitator Product Labels (PTX0026)
2034	Physicians' Desk Reference, 54 th ed., pp. 1343-1344, 2404-2406, 2781-2783 (2000)
2041	Howarth, P. H. "A comparison of the anti-inflammatory properties of intranasal corticosteroids and antihistamines in allergic rhinitis," <i>Allergy</i> , 62: 6-11; 2000 (PTX0337)
2042	Nielsen, Lars P. "Review Article, Intranasal Corticosteroids for Allergic Rhinitis - Superior Relief?" <i>Am. J. Respir Med.</i> , 2(1): 55-65; 2001 (PTX0338)
2043	Shenfield, G. M. "Fixed drug combinations: which ones can be recommended?" <i>Current Therapeutics</i> , 27(11): 15-29; 1986 (DTX-048)
2045	Hampel, F., <i>et al.</i> "Double-blind, Placebo-Controlled Study of Azelastine and Fluticasone in a Single Nasal Spray Delivery Device," <i>Annals of Allergy, Asthma, & Immunology</i> , 105: 168-173; 2010 (PTX0230)
2046	Weiler, J. M., <i>et al.</i> "Azelastine nasal spray as adjunctive therapy to azelastine tablets in the management of seasonal allergic rhinitis," <i>Ann. Allergy Asthma Immunol.</i> , 79: 327-332; 1997 (PTX0329)
2047	Blaiss, M. "Efficacy, Safety, and Patient Preference of Inhaled Corticosteroids: A Review of Pertinent Published Data," <i>Allergy and Asthma Proc.</i> , 22(6): S5-S10; 2001 (PTX0058)
2052	Leung, D., <i>et al.</i> "The Editors' Choice: MP29-02: A Major Achievement in the treatment of allergic rhinitis," <i>J. Allergy Clin. Immunol.</i> , 129(5): 1216; 2012 (PTX0029)
2066	Dymista [®] Prescribing Information 2015 (PTX0024)
2070	Duonase Nasal Spray – Prescribing Information (PTX0134)
2129	FDA, Center for Drug Evaluation and Research, "Allergic Rhinitis: Clinical Development Programs for Drug Products," Guidance for Industry, 2000 (PTX0025)

<i>Cipla's Exhibit #¹</i>	<i>Description</i>
2133	Bousquet, J. <i>et al.</i> , "Management of Allergic Rhinitis and Its Impact on Asthma," <i>Journal of Allergy and Clinical Immunology</i> , 108(5); excerpt; 2001. (ARIA Contributors) (PTX0326)
2138	DataMonitor – "Commercial and Stakeholder Perspectives: Allergic Rhinitis," September 2004 (PTX0098)
2145	U.S. Patent 6,599,914
2157	Hayashi, H. and Hashimoto, S., "Anti-inflammatory actions of new antihistamines," <i>Clinical and Experimental Allergy</i> 29: 1593-1596 (1999)
2161	Barnes, P.J., "Clinical outcome of adding long-acting β -agonists to inhaled corticosteroids" <i>Respiratory Medicine</i> 95: S12-S16 (2001)
2162	Andy, C. and Thering, A., "How effective are nasal steroids combined with nonsedating antihistamines for seasonal allergies?" <i>J. Fam. Pract.</i> 7: 616 (2002)
2164	PTX0110 – Meeting Q & A from September 7, 2007
2165	PTX0114 – Meeting Minutes dated April 15, 2008 (IND 77,363)
2169	Clarinet Product Label (2001)
2170	Storms, W. <i>et al.</i> , "Allergic rhinitis: The patient's perspective" <i>Journal of Allergy and Clinical Immunology</i> (1997)

IV. Summary of Opinions

15. In my opinion, the art at the time of invention would not have motivated a POSA to develop a fixed-dose combination of an antihistamine and a steroid. Many studies had considered pairings of these drugs delivered in separate dosage forms, but in a manner as consistent as possible with a fixed-dose combination. The studies consistently showed no benefit to using an antihistamine

and a steroid together in a fixed-dosing regimen. The results of those studies would have deterred a POSA from developing a fixed-dose combination of an antihistamine and a steroid.

16. In my opinion, rather than motivating a POSA, the prior art would have taught away from a fixed-dose combination of an antihistamine and a steroid. The studies I just mentioned attempted to capture the very concept of complementary mechanisms of action that Dr. Schleimer points to in his declaration. EX1003, ¶¶70, 84. But as I explain below, scientists in the field—in articles Dr. Schleimer relied upon in the related *Apotex* litigation—concluded from these studies that antihistamines and steroids had **redundant** mechanisms of action *in vivo*. Considered alongside other teachings in the art, these studies would have taught away from a fixed-dose combination because such a combination was expected to (1) yield no meaningful clinical benefit beyond that provided by a steroid alone; (2) induce additional side effects; and (3) remove the flexibility mandated by both the prevailing treatment guidelines of the time and prevailing clinical practice.

17. Finally, it is my opinion that the commercial embodiment of the challenged claims exhibits several objective indicia of non-obviousness, including (1) the unexpected results of greater efficacy, accelerated onset, and dramatically reduced side effects; (2) satisfaction of a long-felt need for more effective and

faster-acting Allergic Rhinitis (AR) treatment with reduced side effects; (3) receipt of substantial praise within the AR community; and (4) copying. Moreover, even years after the invention date, Dymista[®] was subject to FDA skepticism related to the known drawbacks. As Dr. Schleimer states in his declaration, “one should also consider whether there are any secondary considerations that support the nonobviousness of the invention.” EX1003, ¶43. Dr. Schleimer heard testimony and saw evidence in the *Apotex* trial regarding each of these objective indicia of nonobviousness.

V. Person of Ordinary Skill in the Art

18. Counsel informed me that a person of ordinary skill in the art (“POSA”) is a hypothetical person presumed to be aware of all pertinent art, who thinks in accordance with conventional wisdom in the art, and has ordinary creativity, as adjudged to the time of invention. I have also been informed that the priority date, or time of invention, for the ’620 patent is June 14, 2002. A POSA at that time would have had the knowledge and experience of both a clinician and a formulation scientist, or would draw upon the knowledge of a multi-disciplinary team. The clinical aspect of this POSA requires a medical degree and 2-4 years of experience as a general practitioner. I defer to Dr. Hugh Smyth for the formulation scientist aspect of this POSA.

19. I disagree with Dr. Schleimer's proposal that experience treating patients is optional for a POSA. EX1003, ¶12. His proposed definition places an emphasis on laboratory work. However, as I explain below, at the time of invention, the activities of steroids and antihistamines were known to differ between laboratory studies, where the two classes exhibited different activity, and in patients where they were effectively redundant. *See, e.g.*, EX1016, 4 (explaining that mechanisms of action suggested by lab testing were not shown *in vivo*). Each claim contains the term "pharmaceutical," and therefore it is clear to me that these claims are directed to formulations used in patients. Accordingly, knowledge of and experience in treatment is more relevant in the context of the '620 patent than laboratory experiments that a Ph.D. or Pharm.D. might undertake. Indeed, as I explain below, several laboratory-based concepts upon which Dr. Schleimer relies were tested *in vivo* and were found not to affect patients. A POSA would have been aware of this art. Nevertheless, my opinion would not change under either definition.

20. I have been informed that Argentum also argues that the '620 patent should not be accorded a priority date of June 14, 2002, but should instead be afforded a priority date of June 13, 2003. My opinion is unchanged under either priority date.

VI. The '620 Patent

21. The '620 patent is directed to pharmaceutical formulations containing azelastine hydrochloride (“azelastine”) and fluticasone propionate (“fluticasone”) with various excipients and in various dosage forms “suitable for nasal administration.” I have been informed that the '620 patent issued from U.S. Patent Application No. 10/518,016 (“the '016 application”), and that the '016 application is the U.S. national stage application of International Application No. PCT/GB03/02557 (“GB 02557”), filed on June 13, 2003. I further understand that GB 02557 claims priority to a UK Patent Application No. 0213739.6, filed on June 14, 2002.

22. Counsel has informed me that the Board has instituted review on the patentability of claims 1, 4-6, 24-26, 29, and 42-44 (collectively, “the challenged claims”). Counsel has informed me that independent claims are to be read on their own, while “dependent claims” incorporate the limitations of each claim from which they depend. I also understand that each of the challenged claims was involved, either directly or dependently, in the *Meda Pharmaceuticals v. Apotex* litigation, in which I testified at trial in December of 2016. *See* CIP2021, 49.

23. In the *Apotex* case, Dr. Michael Kaliner and I offered testimony, on behalf of plaintiffs Cipla and Meda, regarding the *prima facie* and objective indicia that I discuss below. Dr. Schleimer testified on Apotex’s behalf in response to my

testimony and in response to Dr. Kaliner's testimony. Dr. Schleimer's declaration fails to address the testimony Dr. Kaliner and I presented at trial.

VII. Claim Construction

24. Counsel has informed me that claim terms in an unexpired patent subject to *inter partes* review are given the broadest reasonable construction in light of the patent's intrinsic record, i.e., the specification and prosecution history.

25. I agree with Dr. Schleimer's construction of the claim term "condition(s)." It is also my opinion that "condition(s)" means "disease(s) or illness(es)" in the context of the challenged claims.

26. In my opinion, the claim terms "suitable for nasal administration" and "nasal spray," which appear in claims 1 and 25, respectively, mean "pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa."

27. My interpretation of these claim terms is rooted in the prosecution history of the '620 patent. During prosecution, claims 1 and 25 (then listed as claims 1 and 56) were rejected as anticipated under 35 U.S.C. § 102 and/or obvious under 35 U.S.C. §103 in view of EP 0780127 ("Cramer Example III"). EX1002, 507-522. The Examiner concluded that Cramer Example III was the closest prior art. *See, e.g.*, EX1002, 519-520. Testing of Cramer Example III conducted by Cipla confirmed that the disclosed formulation had several defects that rendered

the formulation unstable and intolerable to patients, and thus the formulation was not appropriate for deposition onto the nasal mucosa. EX1002, 286-287.

28. Specifically, Cipla's testing showed three specific problems with Cramer Example III: (1) an unacceptably high osmolality for a product to be used in the treatment of AR, i.e., a product to be used consistently for an extended period of time, because this high osmolality would cause significant burning and other discomfort to the patient; (2) unacceptable spray qualities (i.e., jet spray rather than mist), which could both negatively affect deposition upon the nasal mucosa and risk perforation of the mucosa, another serious tolerability concern; and (3) unacceptable settling of the active ingredients, which again would negatively affect the homogeneity of the drug distribution within the spray which can change the way in which the active ingredients are deposited on the mucosa.

Id.

29. As a result of this testing, Cipla told the Examiner that "Example 3 of *Cramer* (identified by the April 28, 2010 Office Action, page 16, as the closest example) is inoperable and unacceptable as a *pharmaceutical formulation in a dosage form suitable for nasal administration.*" EX1002, 220-221 (emphasis added). The italicized language appears in as-issued claim 1. EX1001, 11:46-51.

30. In addition, Cipla explained that a "nasal spray," as recited in claim 25, is also a particular species of a "pharmaceutical formulation in a dosage form

suitable for nasal administration.” EX1002, 220. Thus, Cramer Example III could not teach the “nasal spray” limitation of claim 25, either.

31. Subsequently, the Examiner allowed the as-amended claims, finding that the claims were “unexpectedly and surprisingly unobvious over, different from, and superior to the prior art of record.” EX1002, 146.

32. Counsel has informed me that Cipla’s statements and amendments, and the Examiner’s reliance thereupon, should be considered in determining the meaning of the claims. In my opinion, a POSA reviewing the prosecution history would understand that the claim terms “suitable for nasal administration” and “nasal spray” incorporate the Applicants’ arguments regarding the deficiencies of Cramer Example III, and those deficiencies speak to tolerability, homogeneity, and operability for use on the nasal mucosa.

VIII. State of the Art

33. AR is defined as the inflammation of the membranes lining the nose. AR is a common health condition that affects millions of people in the U.S. It is characterized by four primary symptoms: itching, sneezing, runny nose (rhinorrhea), and congestion. EX1019, 3. These symptoms can cause other indirect symptoms, like sleep loss, headaches, concentration issues, and other negative factors in a sufferer’s life. *Id.*, 13.

34. AR is characterized as one of two classes: seasonal, which lasts two to four weeks; and perennial, which lasts year-round. *Id.*, 6. The key difference between the two categories is the allergen that gives rise to the symptoms. *Id.* Mold, pollen, and the like are short-term allergens, while pet dander or insect allergies may induce symptoms all year long.

35. In the laboratory setting, AR reactions can be artificially broken down into two phases: the early- and late-phase reactions by exposing cells to a single allergen with no further exposure. EX1024, 49-52. These phases are extremely difficult to isolate in clinical practice because continuous daily exposure to allergens leads to ongoing and simultaneous early- and late-phase reactions. Accordingly, both treatment and FDA approval are based on *symptom* relief. All four symptoms are present in both phases, and congestion can frequently be the predominant symptom in the early phase. EX1019, 5 (explaining that in the early phase, “some subjects have sensations of nasal congestion as their predominant symptom”). Accordingly, clinical AR treatment decisions are made without consideration of theoretical phases.

A. Many of the treatment options available in 2002 had overlapping effects in treating AR.

36. Numerous AR treatment options were known in 2002. These options generally fell into one of six classes: antihistamines, anticholinergics, decongestants, leukotriene receptor antagonists, mast cell stabilizers, and steroids.

Each of these classes had its uses, benefits, and drawbacks, and there was very little clinical distinction between most drugs within each class. For example, the art at the date of invention did not distinguish between intranasal steroids—they were all viewed as equally effective. *See, e.g.*, EX1040, 2 (explaining that fluticasone, beclomethasone, and flunisolide are “equivalent in efficacy”). The vast majority of these drugs were administered through one of two modes: oral or topical.

37. Drugs selected from among the six known drug classes frequently had redundant clinical effects. Specifically, as I explain below, each of the drug classes available at the time of invention was known to work on at least one of the four main symptoms of AR.

38. There were at least 24 antihistamines known in 2002 that worked primarily on itching, sneezing, and runny nose, and the early, “first-generation” antihistamines were also known to cause sedation in patients. These issues were remedied by “second-generation” drugs like fexofenadine (Allegra[®]), loratadine (Claritin[®]), and desloratadine (Clarinex[®]) which caused virtually no sedation. CIP2034, 4, 9; CIP2169, 2. From among the known antihistamines, at least three were known for topical use, including azelastine, levocabastine, and ketotifen. EX1024, 89. The other antihistamines, including the blockbuster drugs Claritin[®], cetirizine (Zyrtec[®]), Allegra[®], and Clarinex[®] were available in oral dosage forms (pills). CIP2034, 3, 5, 8.

39. In addition, there were numerous first-generation antihistamines available over-the-counter. In my experience, patients often took these pills first, before consulting a physician. Such OTC antihistamines included chlorpheniramine and diphenhydramine. *See, e.g.*, EX1019, 38. On some occasions, it made the most sense for a prescribing physician like myself to “recommend” one of these OTC options to patients rather than one of the other oral or intranasal antihistamines. For example, if a patient is having trouble sleeping due to his allergies, a sedating antihistamine may be the best treatment option. Because these were standard considerations in the art, a POSA who treats patients would have been aware of this and other issues, and thus would have known that these first-generation antihistamines were used quite frequently.

40. Anticholinergics decrease secretions from the tissues that line the nasal passage, and thus work very well on a runny nose. EX1024, 98. At least four of these agents were known at the time of invention. EX1019, 31. These drugs had to be administered intranasally as they showed little to no effect when administered orally.

41. Antileukotrienes (or leukotriene receptor antagonists) were orally administered drugs known primarily for their effects on congestion, but they had some effect on the other symptoms of AR. EX1024, 98. At least three antileukotrienes were known prior to the date of invention. *Id.* Studies of these

drugs used in fixed-dosing combinations with antihistamines showed an improvement greater than that offered by either drug alone. *Id.*

42. Decongestants work to reduce congestion in the nasal passage by inducing vasoconstriction, which decreases swelling in the affected organ. *See, e.g.* EX1024, 96. At least nine decongestants were known at the time of invention, including the popular drug pseudoephedrine (Sudafed®). *Id.*, 96-97. Notably, decongestants actually had effects complementary to antihistamines because decongestants work on congestion, but not the other symptoms of AR, while antihistamines tend to work best on itching, sneezing, and runny nose. Thus, antihistamines and decongestants were often combined with great effect in products like Allegra-D®, Claritin-D®, and Zyrtec-D®. *Id.*, 97.

43. Two mast cell stabilizers, or chromones, were known prior to the date of invention. *Id.*, 95-96. Mast cell stabilizers required multiple doses per day. *Id.* Nevertheless, these drugs worked on all four symptoms associated with AR when taken correctly. *Id.*

44. Corticosteroids, available in oral and intranasal dosage forms, were known to work extremely well on all four symptoms of AR. EX1024, 91. Their efficacy in intranasal form led experts to declare them the most effective treatment option for AR available at the time of invention. EX1019, 29. These drugs were

largely used intranasally because of the high incidence of serious side effects when administered orally. *See* EX1024, 94-95.

B. A POSA would have known that co-administration of antihistamines and steroids provided no meaningful benefit as compared to steroids alone.

45. By the date of invention, it was established in the field that the addition of an antihistamine to a steroid (via co-administration of two separate monotherapies) conferred *no meaningful benefit* over the steroid alone when used *in vivo*. Although co-administration of two drugs yielded no greater efficacy, it was shown to increase side effects. EX1035, 8; EX1036, 5; EX1039, 6.

46. Intranasal steroids first become commonplace for use in the treatment of AR in the early- to mid-1990s. EX1024, 90 (explaining that “the role of intranasal glucocorticosteroids is now changing.”). As these drugs were used more frequently, studies were conducted to compare their efficacy to the prevailing “first-line” treatment: oral antihistamines. It was determined that steroids were superior to oral antihistamines, such that intranasal corticosteroids became the new first-line treatment. EX1024, 94; EX1019, 29.

47. At the same time, physicians recognized that steroids alone were unable to adequately address the most severe symptoms of AR that some patients experienced. Accordingly, researchers began studying the co-administration of various drugs to patients to see if any pair of drugs yielded greater efficacy than the

monotherapies. *See, e.g.*, EX1034-EX1040; *see also* EX1024, 98 (describing benefits of co-administration of ipratropium bromide with either steroids or with antihistamines). Some of these pairs, like the antihistamine-decongestant combinations I described above, were extremely successful. The improvements of these combinations were readily foreseeable: these two drug classes were completely complementary in the *symptoms* they treated—antihistamines worked primarily on itching, sneezing, and runny nose, while decongestants worked on congestion. EX1024, 97. Other similarly complementary combinations also showed promise, including antihistamines and leukotriene receptor antagonists (which, like decongestants, worked primarily on congestion). *Id.*, 98.

48. One pair of drug classes that was the subject of extensive study was that of antihistamines and steroids. It was hypothesized that antihistamines, by way of their activity in the early phase, and corticosteroids, by way of their activity in the late phase, would yield some improvement in the treatment of AR. *See* EX1035, 2. This is exactly the claim that Dr. Schleimer makes in his opinions in this proceeding. EX1003, ¶¶70, 84. But this concept—as it applied to the co-administration of antihistamines and steroids—was squarely rejected in the art prior to the date of invention. A POSA would have known that this concept had been rejected and would have seen no reason to pursue such a combination.

49. The results of clinical studies differed significantly from the hypothesis proposed in the mid-1990s (and reiterated by Dr. Schleimer here). Antihistamine and corticosteroid co-therapy frequently yielded the expected increase in side effects (EX1035, 8; EX1036, 5; EX1039, 6), but with no meaningful clinical improvement. Below, I summarize these studies and explain why they would have dissuaded a POSA from developing a fixed-dose combination of an antihistamine and a steroid.

50. Before I begin my summary of the numerous studies, I would like to clarify the meaning of the terminology I use below. First, I refer to “fixed-dosing regimens,” which are treatment regimens in which the patient is prescribed a specific amount of two drugs, to be used consistently each day. This is distinct from other *ad hoc* practices described below in which the ratio of the two drugs varies based on the patient’s needs. *See infra*. VIII.C. Second, I refer to two concepts for the data I discuss. The first is “statistical significance,” which is a measure of how reliable the study data is, or how likely it is that any result shown by the data will also be “the result” in clinical practice. The second is “meaningful” improvement, which describes whether the statistically significant showing is actually of clinical relevance; i.e., does the treatment have a noticeable effect on the patient?

51. With these concepts in mind, I reviewed the many studies prior to the date of invention that considered fixed-dosing regimens of antihistamines and steroids. Both statistical significance and meaningful improvement are important in comparing the two treatment arms with active ingredients because both are needed to determine whether one treatment offers an improvement over the other.

52. The first study I am aware of that compared the co-administration of a steroid and an antihistamine to the use of a steroid alone was published by Juniper in 1989. EX1039. This study analyzed the effects of beclomethasone dipropionate when used alone and when used in a fixed-dosing regimen with astemizole. EX1039, 1. This study concluded that “[b]eclomethasone plus astemizole provided no better control of rhinitis than beclomethasone alone.” *Id.* The study also showed an increase in side effects from the fixed-dosing arm as compared to either monotherapy. *Id.* at 6.

53. While the study did note a benefit to ocular symptoms, these findings were not shown to be statistically significant. *See id.* at 5, Table III. As I explained above, this means that there was no scientific proof that this pair of drugs could actually be expected to achieve this benefit in clinical practice. Accordingly, a POSA would recognize that the claimed improvement was not clinically relevant.

54. Dr. Schleimer relies on these non-statistically significant improvements, along with two references—Hettche (EX1007) and Berger

(EX1021)—to suggest that the use of azelastine could obviate the need for eye drops. EX1003, ¶65; Pet. 34-35. But Hettche contains no clinical data to support its claims (made in 1990) (*see generally* Exhibit 1007) and Berger refers to clinical trials conducted between 1994 and 1996. EX1021, 7 n.13-17. The claims in these references were published before intranasal azelastine received FDA marketing approval in November of 1996. Based on this FDA approval, a POSA would have known that azelastine *was not* able to show an improvement in ocular symptoms because no such claims appear in its label. *See generally* EX1008. Moreover, a POSA would have known that nasal antihistamines were never considered for use in treating ocular symptoms. Even the recommendations in the Guidelines that Dr. Schleimer relies upon explicitly state: “If the patient suffers from conjunctivitis [ocular allergies], the options (not in preferred order) are: ocular H1-antihistamines, ocular chromones, saline, [and] oral H1-antihistamines.” EX1024, 111. The claim that nasal azelastine could treat ocular symptoms is simply not supported by clinical data, and the art that taught the way to address ocular allergy symptoms was to use either an ocular or oral dosage form. *Id.*; *see also* EX1019 (describing use of oral antihistamines to treat ocular symptoms).

55. The Simpson study, published in 1994, studied the efficacy of a fixed-dosing regimen of budesonide and terfenadine. *See* EX1036, 1. Dr. Schleimer relies on this study to claim that a minor improvement in sneezing would have

motivated a POSA to combine antihistamines and steroids. EX1003, ¶86. Although Simpson shows a statistically significant difference in sneezing between the steroid-only and the fixed-dosing arms, a POSA would have understood that the authors of the article themselves concluded that “[b]udesonide and terfenadine combination treatment produced a similar effect to treatment with budesonide alone.” EX1036, 3. The lack of clinical relevance is confirmed by the authors’ conclusions. Instead of recommending the use of both drugs together, they ultimately concluded that “[b]udesonide *alone* is a highly effective treatment for hay fever with few side effects.” *Id.*, 1 (emphasis added). The results of the Simpson study demonstrate that budesonide alone is as effective as budesonide taken together with terfenadine. It also showed that the co-administration group suffered from an increase in side effects. *Id.*, 6.

56. The Benincasa study, also published in 1994, studied the effects of co-administering fluticasone propionate (one of the active ingredients claimed in the ’620 patent) and cetirizine. Benincasa concluded that “there is no significant difference in efficacy between [fluticasone propionate], taken once daily in the morning, and [fluticasone propionate] once daily in combination with oral cetirizine.” EX1040, 1. The Benincasa study showed an increase in several side effects when both drugs were used together. *Id.*, 6.

57. The Ratner 1998 study considered the co-administration of fluticasone propionate and loratadine. EX1034, 1. Dr. Schleimer opines that this study showed improved treatment of patients' symptoms (EX1003, ¶90), but he ignores the authors' conclusion: "adding loratadine to [fluticasone propionate] does not confer meaningful additional benefit." EX1034, 1.

58. Two other studies, Drouin (EX1035) and Brooks (EX1038), both tested the same pair of drugs (neither of which is claimed in the '620 patent): loratadine and beclomethasone dipropionate. Dr. Schleimer relies on these studies to claim that it was known that antihistamines and steroids worked better together than a steroid alone.

59. First, Dr. Schleimer claims that Drouin "found that combining the two [drugs] improved the treatment of patients with allergic rhinitis." EX1003, ¶69. He opines that a POSA "would have recognized that combining antihistamines and intranasal steroids provided additional relief beyond each of the monotherapies." *Id.* While Drouin makes such a claim, a POSA would have immediately recognized that, like the other studies I just discussed, Drouin does not show a meaningful improvement from the co-administration therapy. As Drouin explains, patients in the study were required to have a total nasal symptom score ("TNSS")

of at least 6,² from which nasal discharge (runny nose) and at least one other symptom had to be moderate (i.e., rated a “2”). EX1035, 3. The study data, summarized in Table 2 of the publication, shows the percentages of improvement in the study. *Id.*, 5. The TNSS numbers reported for the combination and steroid-only groups differ by 7%, meaning that the total difference between the combination group and the steroid-only group was approximately 0.4 points—a clinically meaningless difference. This “improvement” is less than that typically obtained from placebo.³ A POSA would have seen no meaningful improvement in symptoms.

² A given drug’s efficacy was generally measured based on a total nasal symptom score, or TNSS, that is a rating assigned either by the patient or physician for each primary symptom on a scale of 0 to 3, with 0 being no symptoms and 3 designating severe symptoms. *See* CIP2129, 15. Thus, a patient suffering no symptoms would have a TNSS of 0 while a patient suffering from severe itching, sneezing, runny nose and congestion would have a score of 3. Other scales have been used in the past, but they can be difficult to translate directly into the modern 12-point scale that was used at the date of invention, and which remains the predominant scale used today.

³ Placebo is generally included in studies to remove bias and account for the placebo effect that occurs during the conduct of real-world clinical trials. Studies

60. A year later, another research team led by Brooks considered exactly the same pair of drugs. EX1038, 1. Dr. Schleimer relies on this study for its claim of “additive symptom suppression almost across the board.” EX1003, ¶70; EX1038, 6. Here, Dr. Schleimer specifically identifies itching and sneezing as the symptoms improved by the combination. EX1003, ¶70. But again, a POSA would have doubted any improvement claimed in Brooks because it found that the steroid was neither statistically significantly nor meaningfully better than the antihistamine: “[beclomethasone] alone appeared to protect slightly better than [loratadine] alone, but statistical testing did not confirm the significance of this trend.” EX1038, 3. A POSA would have known that a steroid *should* be substantially better than an antihistamine (EX1019, 29; EX1024, 94), and thus a POSA would have interpreted the “improvement” seen in Brooks to be from the steroid working properly in the co-administration population. Again, this study suffers from potential bias due to the lack of placebo.

61. My analysis of the import of these studies was confirmed in the art prior to the date of invention. A review article published by Howarth confirmed my reading: Dr. Howarth concluded that the fixed-dosing combination studies published in the field “do not support a superior effect with long-term regular

that do not include a placebo arm are considered inferior and potentially flawed given the risk of bias.

therapy with the combination [of an antihistamine and a steroid] compared with topical corticosteroid alone.” CIP2041, 4-5. Dr. Howarth went on to conclude that “[t]he lack of additional clinical benefit when antihistamines are used in combination with corticosteroids indicates that, *in vivo*, the anti-inflammatory effects on the airway of corticosteroids overlap those of the H₁-antihistamines, ***making the action of the latter redundant.***” CIP2041, 5 (emphasis added). This observation is important because it rejected Dr. Schleimer’s premise of complementary mechanisms prior to the date of invention. The remainder of Dr. Howarth’s discussion, i.e., that an alternative explanation for the lack of benefit is the lack of potency of antihistamines at the dose used in these studies (CIP2041, 5) would neither motivate a POSA to try an intranasal steroid nor provide a reasonable expectation that doing so would yield better results: as I already explained, azelastine was known to have efficacy equal to that of oral antihistamines. EX1041, 9.

62. Another team of scientists, led by Nielsen and Mygind, expressly reviewed the Juniper 1989, Ratner 1998, Simpson, and Brooks studies I discussed above as well as Juniper 1997 (CIP2042, 10) and concluded that these studies show that “[c]ombining antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis does not provide any additional effect to intranasal corticosteroids alone.” CIP2042, 2. Nielsen’s findings are consistent with

Howarth's, and would further confirm to a POSA that antihistamines and steroids had redundant activity *in vivo*. It is also notable that Howarth and Mygind are credited as authors of both the Cauwenberge and ARIA guidelines. CIP2133, 4-6. These authors rejected in 2000 and 2001, respectively, the concept of fixed co-administration of antihistamines and steroids. A POSA would have been aware of this and read Cauwenberge and ARIA with that in mind.

63. Similarly, another review article published in 2002 stated that “[c]ombining nasal steroids and nonsedating antihistamines yields no additional benefit” over steroids alone. CIP2162, 1. Notably, the review assigned a grade for the evidence supporting this conclusion and assigned it an “A.” *Id.*

64. In short, it is my opinion that the available literature did not teach any benefit to the use of antihistamines and steroids together. My opinion is confirmed by publications prior to the date of invention authored by experts in the field of AR treatment. CIP2041, 4-5; CIP2042, 2; CIP2162, 1.

C. The treatment recommendations and general practices prior to the date of invention were consistent with the co-administration studies' findings, and would not have encouraged a POSA to pursue a fixed-dose combination.

65. A POSA would not have been motivated by the various Guidelines or other references cited to develop a fixed-dose combination of azelastine and fluticasone.

66. First, Dykewicz and Cauwenberge/ARIA⁴ all provide similar teachings with respect to the treatment of AR. In its discussion of “Important Considerations in Management,” Dykewicz specifically teaches that “[m]anagement of [allergic] rhinitis should be individualized,” suggests the “utilization of both step-up and step-down approaches,” and recognizes that “modifications of the medication or immunotherapy program” may be required. EX1019, 34. I use this stepwise approach, which is intended to give the patient the minimum dosage necessary to control his/her symptoms. Thus, a physician would typically begin with a high dose (either of two drugs or a larger dose of one drug) and tell the patient to reduce the dosage after his/her symptoms are under control. And if symptoms peaked again for the patient, the patient would “step up” his/her treatment by using the higher dose or second drug “as needed.”

67. Cauwenberge and ARIA contain the same recommendation, which is specific to azelastine:

Topical antihistamines usually require bi-daily (BID) administrations to maintain a satisfactory clinical effect. Their use may therefore be recommended for mild organ-limited disease, as an “on demand” medication in conjunction with a continuous one.

⁴ I group these two references together because they are written by the same authors and contain nearly identical teachings.

EX1024, 90; *see also* EX1022, 5 (same). Dr. Schleimer claims that ARIA would have motivated a POSA to develop a fixed-dose combination of azelastine and fluticasone, but this recommendation is contrary to his claim. In my experience, “on demand” or “as needed” therapy was the prevailing practice in AR treatment, whereby a patient would take one drug consistently (e.g., a steroid), and use the second drug only when symptoms worsened. Accordingly, the two drugs in this practice had to be kept separate. This is similar to the step-up and step-down approach described above—a POSA would have known that these approaches required varying the ratio of the drugs used. A POSA also would have known that a patient cannot use the azelastine “on demand,” or step it up or down, if it is in the same formulation as the “continuous” treatment. A POSA would not have been motivated to do something wholly inconsistent with the teachings that he read.

68. The Juniper 1997 reference applies this flexible approach. *See* EX1003, ¶89 (citing EX1031). While Juniper 1997 did suggest that “at least 50% of patients will need to take both types of medication in combination to control symptoms adequately,” (EX1031, 1), Dr. Schleimer ignores the context of this statement. First, Juniper 1997 does not show a benefit to using both drugs together.⁵ In fact, Juniper 1997 simply shows that patients sometimes found even

⁵ In fact, both drugs in Juniper 1997—fluticasone and terfenadine—had already been shown not to yield any benefit when used with other antihistamines or

the most effective treatment option (a steroid) inadequate to treat their symptoms so they needed to try something else. This shows a need, but it does not show any improvement from the co-administration that might have motivated a POSA to develop a fixed-dose combination.

69. Juniper 1997 actually applied the approaches later recommended by Dykewicz, Cauwenberge, and ARIA, which are, again, contrary to a fixed-dose combination. Juniper 1997 explains that the patients in the steroid group were instructed to take the steroid and “[i]f the symptoms continued to be troublesome we advised patients to *add* terfenadine (60 mg) when needed, up to 120 mg/d, and to cut back on the terfenadine once the symptoms were controlled.” EX1031, 3 (emphasis in original). The data showed that patients in the fluticasone group used an average of 0.13 terfenadine tablets per day (*id.*, 7) which, over the 6-week study period, equals about 5.5 pills. To be clear, the patients used approximately one antihistamine per week. In contrast, the patients used fluticasone seven times—once each day. *Id.*, 3. This ratio *cannot* be achieved with a fixed-dose combination. And because antihistamines have several significant side effects, regardless of dosage form, a POSA who actually treats patients would have immediately recognized that a fixed-dose combination would needlessly expose his/her patients

steroids, respectively. *See* EX1040 (no benefit from adding cetirizine to fluticasone); EX1036 (no benefit from adding terfenadine to budesonide).

to potentially unnecessary drugs and an increased risk of side effects. CIP2043, 13.

This study comports with my experience, which is that when a patient feels the need for a drug, they are very likely to take it. *See* CIP2043, 18 (suggesting that symptomatic treatment, such as AR, is likely to have high compliance). As I explain below, the various treatment teachings in the art motivated a POSA to keep the drugs separate; not to combine them. And indeed, the art established several reasons not to pursue a fixed-dose combination in this scenario.

70. The teachings of the Berger reference are consistent with the recommendations above and the teachings of Juniper 1997; however, Dr. Schleimer claims that Berger would have motivated a POSA to develop a fixed-dose combination of azelastine and fluticasone. EX1003, ¶¶52 (citing EX1021, 2), 73 (citing EX1021, 6), 96. The cited passages state that physicians can prescribe an antihistamine with a steroid and suggest that azelastine can be used as the antihistamine in this prescription. But Dr. Schleimer fails to recognize that the prescriptions referenced are consistent with Dykewicz, Cauwenberge, ARIA, and Juniper 1997—that is, physicians prescribed the steroid for continuous use and recommended the use of azelastine as an “on demand” therapy, which meant infrequent and non-fixed dosing of the antihistamine. EX1024, 90; EX1022, 5; EX1031, 7.

71. The remainder of Dr. Schleimer's citations to Berger rely upon his inaccurate claim that intranasal antihistamines were preferred over oral ones because of their efficacy in relieving congestion. *See* EX1003, ¶56 (citing EX1021, 2).

72. Nevertheless, Dr. Schleimer extends this congestion concept into his reliance on early- and late-phase responses, and points to Spector as suggesting the approach of treating both phases. *See* EX1003, ¶¶57, 58 (citing EX1023, 2). But Spector simply suggested the concept of a drug that treats both early and late phases. As explained above, however, antihistamines and steroids did not satisfy that teaching as their mechanisms of action are redundant *in vivo*. CIP2041, 5. Moreover, Spector explicitly teaches that the proposed "ideal pharmacologic therapy" would "have a favorable safety profile." EX1023, 2. Spector also teaches that "the safety of [nasal steroids] remains a concern" due to their effects on serum and urinary cortisol levels and suppression of bone growth. *Id.* Spector explicitly identifies fluticasone as one such steroid subject to concern. *Id.* Accordingly, a POSA reading Spector as a whole would understand that Spector's "ideal pharmacologic therapy" was a not a combination of a steroid with any other drug,

but instead a recommendation that scientists develop a single drug that acts in both the early- and late-phases and has a favorable safety profile.⁶

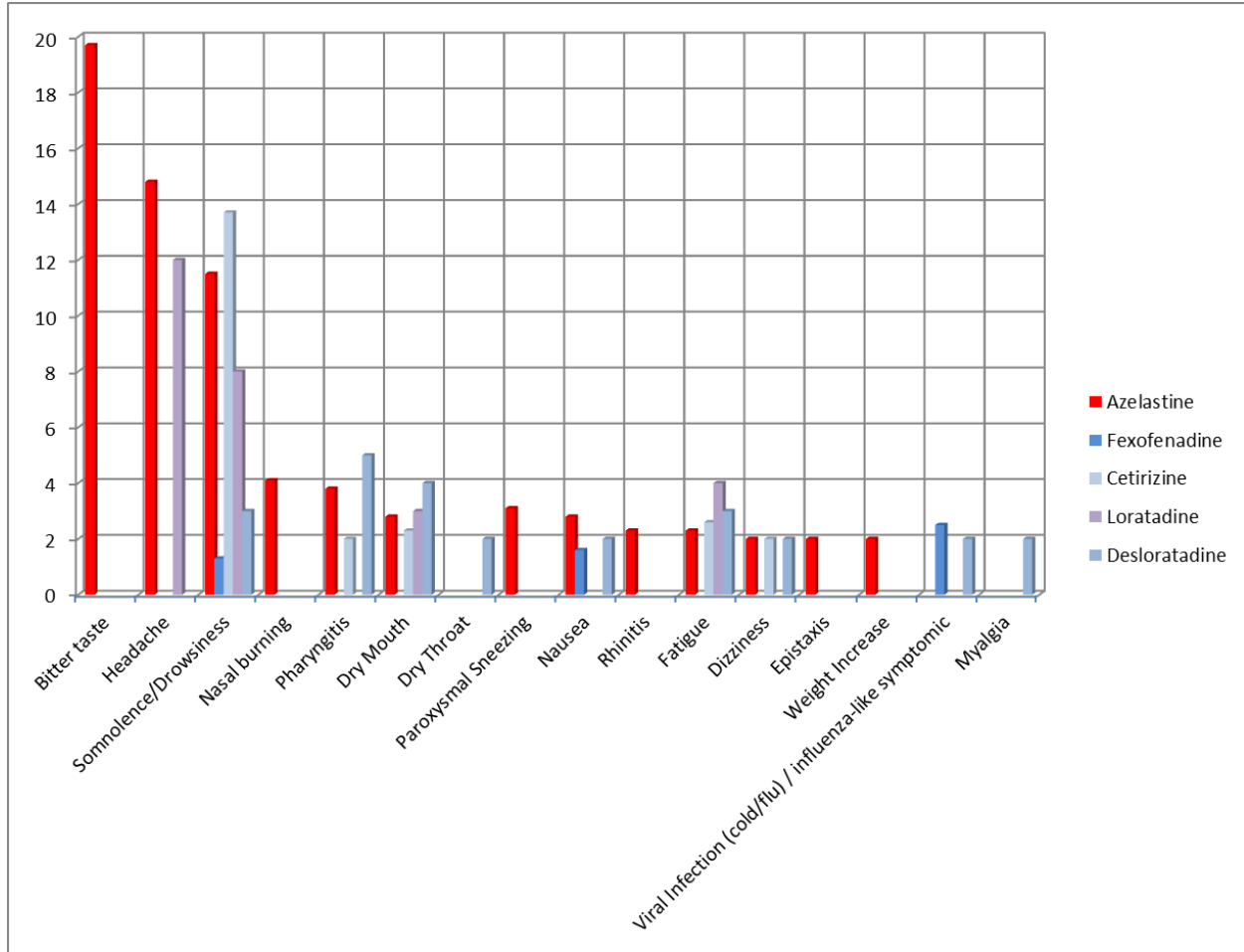
73. Indeed, the art is replete with evidence that persons of skill understood Spector to teach what I propose. Numerous studies were conducted to determine whether newer antihistamines—like cetirizine, terfenadine, loratadine, desloratadine, ketotifen, and mizolastine—actually had both early- and late-phase activity. Some of these studies are cited in the Kusters reference (*see* EX1016, 3-4), and still more are cited in a patent that Dr. Schleimer filed in 2001 and references cited therein. *See* CIP2145; CIP2157. Indeed, Dr. Schleimer’s patent attempts to capture the concept disclosed by Spector by suggesting that

⁶ To the extent that Dr. Schleimer asserts that Advair DISKUS, a combination of salmeterol and fluticasone, might be relevant (EX1003, ¶84; citing EX1030; EX1025, 1213), I observe that the practical bases of the Advair DISKUS is very different from the claimed invention. First, Advair DISKUS is used to treat asthma, not AR. EX1030, 16. Contrary to the combination of antihistamines and steroids, which had repeatedly been shown not to exhibit any meaningful clinical benefit, it was well-known that bronchodilators and steroids exhibit substantial improvement when used together. *See* CIP2161, 1 (“Many studies have shown that the addition of a β_2 -agonist with long-acting properties is more effective at controlling asthma symptoms than increasing the dose of corticosteroid alone.”).

desloratadine—an antihistamine—has activity in both phases. In his patent, Dr. Schleimer stated that “desloratadine provides combined antihistaminic and anti-allergic inflammatory effects *to control both early and late phase allergic reactions.*” CIP2145, 12:23-25.

74. Dr. Schleimer’s claims that there was a preference in the field for nasal antihistamines because they “possess fewer side effects than their oral counterparts” and “[t]he reduction of systemic side effects clearly makes intranasal antihistamines superior to oral antihistamines” (EX1003, ¶56), is demonstrably false.

75. A POSA with clinical experience would know that azelastine had substantially more side effects, including systemic side effects, than several available oral antihistamines. Below is a chart comparing the incidence and number of side effects across several oral antihistamines and intranasal azelastine in adult doses, as established in FDA testing that Dr. Schleimer rightly testified offers “a rigorous review” of drug candidates. CIP2021, 364:5-8.



CIP2034, 4, 6, 9; CIP2169, 2.

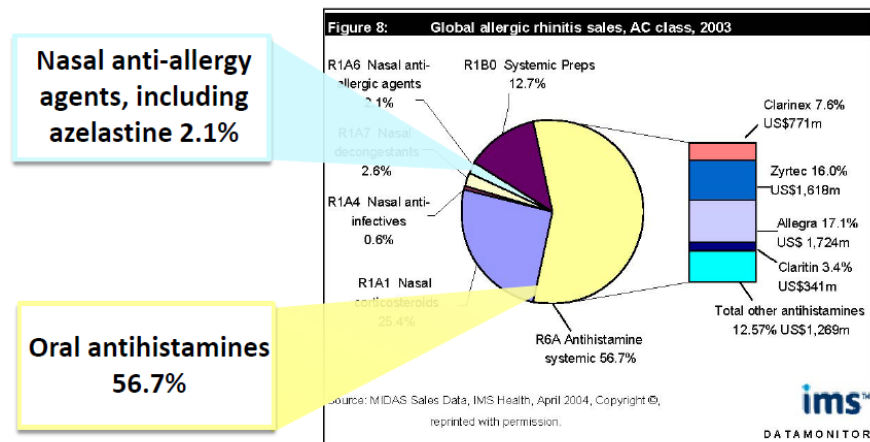
76. There are three important takeaways from this comparison. First, azelastine has thirteen different reported side effects. EX1008, 3. Fexofenadine, cetirizine, loratadine, and desloratadine have fewer total side effects combined. CIP2034, 4, 6, 9; CIP2169, 2. Scientific data, subject to “rigorous” review—Dr. Schleimer’s words from the Apotex trial (CIP2021, 364:5-8)—and well-known prior to the date of invention, disproves Dr. Schleimer’s claim that intranasal antihistamines “possess fewer side effects than their oral counterparts.” EX1003,

¶56. A POSA who actually treated patients would have known that the opposite was true. And in fact, Dr. Schleimer appears to have agreed in 2001, when his patent application explained that even though desloratadine could be administered in any number of ways (including intranasal), “[p]referably desloratadine is administered orally.” (CIP2145, 5:26-27.) Dr. Schleimer’s preference in 2001 for oral antihistamines is consistent with the POSA’s view as of the invention date; his suggestion in 2017 that oral antihistamines are not “relevant,” on the other hand, is inconsistent with the state of the art at the relevant time and, in my opinion, improperly excludes approximately 60% of the drugs being used at the time of invention. *See* CIP2138, 29 (showing that oral antihistamines comprised 57% of the market while several non-steroid nasal sprays, including azelastine, barely held 2% of the market.).

77. Second, several of the side effects exhibited by azelastine (somnolence, nausea, fatigue, dizziness, and weight increase) are systemic side effects exhibited by azelastine at frequencies equal to or greater than its oral antihistamine counterparts. Again, while Dr. Schleimer opines that “[t]he reduction of systemic side effects clearly makes intranasal antihistamines superior to oral antihistamines,” (EX1003, ¶56) a POSA would have known in 2002 that the opposite was true.

78. Third, to emphasize the stark contrast between intranasal and oral antihistamines, the frequency at which patients experience these side effects is generally greater for azelastine than any of the oral antihistamines. For example, the somnolence caused by azelastine is comparable to cetirizine, but significantly higher than fexofenadine, loratadine, or desloratadine. *Supra*, ¶75. Meanwhile, azelastine causes each of the following side effects more often than most of the oral antihistamines combined: (1) bitter taste; (2) headache; (3) nasal burning; (4) pharyngitis; (5) paroxysmal sneezing; (6) nausea; (7) rhinitis; (8) epistaxis; and (9) weight increase. *Supra*, ¶75. Notably, azelastine has eight side effects that occur in at least 2.6% of patients; the four oral antihistamines have that many combined. Simply put, the low dosage of azelastine did not prevent it from causing substantial complications that were avoided through the use of oral antihistamines.

79. This is why, at the date of invention, oral antihistamines were the preferred treatment options (even over more effective nasal steroids). My experience is that patients would prefer the ease of an oral treatment, even if it is less effective than a nasal option. And my experience is confirmed in the literature—in a 2004 publication (referencing 2003 sales, which would have been comparable to 2002), oral antihistamines accounted for nearly 57% of the market, while similarly effective nasal antihistamines comprised less than 2.1% of the market.



CIP2138, 29. It is my understanding that the designation for nasal anti-allergy agents includes at least azelastine, cromoglicic acid, ketotifen, and levocabastine.

IX. The art did not motivate a POSA to combine azelastine and fluticasone into a fixed-dose combination as recited in claims 1, 4-6, 24-26, 29, and 42-44.

80. Counsel has informed me that a patent can be found obvious only if a POSA, reading the art as a whole, would have found the invention itself obvious. I understand that four factors should be considered: (i) the level of ordinary skill in the art; (ii) the scope and content of the prior art; (iii) the differences between the prior art and the claims at issue; and (iv) the applicable objective indicia of non-obviousness. Counsel has also informed me that I must evaluate the prior art from the perspective of a POSA, and that I must consider any objective indicia of non-obviousness.

81. Dr. Schleimer opines that a POSA would have been motivated to arrive at claims 1, 5-6, 24-26, and 29. Notably, he says nothing whatsoever about a

POSA's motivation to arrive at claims 4 and 42-44. It, therefore, appears that Dr. Schleimer and I agree: a POSA would not have been motivated to develop the pharmaceutical formulations covered by claims 4 and 42-44.

82. Aside from our apparent agreement that a POSA would not have been motivated to develop the formulations covered by claims 4 and 42-44, it is my opinion that Dr. Schleimer's stated views are driven solely by hindsight as they are contradicted by the stated views of experts after they conducted their own studies and by the views of independent expert analyses of the studies as a whole prior to the date of invention.

83. In my opinion, the challenged claims would not have been obvious to a POSA at the time of invention. Counsel has informed me that a critical step of the obviousness analysis is that the prior art as a whole must be accounted for. Therefore, whereas Dr. Schleimer's declaration makes clear that he only considered azelastine and compared it only to another intranasal antihistamine (levocabastine) (EX1003, ¶¶62-63), I respond to Dr. Schleimer's arguments only after considering the art as a whole. My analysis accounts for other available treatment options and modes of administration, like oral antihistamines, while Dr. Schleimer's declaration makes clear that he ignores these critical and preferred treatment options.

A. The art as a whole did not motivate a POSA to develop an inflexible fixed-dose combination.

84. As explained above, all of the references cited by Dr. Schleimer suggested the stepwise approach or “on demand” use of azelastine. EX1019, 34; EX1022, 5; EX1024, 90. These recommended approaches required flexibility to increase or decrease dosages, and to add and subtract drugs to the patient’s therapy. Meanwhile, Shenfield taught that “[o]ne of the major problems [with fixed-dose combinations] is that the prescribing doctor loses flexibility in patient management.” CIP2043, 12. Because it was known that a fixed-dose combination eliminated flexibility, and all of the art taught AR treatment required flexibility, a POSA would have been led in a direction divergent from the path that Cipla took.

B. The art as a whole did not motivate a POSA to develop a fixed-dose combination that would be expected to yield no clinical benefit but exhibit increased side effects.

85. Shenfield also explained that “[t]he use of 2 drugs will always increase the risk of adverse drug reactions both idiosyncratic and pharmacological.” CIP2043, 13. In the same passage, Shenfield recognized a key problem with fixed-dose combinations: “[i]n some circumstances patients may be exposed to additional ingredients with little therapeutic benefit and major potential side effects.” *Id.* The co-administration studies discussed above showed that the co-administration of antihistamines and steroids yielded side effects at least as significant as the monotherapies, but often greater than the side effects of either

drug alone. Because it was known that a fixed-dose combination of an antihistamine and a steroid increases side effects while offering no meaningful clinical benefit, a POSA would have been led in a direction divergent from the path that Cipla took.

C. The art as a whole did not motivate a POSA to select azelastine for use in a fixed-dose combination with a steroid in order to improve compliance.

86. The art contradicts Dr. Schleimer's claim that improved compliance would have motivated a POSA to develop a fixed-dose combination. Specifically, Shenfield observed that studies had shown that combining two drugs into a fixed-dose combination "had no effect on compliance." CIP2043, 6. Shenfield explained that "[o]verall, it appears that the vital factor is not the number of tablets [or nasal sprays] taken, but the number of doses prescribed." *Id.* A POSA would understand that Shenfield did not suggest that a fixed-dose combination would yield improved compliance; two tablets, or a spray and a tablet, for example, are still "one" dose according to Shenfield. It is the number of doses required each day that decreases compliance.

87. Similarly, the Galant reference taught that "[t]he clinician can improve adherence by selecting *oral* medications that *taste good*, require *once daily* administration, and have an obvious beneficial effect with *minimal adverse effects*." EX1041, 10. As shown below, the selection of azelastine for use with

fluticasone in a fixed-dose combination is inconsistent with each of these teachings.

88. First, it was well-known that azelastine had a bad taste that is unique among antihistamines. EX1024, 90 (describing as “specific” to azelastine the side effect of bad taste). Based on Galant’s teachings, a POSA would have expected the bad-tasting azelastine to *reduce* compliance with fluticasone—not improve it.

89. Second, it was well-known that azelastine had a short duration of action and thus had to be administered twice per day. EX1022, 5; EX1024, 90. Fluticasone, on the other hand, had a long duration of action that allowed it to be administered once per day. EX1010, 8. Thus, a POSA would have understood that azelastine’s duration of action would drive the dosing schedule. The result of a fixed-dose combination would be that fluticasone would have to be dosed *twice* a day instead of once. A POSA would also understand from Dykewicz, Shenfield and Galant that this increase in the “number of daily doses” would *decrease* compliance—not improve it. *See* EX1019, 35 (“[c]ompliance is enhanced when: (1) a fewer number of daily doses is required...”); *see also* CIP2043, 6 (“the vital factor [in patient compliance] is ... the number of [daily] doses prescribed.”); EX1041, 10. Moreover, many popular oral antihistamines had durations of action long enough to require only once-daily administration. *See, e.g.*, CIP2034, 7, 10 (cetirizine and loratadine once daily); CIP2169, 2 (desloratadine once daily).

90. Third, as I explained above, azelastine had many more side effects, which occurred far more often, than several oral antihistamines. *Supra*, ¶¶75-79. These side effects of azelastine would similarly have been expected to reduce compliance, not improve it.

91. Accordingly, a POSA seeking to improve compliance would have been led in a direction divergent from the path that Cipla took. The POSA would have understood that azelastine was contrary to each of the factors that typically improve compliance.

D. A POSA would not have been motivated to select azelastine based on any anti-inflammatory activity.

92. I disagree with Dr. Schleimer's claim that azelastine was somehow unique among antihistamines for its activity on antihistamines. To the extent that any antihistamines were thought to have some anti-inflammatory effect (i.e., decongestive effect), several oral antihistamines were shown to have activities similar to that of azelastine.

93. First, Dr. Schleimer relies on Kusters to support his claim that azelastine was uniquely anti-inflammatory among antihistamines. EX1003, ¶¶66-67. His reliance on this study is misguided, as Kusters shows that terfenadine (which is metabolized into fexofenadine) was "equally effective as azelastine" in inhibiting inflammatory mediators. EX1016, 3-4. Kusters also explained that at

least loratadine, desloratadine, and mizolastine have shown similar promise in inhibiting inflammatory mediators. EX1016, 3-4.

94. Second, Dr. Schleimer's patent and a reference cited in it provide further knowledge regarding antihistamines' effects on inflammation. Dr. Schleimer's patent (CIP2145) is replete with statements regarding the anti-inflammatory effects of desloratadine. *See generally* CIP2145. The Hayashi reference cited on the face of Dr. Schleimer's patent further explains that cetirizine and ketotifen had similar effects. CIP2157, 1-2.

E. A POSA would not have been motivated to pursue a fixed-dose combination of an antihistamine and a steroid.

95. For the reasons discussed above, a POSA would not have been motivated to develop a fixed-dose combination on the basis of improved efficacy, complementary mechanisms of action, or improved compliance. The available studies showed no improvement in efficacy (Section VIII.B), leading to the conclusion that the activity of the two drug classes was **redundant** *in vivo*. CIP2041, 5. And, as explained immediately above, the use of a short-acting drug like azelastine in combination with fluticasone would be expected to *reduce* compliance with the fluticasone treatment.

X. Objective indicia of non-obviousness suggests that the challenged claims are not obvious.

96. Counsel has informed me that real-world factors—so-called “objective indicia”—must be considered when present. This evidence was presented in the *Apotex* trial, which Dr. Schleimer attended in full. I address several of these objective indicia below, and I understand that another expert will address other objective indicia.

A. Dr. Schleimer was present at the trial in district court.

97. At trial against Apotex in the district court, Cipla and co-plaintiff Meda presented evidence of multiple objective indicia of non-obviousness including: (1) unexpected results; (2) failure of others; (3) licensing; (4) skepticism; (5) unmet need; (6) commercial success; (7) copying; and (8) industry praise. CIP2022, ¶¶99-149. This evidence was presented by Dr. Michael Kaliner, a physician renowned in the field of AR, Dr. Hugh Smyth, and myself.

98. Dr. Schleimer was an expert for Apotex in the district court litigation over the '620 patent. I observed Dr. Schleimer, who attended the entire trial. In fact, Dr. Schleimer opined on several of these objective indicia during the course of the Apotex litigation and at trial (CIP2021, 334:25-335:18), but they appear nowhere in his opinions or in Argentum's Petition.

B. The patents-in-suit exhibit several significant, unexpected clinical results.

99. Counsel has informed me that unexpected results exhibited by the claimed invention can be evidence of non-obviousness if those results are greater than would have been expected over the closest prior art. I also understand that these results must be of a difference in kind, not just in degree.

100. At trial in the district court, I presented testimony explaining that Dymista[®], a commercial embodiment of the challenged claims, exhibits three unexpected results: (1) it is unexpectedly more effective than the closest prior art; (2) it is unexpectedly faster-acting than the closest prior art; and (3) it has unexpectedly reduced side effects than the closest prior art. CIP2022, ¶123; CIP2021, 75:21-77:23, 95:13-17, 89:18-92:23. The combination of these three outcomes is also itself an unexpected result, because in my experience efficacy and side-effects are frequently directly correlated, meaning that as efficacy increases, so too do side effects. Surprisingly, Dymista[®] reverses this trend by yielding a significant improvement in efficacy with an equally significant reduction in side effects. Dr. Schleimer listened to all of my testimony, and even offered opinions in response to my testimony. Yet neither he nor Argentum acknowledge these unexpected results.

1. From a clinical perspective, the closest prior art comprises the studies and review articles finding no additional benefit from adding an antihistamine to a steroid.

101. In my opinion, the closest prior art from a clinical perspective is the series of studies I discussed above that considered whether the use of an antihistamine and a steroid together exhibited any improvement over a steroid alone. My opinion is rooted in several factors that would have influenced a POSA's understanding of the meaning of these studies.

102. First, it was widely thought that each antihistamine—even the first-generation ones—exhibited similar efficacy. That is to say, at the time of invention antihistamines, like cetirizine, loratadine, fexofenadine, and azelastine, were thought to be approximately equal in efficacy. For example, one reference—upon which Dr. Schleimer relies (EX1003, ¶¶27, 53)—found in a meta-analysis that “[t]here are no significant advantages in efficacy among the 4 second-generation antihistamines [the four just listed] approved for children 11 years of age or younger.” EX1041, 9. Although another meta-analysis acknowledged one outlier, it found that the majority of studies “have demonstrated azelastine to be equally effective as [oral antihistamines] cetirizine, ebastine, loratadine, and terfenadine.” CIP2042, 4. In short, there was no reason whatsoever for a POSA to expect that azelastine would somehow work differently with a steroid than the many oral antihistamines cited in the studies that found no additional benefit.

103. Likewise, every steroid was thought to be equal in efficacy. Dr.

Schleimer relies on *potency*—which merely refers to the concentration of the drug needed to obtain the same result. EX1003, ¶¶59-61. But in practice, each of these steroids is administered at a dosage that achieves a normalized efficacy; they are not distinguishable from one another. CIP2047, 3. Dr. Schleimer has not offered any reason why a POSA would select a steroid based on *in vitro* potency studies when *in vivo* clinical studies showed equivalence. I cannot think of any justification given the known equivalence of these drugs.

104. Second, multiple fixed-dosing studies used fluticasone propionate as the steroid in question. *See* EX1034, 1; EX1040, 1. These studies—Benincasa and Ratner 1998—found no improvement when two different antihistamines (cetirizine and loratadine) were used with fluticasone. As I explained above, the art did not show any difference in efficacy between azelastine, cetirizine, and loratadine. EX1041, 9; CIP2042, 4. Accordingly, a POSA had no reason to think that azelastine would achieve a result different from those found in Benincasa and Ratner 1998.

105. Third, even if one accepts that loratadine and beclomethasone dipropionate—the combination studied in both Drouin and Brooks, which I refuted above—achieved some true benefit, this is far from indicative that azelastine and fluticasone would do the same. Indeed, Dr. Schleimer admitted at trial that it is

impossible to extrapolate from studies of one combination about the efficacy of another antihistamine/steroid combination. CIP2019, 34:8-11.

106. As I show below, Dymista[®] provides more complete relief of AR symptoms than any other treatment. It achieves this improvement by way of its unexpectedly improved efficacy and onset, which is accompanied by significantly reduced side effects.

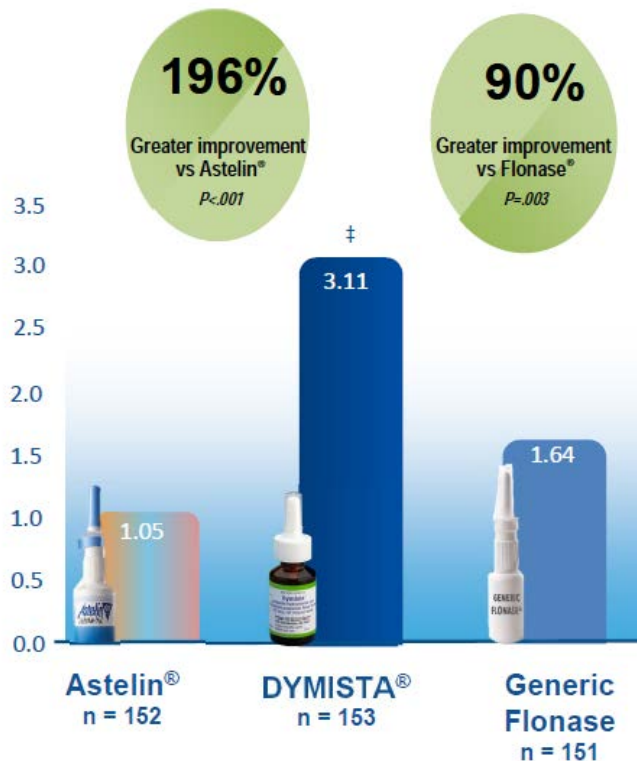
2. Dymista[®] shows an unexpected improvement in efficacy when compared to the closest prior art.

107. When compared to the closest prior art, Dymista[®] exhibits clinical effects unpredicted and unprecedented in the art. Because the closest prior art would have led a POSA to expect no meaningful improvement in efficacy when compared to fluticasone, Dymista[®]'s substantial improvement is different in kind from what a POSA expected at the date of invention.

108. As I explained above, numerous studies established that adding an antihistamine to a corticosteroid was no more effective than the steroid alone. *See supra*, Section VIII.B. These studies included fluticasone, but never azelastine. Again, the co-administration studies—Juniper 1989, Simpson, Benincasa, and Ratner 1998—did not find any meaningful additional benefit when an antihistamine was added to a steroid. *Id.* The findings of the two studies that claimed a benefit—Drouin and Brooks—were not credible for the reasons I explained above. *Id.* That is why even expert reviewers concluded, after reviewing

all of the relevant literature, that the addition of antihistamines to steroids would not improve upon the steroid. CIP2041, 4-5; CIP2042, 2.

109. Dymista[®], a commercial embodiment of the challenged claims, unexpectedly exhibits a substantial improvement of approximately 40% over fluticasone alone. CIP2045, 3. When one accounts for placebo (which, again, is used in clinical studies as a control to remove false positives), the improvement of Dymista[®] over fluticasone increases to 90 percent, as shown in the chart below (adapted from CIP2045, 3).



110. A POSA would have found these results to be unexpected because the closest prior art showed that the addition of an antihistamine to a steroid did not

confer meaningful benefit beyond the steroid. *See Supra* Section VIII.B. Moreover, because a POSA would have expected no improvement based on the art, it is my opinion that the unexpectedly improved efficacy of Dymista[®] is different in kind from what was expected in the art as of 2002.

111. Counsel has informed me that a patentee does not need to compare the invention to something that did not exist in the prior art. Therefore, it is my opinion that Dr. Schleimer's reliance on Ratner 2008 is misplaced. Ratner 2008 was the first and only instance I am aware of (aside from the Dymista[®] studies) in which azelastine and fluticasone were provided in a fixed manner but in separate devices. *See* EX1045, 1. The art that Dr. Schleimer relies on explicitly taught that, when azelastine was used with another drug, it should only be used as an "on demand" therapy. EX1024, 90; EX1022, 5. As shown in Juniper 1997, "on demand" (or "as needed") therapy required only infrequent use of the antihistamine. EX1031, 7. Simply put, Ratner 2008 is not indicative of what was happening in the art prior to the date of invention.

112. Ratner 2008 confirms my view that the dosage regimen in Ratner 2008 was distinct from any practice known prior to the date of invention. The authors of Ratner 2008—the same team as Ratner 1998—explained that "[t]he significant improvement in the TNSS with combination therapy relative to the individual agents alone is in contrast to previously published studies that found no

advantage with an oral antihistamine and an intranasal corticosteroid in combination.” EX1045, 1. The authors also concluded that “[t]he use of intranasal azelastine in combination with intranasal fluticasone produced an unanticipated magnitude of improvement in rhinitis symptoms among patients...” *Id.*, 7. In other words, six years after the date of invention, the Ratner 2008 authors still (1) found their results to contrast with the previous studies (like those I discussed above); and (2) found these results unexpected.

3. Dymista[®] exhibits an unexpectedly fast onset of action compared to the closest prior art.

113. Nothing in the art suggests that, by using a fast-acting antihistamine and a slow-acting steroid together, one can achieve an onset *faster* than the onset of the antihistamine. The closest prior art co-administration studies did not suggest that co-administration would accelerate the onset as compared to the onset of the antihistamine alone. *See generally* EX1036; EX1039; EX1040; EX1045.

114. In the district court litigation, I testified regarding the unexpected onset of action of Dymista[®]. I explained that the art established that, in clinical *in vivo* use, azelastine was known to have an onset of action of three hours. CIP2021, 94:23-95:17. I also explained that Dymista[®] has a much faster onset of 30 minutes. *Id.*, 95:4-17. This is a difference in kind from what was expected in the art at the date of invention.

115. With regard to azelastine and fluticasone, which had clinical onsets of 3- and 12-hours, respectively (EX1008, 3; EX1010, 5), a POSA in 2002 would have anticipated that co-administration (either separately or in a fixed-dose combination) would result in azelastine's 3-hour onset. Nothing in the art suggested that, by co-formulating these two drugs, a *faster* onset could be achieved.

116. Unexpectedly, Dymista[®] has an onset of 30 minutes, an onset that is six times faster than the onset of azelastine. CIP2066, 18; EX1008, 3. Because in 2002 no difference would have been expected in Dymista[®]'s onset as compared to azelastine's onset, it is my opinion that the rapidity of Dymista[®]'s onset is a different kind of result than what a POSA would have expected.

117. I recognize that Dr. Schleimer attempts to portray azelastine's onset as being 15 minutes, but the art he relies upon—ARIA, Cauwenberge, and Falser—does not support his position. *See, e.g.*, EX1003, ¶¶55, 64, 76, 84. As I have already explained, the passage in ARIA that Dr. Schleimer cites to support his claim of a 15-minute onset cites to a single reference—Weiler. *See* EX1024, 90; *id.*, 178, n.2088. Weiler says absolutely nothing about a 15-minute onset, but rather states that azelastine merely “showed a trend toward statistical significance ... *from* the second [hour] through the first ten hours after the initial dose.” CIP2046, 1. A POSA would recognize that this reference does not support a 15-minute onset

for azelastine. The passage in Cauwenberge was written by the same authors as ARIA, includes much of the same language, and offers no additional data regarding the onset of azelastine. EX1022, 4. Indeed, as explained by the FDA prior to the date of invention, onset must be adjudged across the entire symptom spectrum and compared to a placebo. CIP2129, 17. Neither Cauwenberge nor ARIA contain any data that meets this requirement.

118. The other reference Dr. Schleimer relies on is Falser. *See* EX1003, ¶64 (citing EX1015). Again, the reference Dr. Schleimer points to does not support a claim that azelastine has a 15-minute onset. To be clear, this reference asked patients to measure their symptom scores before a first morning dose and after a second evening dose. EX1015, 2 (“The severity of symptoms was documented by each patient in diary cards each morning before drug application and each evening 15 min after drug application.”). The passage Dr. Schleimer relies upon states: “Symptom relief was *particularly evident after the daily evening administration* of azelastine; patients were asked to make this recording into their diary cards just 15 minutes after administration of treatment.” *Id.*, 6. Read in context, this reference does not claim a 15-minute onset.

119. First, Falser only states that symptom relief was most effective after the second daily dose of azelastine—which does not suggest an onset of 15 minutes. EX1015, 6. Second, the passage does not even claim a 15-minute onset; it

only states that patients were asked to record their observations starting at “just 15 minutes after administration of treatment.” *Id.*

120. In any event, at the time of invention, it was understood that “onset of action” was defined as “the point at which patients might reasonably expect to see a meaningful decrease in their allergic rhinitis symptoms. Statistically, it is the first time point after initiation of treatment when the drug demonstrates a change greater than the placebo treatment from baseline in the primary efficacy endpoint.” CIP2129, 17. Falser did not have a placebo group, which prevented the study from establishing a clinical onset of action. *See* EX1015, 3.

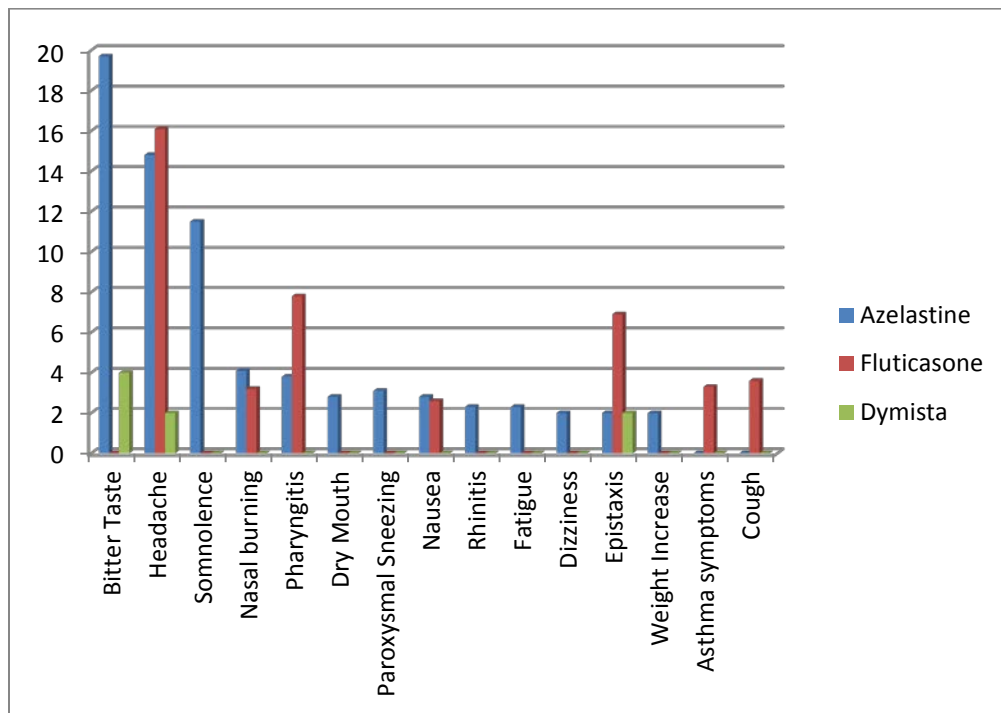
121. I also observe that, to the extent Dr. Schleimer believes that Ratner 2008 has any bearing on the state of the prior art, this study is silent as to the onset of action. *See generally* EX1045. Accordingly, even if a POSA were to credit Ratner 2008’s efficacy data, it does not suggest an accelerated onset.

4. Dymista[®] has unexpectedly reduced side effects as compared to either azelastine or fluticasone monotherapies.

122. A POSA at the date of invention would have expected that the use of two drugs together would yield increased side effects as compared to those exhibited by either drug alone. For example, one reference explained that “[t]he use of 2 drugs will always increase the risk of adverse drug reactions.” CIP2043, 13. This expectation is confirmed by the co-administration studies I discussed above, where frequently more patients experienced increased side effects. EX1035,

8; EX1036, 5; EX1039, 6. Ratner 2008, the post-invention reference Dr. Schleimer relies on, confirms this expectation of an increase in side effects: it showed near-additive and synergistic increases in headache and bitter taste, respectively. EX1045, 5.

123. While the closest prior art showed an increase in side effects, Dymista[®] unexpectedly shows no increase in side effects as compared to the monotherapies. In fact, it shows a reduced side effect profile as compared to those of either of the individual active ingredients. For example, the FDA-approved labels for Astelin[®] (azelastine) and Flonase[®] (fluticasone) show the following side effects:



See EX1008, 3; EX1010, 7; CIP2066, 6.

124. A POSA would recognize that fluticasone and azelastine have high incidences of bitter taste, headache, somnolence, nasal burning, pharyngitis and epistaxis. And between the two drugs, at least fourteen different symptoms occurred in more than 2% of patients.

125. A comparison of the two monotherapies to Dymista[®] reflects a substantial and surprising reduction in side effects from the combination as compared to the commercially-available monotherapies. I also observe that the azelastine and fluticasone data recorded in the Dymista[®] label reflect the two drugs reformulated with the claimed excipients, not the excipients found in their commercial forms. Surprisingly, when placed in the Dymista[®] formulation, even the monotherapies exhibit substantially reduced side effects as compared to their prior art forms.

126. A few side effects are worth noting specifically. In commercial azelastine, patients experienced dysgeusia (bitter taste) at a 19.7% rate, while in Dymista[®] it is 4%. This five-fold decrease was surprising, because the bitter taste was known to be a characteristic of the azelastine molecule. This side effect was so bad that patients complained of the bad taste (and, thus, poorly complied with treatment) even when using azelastine eye drops.

127. Likewise, azelastine and fluticasone showed an incidence of headache at 14.8% and 16.1%, respectively. Dymista[®] is only 2%. This seven- to eight-fold decrease was surprising.

128. Finally, azelastine exhibited somnolence in 11.5% of patients. EX1008, 3. As emphasized in the Dymista[®] label, somnolence occurred in less than 1% of patients. CIP2066, 6. Again, this eleven-fold decrease was surprising.

129. In my opinion, because a POSA would have expected an increase in side effects, but Dymista[®] shows a substantial reduction in those same side effects, these surprising decreases are a difference in kind from what a POSA would have expected at the time of invention.

C. Dymista[®] satisfies a long-felt but unmet need in the treatment of AR.

130. I understand that, when there is a long-felt, but unmet need in the art that is satisfied by an invention, that satisfaction is indicative of non-obviousness. I understand that in order to show a long-felt need, (1) the need must have been persistent and recognized by persons of ordinary skill in the art; (2) the need must not have been satisfied prior to the invention; and (3) the invention must actually satisfy any long-felt need(s). Here, in my opinion, there were long-felt needs for (1) more effective, (2) faster-acting, and (3) safer drugs to treat AR.

1. Dymista[®] satisfies the long-felt need for more effective AR treatment.

131. In my opinion, the art established a need for more effective AR treatment. Indeed, steroids were known as the most effective treatment, but they were not strong enough to manage patients' most severe symptoms. This fact is confirmed in the co-administration studies that I described above. Indeed, Juniper 1989 showed that beclomethasone dipropionate was inadequate to treat patients' most severe AR symptoms because it sought a treatment better than beclomethasone alone. *See* EX1039. The inability to improve efficacy beyond that of steroids was repeatedly shown in the art through 1998, as evidenced by the studies I discussed above. *See supra*, Section VIII.B.

132. For at least the 13 years between Juniper 1989 and the date of invention, no AR treatment was shown to be more effective than a steroid alone. Section VIII.B. But Dymista[®] was shown to be significantly and meaningfully more effective than a steroid alone. CIP2045, 3; CIP2052, 1. Accordingly, it is my opinion that Dymista[®] satisfies a need, unmet for at least 13 years, for an AR treatment superior to steroid monotherapy.

2. Dymista[®] satisfies the long-felt need for an AR treatment with a faster onset.

133. There was also a need for an AR treatment that had a faster onset across all symptoms than what was available at the time of invention. As Dr.

Schleimer admits, “delayed onset of action causes many patients to either stop treatment or to perceive that they do not work well at controlling the symptoms of AR.” EX1003, ¶54.

134. Dr. Schleimer’s statement is true; onset of action across all symptoms is an important characteristic of AR treatments. For example, it was known that intranasal decongestants had an onset of less than 10 minutes, but they did not work on itching, sneezing, or runny nose. EX1019, 28. Meanwhile, oral antihistamines had a fast onset of action, but did not manage congestion. *Id.*, 23. Azelastine, which worked well on itching, sneezing, and runny nose, and may have had some efficacy on congestion, had an established onset of three hours. EX1008, 3. And although steroids worked on all four symptoms, they had a very slow onset of action. EX1024, 92. Thus, even to the extent that a patient happened to use both azelastine and fluticasone together prior to the date of invention, the onset of action was still three hours for the pair.

135. Dymista[®], as an embodiment of the claims, meets this need for a faster onset across all four primary symptoms of AR. As I explained above, its FDA-approved onset of action is 30 minutes, and this onset is across all four symptoms. CIP2066, 18. This is six times faster than the onset of action for the co-administration of the separate monotherapies, which further confirms that

Dymista[®] is the first to satisfy the need for a fast-onset treatment across all four symptoms.

3. Dymista[®] satisfies the long-felt need for an AR treatment with fewer side effects.

136. For years prior to the date of invention, patients and researchers sought an AR treatment that did not exhibit significant side effects. This need is specifically shown by the evolution of oral antihistamines and intranasal steroids.

137. With respect to oral antihistamines, I explained above that the first-generation antihistamines were known to cause severe somnolence. EX1024, 84-85. From the early 1990s to the time of invention, several new second-generation antihistamines were released specifically with the goal of reducing the incidence of somnolence associated with this drug class. *Id.*, 85.

138. Steroids were known for oral and intranasal use. Beginning in the late 1970s, physicians began to use steroids in intranasal dosage forms because use of the oral forms risked significant systemic side effects. *Id.*, 82. And even in an intranasal form, it was quickly observed that certain steroids—like dexamethasone—still caused systemic side effects, such as growth suppression, cataracts, and glaucoma. *Id.*, 92. Accordingly, efforts were directed to finding the safest topical steroids. Throughout the 1980s and 1990s, a series of these drugs was released: beclomethasone dipropionate, triamcinolone acetonide, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and ciclesonide, among

others. Nevertheless, even the later steroids, like fluticasone, were known to cause substantial side effects:

**Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate
in Controlled Clinical Trials With FLONASE Nasal Spray
in Patients ≥4 Years With Seasonal or Perennial Allergic Rhinitis**

	Vehicle Placebo (n = 758) %	FLONASE 100 mcg Once Daily (n = 167) %	FLONASE 200 mcg Once Daily (n = 782) %
Headache	14.6	6.6	16.1
Pharyngitis	7.2	6.0	7.8
Epistaxis	5.4	6.0	6.9
Nasal burning/nasal irritation	2.6	2.4	3.2
Nausea/vomiting	2.0	4.8	2.6
Asthma symptoms	2.9	7.2	3.3
Cough	2.8	3.6	3.8

Other adverse events that occurred in ≤3% but ≥1% of patients and that were more common with fluticasone propionate (with uncertain relationship to treatment) included: blood in nasal mucus, runny nose, abdominal pain, diarrhea, fever, flu-like symptoms, aches and pains, dizziness, bronchitis.

EX1010, 7. The 200 mcg dosage is the recommended dose; 100 mcg is the reduced dosage to be used after a patient's symptoms are controlled.

139. The development of second-generation antihistamines and intranasal corticosteroids in the decades leading up to the date of invention shows that there was a long-felt need for drugs that offered safer treatment for AR. That need was not solved by the existence of azelastine and fluticasone monotherapies. As I explained above, both of these drugs had significant side effect profiles. *Supra*, ¶¶73, 135.

140. Indeed, to the extent that Dr. Schleimer believes that knowledge of the results of the Ratner 2008 study can somehow be extrapolated back from 2008 to

the POSA's knowledge at the invention date, Ratner 2008 only serves to confirm that separate administration of azelastine and fluticasone did not satisfy this need. For example, Ratner 2008 reported bitter taste in 8.2% of the azelastine group, 2% of the fluticasone group, and 13.5% of the co-administration group, reflecting a *synergistic* increase in side effects. EX1045, 5. Likewise, 4.1% of patients in the azelastine group reported headaches, 4.0% of the fluticasone group reported the same, and 5.8% of patient reported this side effect in the co-administration group, indicating a near-additive increase in side effects. *Id.*

141. Meanwhile, as I have explained above, Dymista[®] exhibits substantially reduced side effects as compared to either monotherapy. Dymista[®] works on all symptoms with virtually no adverse effects shown. This is the first AR treatment to satisfy the need for reduced side effects.

D. FDA was skeptical of Dymista[®].

142. Years after the invention date, FDA was skeptical that an azelastine/fluticasone fixed-dose combination product could obtain approval. When Meda submitted Dymista[®] for approval, the application was reviewed by FDA's Division of Pulmonary and Allergy Products ("DPAP"), where I worked during my time at FDA. The documents discussed below are a typical type of communication document between FDA and pharmaceutical companies seeking marketing approval for new drug products.

143. At the time Meda submitted its application to FDA, Dymista[®] was the first fixed-dose combination that DPAP had ever considered. The product was so unexpected that DPAP did not even have a review process in place, and thus eventually had to develop new rules for review of similar products. *See generally* CIP2165. But even before DPAP developed these new rules, it raised several concerns about Dymista[®].

144. First, FDA stated that the very bases Dr. Schleimer relies on were not sufficient bases for approval: Meda could not rely on rationales “such as mechanism of action, onset of symptom relief, etc.” to justify approval for Dymista[®]. CIP2165, 5. Consistent with the statements in the art above regarding complementary mechanisms, FDA’s reviewers recognized that the simple fact that two drugs work differently does not mean that they will work better together. Indeed, FDA required fixed-dose combination drugs (in other fields of medicine) to satisfy the so-called “combination rule,” which required *both* drugs to contribute to the efficacy of a combination product. CIP2165, 4; CIP2164, 2. Again, the art established an expectation that an antihistamine/steroid combination would not satisfy this rule.

145. Second, FDA stated its concern that Dymista[®] “eliminates flexibility with dosage titration and potentially exposes patients to unnecessary medication, and thus unnecessary risk.” CIP2165, 5. These concerns, stated years after the

invention date, mirror exactly the problems with combination products raised by Shenfield prior to the invention date. CIP2043, 12-13.

146. FDA’s skepticism reflects the fact that, even in the years following Cipla’s invention, the concerns in the art regarding increased side effects, no improvement in efficacy, and reduced flexibility had not been resolved. And indeed, they were not resolved until Dymista[®] was approved under DPAP’s new pathway—a pathway that, to date, no other drug product has successfully navigated.

147. Based on my experience at FDA, these issues are not run-of-the-mill FDA concerns. They are related specifically to the claimed invention in that the allergy field did not have, or even anticipate, a product like Dymista[®], even years after the filing date.

E. Dymista[®] has been widely praised in the industry as the new gold standard for the treatment of AR.

148. Editors of the world’s leading allergy journal—the *Journal of Allergic and Clinical Immunology* (“JACI”)—published an independent review of the clinical data on what became Dymista[®]. After noting that steroids alone (not steroids and antihistamines) had previously been viewed as the most effective therapy for treating AR, and reviewing the data from the FDA pivotal studies, the Editors declared Dymista[®] to be “the drug of choice for the treatment of AR.” CIP2052, 1. Because the various steroids available at the time of invention were all

equally effective, none of them had been praised as the best treatment. To my knowledge, no other product has received similar praise.

149. I agree with the JACI editors. Dymista[®] is the single best AR treatment available.

F. Dymista[®], Duonase, and several Indian copycat products are covered by the challenged claims.

150. I understand that copying can be indicative of non-obviousness. Although I understand that another expert discusses the formulation aspects of the copycat products, I offer my opinions on the clinical aspects of copying here.

151. I have discussed Dymista[®] in detail above. I also understand that Dymista[®] is a domestically licensed version of Duonase, Patent Owner Cipla's Indian product. The Duonase label shows that contains the same active ingredients as Dymista[®]. CIP2070, 1. In my opinion, both of these products meet the clinical aspects of the challenged claims.

152. Other than the term "pharmaceutical," which I discussed above (*see* Section VII), the only limitation in the challenged claims that is uniquely clinical is the limitation in claim 24 that recites "wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated." EX1001, claim 24. Dymista[®] and Duonase are both used to treat AR, and AR is a condition for which both antihistamines and steroids are indicated. Accordingly, it is my opinion that both

products are embodiments of claim 24. The objective indicia I discussed above, and in this section, therefore bear a nexus to the claims.

153. In my opinion, many other copycat products also support the non-obviousness of the challenged claims. At least three companies seek to develop copycat products in the United States, while numerous other companies have openly copied the claimed invention in India.

154. First, in the United States, I understand that Apotex has admitted infringement of most of the challenged claims of the '620 patent. I understand that Teva and Perrigo also seek to copy Dymista[®]. Given that Dymista[®] meets the clinical claim limitation I discussed earlier in this section, and Teva and Perrigo must also meet those limitations to obtain FDA approval of their proposed generic products, it is my opinion that Teva and Perrigo will also meet each of these limitations.

155. Second, Duonase—Patent Owner Cipla's commercial embodiment in India which launched in 2004 (CIP2070)—has been subject to numerous copycats, suggesting to me that again, only after the specific formulation was made available to imitators, were other formulators able to develop a fixed-dose combination product as recited in the challenged claims.

156. Combinase AQ is manufactured by Zydus Cadila. Combinase AQ is a nasal spray that incorporates azelastine hydrochloride, fluticasone propionate, and

various excipients. CIP2031, 2. The label explicitly states that Combinese AQ “is indicated for the management of allergic rhinitis.” *Id.* In my opinion, Combinese AQ is a copy of Duonase and it falls within the scope of the clinical limitation I discussed above.

157. Azeflo is manufactured by Lupin. Azeflo is a nasal spray that incorporates azelastine hydrochloride, fluticasone propionate, and various excipients. CIP2031, 20. The label does not explicitly state an indication, but the only one for which both of these active ingredients would be incorporated into a nasal spray is allergic rhinitis. In my opinion, Azeflo is a copy of Duonase and it falls within the scope of the clinical limitation I discussed above.

158. Nazomac-AF is manufactured by Macleods. Nazomac-AF is a nasal spray that incorporates azelastine hydrochloride, fluticasone propionate, and various excipients. CIP2031, 34. The label clearly states that this is a nasal spray for use in treating allergic rhinitis. *Id.* 30-33. In my opinion, Nazomac-AF is a copy of Duonase and it falls within the scope of the clinical limitation I discussed above.

159. Floresp-AZ is manufactured by Emcure. Floresp-AZ is a nasal spray that incorporates azelastine hydrochloride, fluticasone propionate, and various excipients. CIP2031, 10. The label clearly states that Floresp-AZ is a nasal spray

for use in treating allergic rhinitis. *Id.* In my opinion, Floresp-AZ is a copy of Duonase and it falls within the scope of the clinical limitation I discussed above.


160. Ezicas-AZ is manufactured by Intas. Ezicas-AZ is a nasal spray that incorporates azelastine hydrochloride, fluticasone propionate, and various excipients. CIP2031, 15. The label clearly states that Ezicas-AZ is a nasal spray for use in treating allergic rhinitis. *Id.* In my opinion, Ezicas-AZ is a copy of Duonase and it falls within the scope of the clinical limitation I discussed above.

161. Nasocom-AZ is manufactured by Dr. Reddy's Labs. Nasocom-AZ is a nasal spray that incorporates azelastine hydrochloride, fluticasone propionate, and various excipients. CIP2031, 5. The label clearly states that Nasocom-AZ is a nasal spray for use in treating allergic rhinitis. *Id.* In my opinion, Nasocom-AZ is a copy of Duonase and it falls within the scope of the clinical limitation I discussed above.

*Inter Partes Review of U.S. Patent No. 8,168,620
Second Declaration of Dr. Warner Carr (Exhibit 2147)*

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct to the best of my knowledge.

Date: November 20, 2017

A handwritten signature in black ink, appearing to read "W. Carr", is written over a horizontal line.

Warner Carr, M.D.