

UNITED STATES PATENT AND TRADEMARK  
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BEFORE THE PATENT TRIAL AND APPEAL  
BOARD

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ARGENTUM PHARMACEUTICALS LLC

Petitioner

v.

CIPLA LTD.

Patent Owner

Patent No. 8,168,620

Issue Date: May 1, 2012

Title: COMBINATION OF AZELASTINE AND STEROIDS

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*Inter Partes* Review No.: IPR2017-00807

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**SECOND DECLARATION OF ROBERT P. SCHLEIMER, Ph.D.**

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## **I. Introduction**

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

2. I have been retained as an expert witness on behalf of Argentum Pharmaceuticals LLC for a *inter partes* review of U.S. Patent No. 8,168,620 (EX 1001). I am being compensated for my time in connection with this IPR at my standard consulting rate, which is \$400 per hour for any consulting and \$600 per hour for any deposition appearances. I understand that my declaration accompanies a petition for *inter partes* review involving the above-mentioned U.S. Patent.

## **II. Background and Qualifications**

3. My background and qualifications remain essentially unchanged from my first declaration, EX1003. My most recent *curriculum vitae* is concurrently submitted with this document as EX1163.

## **III. Basis for My Opinions**

4. In formulating my opinion, I reviewed Dr. Carr's Second Declaration (CIP2147), his deposition transcript (EX1142), and relied on the documents cited herein.

#### **IV. Summary of My Opinions**

5. It remains my opinion that claims 1, 5-6, 24-26 and 29<sup>1</sup> would have been obvious to a person of ordinary skill in the art (POSA) in view of the combined teachings of Segal, Hettche and Phillipps for the reasons I gave in my first declaration (EX1003) and the additional reasons I give herein. Segal, as well as Cramer expressly suggested a single nasal spray containing the active ingredients of Dymista®, azelastine hydrochloride (“azelastine”) and fluticasone propionate (“fluticasone”). The clinical art also establishes the use of these drugs together for the treatment of allergic rhinitis. However, it did not mandate the inflexible approach of only treatment by the individual monotherapies. The complementarity of antihistamine/steroid pairing and particularly of azelastine/fluticasone, the anti-inflammatory properties of azelastine when topically applied, and the expected convenience and compliance would also have prompted a POSA to develop a single nasal spray containing these ingredients.

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<sup>1</sup> Dr. Carr’s contention that I agree with him that claims 4 and 42-44 are non-obvious because I did not discuss their obviousness is presumptuous. Counsel did not ask me to consider these claims because it asked a formulation expert to weigh in on them. To be clear, I consider the combination of azelastine and fluticasone in a formulation suitable for nasal administration to be obvious for claims 4 and 42-44 for the same reasons as all the claims discussed herein.

## **V. Person of Ordinary Skill in the Art and Obviousness**

6. I stand by my previous testimony regarding the POSA described in my first Declaration. EX1003 ¶¶11-12. Dr. Carr suggests that “knowledge of and experience in treatment is more relevant in the context of the ‘620 patent than laboratory experiments.” CIP2147 ¶19. I agree that clinical knowledge is relevant to a POSA in the present context. I disagree to the extent he suggests that knowledge of the cellular basis of allergic rhinitis (AR) is somehow less relevant to the development and use of pharmaceuticals to treat this condition.

## **VI. The early and late phase reactions of AR were well known and clinically relevant prior to June 14, 2002**

7. Dr. Carr’s assertion that “several laboratory concepts” upon which I rely “were tested in vivo and were found not to affect patients” (*Id.* ¶19) is wrong and a mischaracterization of the state of the art prior to June 14, 2002. The early phase reaction (EPR) and late phase reaction (LPR) are not merely laboratory concepts as Dr. Carr would have it, but are established phases of AR (AR) that can in fact be clinically distinguished. EX1041, 455; EX1035, 341; EX1003 ¶¶27-28. For example, if a person with seasonal allergies to ragweed steps outdoors in the morning on the first day of ragweed season, that person can experience immediate sneezing and runny nose (the EPR), while later that evening can experience complete nasal blockage and inability to sleep due to her symptoms (LPR).

Another example is when a person allergic to cats visits a friend with cats for a short time; they will likely experience both phases of allergic response.

8. In my first declaration, I discussed how the EPR occurs when mast cells in the nose release histamine, tryptase, prostaglandin D2 and other mediators. Antihistamines exert their effects on EPR symptoms primarily by blocking histamine from binding to H<sub>1</sub>-histamine receptors. By contrast, the LPR is characterized by continued release of cytokines by mast cells and by extensive infiltration of inflammatory cells from the blood to the site of inflammation and also by activation of migrating and resident cells. Corticosteroids work by setting in motion a chain of events that interrupts the complex cascade of events causing inflammation. EX1003 ¶¶27-28; EX1041, 455; CIP2041, 6-8.

9. Even in cases where the phases overlap in time and could be difficult to clinically distinguish due to overlapping symptoms, that does not mean that topical antihistamines were understood to be ineffective or provide no additional benefit over intranasal steroids, as Dr. Carr asserts. CIP2047 ¶45. Because the two phases have different etiologies, a patient suffering from, *e.g.*, severe AR, can still benefit from a combination of antihistamine and intranasal steroids (INS) for the reasons I previously outlined. INS were well known before June 2002 to be effective in treating AR. EX1003 ¶¶53-54. However, while antihistamines have a fast onset of action and work quickly to provide relief from EPR symptoms, topical

steroids can take a week or more to inhibit LPR and all symptoms of AR. *Id.*; EX1024, S231-S232; EX1010, 2; CIP2042, 1567. During that one to two-week period—the same period of time over which Dymista® was later tested—the prior art shows the combination of antihistamine and INS had an additive effect in relieving symptoms of AR. As I show below, this known concept of complementary mechanisms of action explains the results of all studies, including those which did not find benefit to the combination of antihistamine and INS. By contrast, Dr. Carr simply tries to discount and disparage studies that don't agree with his viewpoint.

**VII. The prior art clearly suggests a combined nasal formulation of azelastine and fluticasone**

10. My understanding of obviousness is set forth in my first declaration. EX1003 ¶¶42-44. I have been further advised by counsel that when a reference discloses a combination of products, even from among many possible combinations, the combination is obvious.

11. In my first declaration, I pointed out that Segal (EX1012) discloses pharmaceutical formulations for nasal administration that contain a corticosteroid and an antihistamine. EX1003 ¶¶80, 45, 32-40. Included among those formulations were nasal sprays. *Id.* ¶¶80, 45, 36. I also pointed out that Segal discloses that the corticosteroid can be fluticasone propionate and the antihistamine can be azelastine. *Id.* Cramer (EX1011) contains the same disclosures. *Id.* ¶¶78-

79. Dr. Carr does not dispute any of these disclosures and does not mention Segal even once in his 71-page declaration (CIP2147). Hence, his arguments that a POSA would not have selected azelastine (*Id.* ¶¶86-94) or that my views are driven by hindsight (*Id.* ¶82) are flat wrong. Segal and Cramer both suggest using azelastine in combination with fluticasone propionate as a single nasal spray. EX1012, 2:22-26, 3:19-20, claims 2 and 4; EX1011, 2:34-35.

12. Because Segal discloses the combination of a nasal pharmaceutical formulation of fluticasone propionate and azelastine, it remains my opinion that this combination is obvious. It also remains my opinion that claims 1, 5-6, 24-26, and 29 would have been obvious over Hettche, Phillips and Segal together for the reasons given in my first declaration. *Id.* ¶¶45-51, 80. Moreover, as discussed in my first declaration, and as I elaborate below, the clinical literature as a whole also supports my contention that the claims of the '620 patent would have been obvious.

#### **VIII. The beneficial effect of the combination of antihistamine with intranasal steroid was known in the art**

13. My discussion in my first declaration of clinical knowledge and practice concerning fluticasone propionate, azelastine and the treatment of AR with the combination of INS and antihistamines showed it to be consistent with Segal (and Cramer). *Id.* ¶¶52-91. Dr. Carr spends pages and pages of his declaration



trying to escape the simple fact that prior to June 14, 2002, antihistamines and INS were routinely combined in normal clinical practice (*see* EX1019, 505; EX1022, 125; EX1024, S230), as they still are today. Dykewicz, *e.g.*, expressly recommends the use of INS with intranasal antihistamines and discusses only azelastine. EX1019, 505. Their combined use then and now reflects the well-formed and durable perceptions of both clinicians and patients that combining these two types of drugs provides greater relief in some cases than using only one or the other. I therefore disagree with Dr. Carr that a POSA would have known the co-administration of antihistamines and steroids provides no meaningful benefit over steroids alone or that treatment guidelines and practices would have discouraged a POSA to pursue a fixed dose combination product.

14. In his declaration, Dr. Carr boldly states that complementarity of action “as it applied to the co-administration of antihistamines and steroids was squarely rejected in the art prior to the date of invention.” CIP2147 ¶48. This misleading statement finds little support in the prior art discussed by Dr. Carr and myself in our respective declarations. As shown below, studies focusing on the first 1-2 weeks of combined treatment with antihistamine and INS showed additive effects whereas longer trials showed little to no additive effects. In addition, these additive effects were most apparent in reduced symptoms of sneezing and itchy nose, two of the EPR symptoms that antihistamines are most effective at treating.

EX1023, S386; see also EX1035, 341; EX1038. When authors focused solely on mean total nasal symptom score (TNSS), these effects were of course less prominent, being in effect “diluted” by antihistamine’s lack of efficacy against nasal congestion and lower efficacy against nasal discharge. Likewise, studies that focused symptoms at the end of the study period, especially those longer than a couple weeks would miss these effects. Finally, none of the studies considered azelastine.

15. For example, the Drouin study (EX1035) was a 7-day study of the combination of intranasal beclomethasone dipropionate (BDP) and loratadine versus intranasal BDP and placebo. It tested whether therapeutic efficacy could be maximized by combining drugs having “complementary effects” on different components of the allergic response, *i.e.*, the EPR and LPR. *Id.*, 341. Data was collected on days 3 and 7 in terms of total nasal score, total ocular score and total symptom score. *Id.*, 343. Table 2 (reproduced below) shows statistically significant reductions in total nasal score (day 3), nasal itching (days 3, 7), and sneezing (day 3). Based on these results, the authors concluded that “[p]atients treated with BDP plus loratadine achieved significantly greater ( $p<0.05$ ) relief of both nasal and non-nasal symptoms than those treated with BDP plus placebo.” *Id.*, 341 (Abstract). The combination therapy did not raise any safety concerns for

the authors who noted “both groups reported similar incidence and types of adverse effects.” *Id.*, 345.

**Table 2. Improvement in Symptom Scores at Days 3 and 7**

	Evaluation Day	Loratadine + BDP, %	Placebo + BDP, %	P Value
Total symptom score	3	54	46	.08
	7	68	58	<.05
Total nasal score	3	55	48	<.05
	7	66	59	NS
Nasal discharge	3	58	52	NS
	7	67	65	NS
Nasal stuffiness	3	43	40	NS
	7	62	55	NS
Nasal itching	3	61	48	<.05
	7	72	62	<.05
Sneezing	3	57	46	<.05
	7	67	59	.07
Total ocular score	3	53	45	NS
	7	70	57	<.05
Itching	3	48	39	NS
	7	65	52	<.05
Tearing	3	56	52	NS
	7	72	61	<.05
Redness	3	53	46	NS
	7	73	54	.07
Ear/palate itching	3	60	38	<.05
	7	80	50	<.05

NS = not significant.

16. Dr. Carr alleges (without showing any calculation) that the TNSS differential between the combination and steroid was approximately 0.4 points and characterizes that difference as clinically meaningless. CIP2147 ¶59. In fact, the

difference is 0.5 points,<sup>2</sup> and is at least as much if not more than the difference observed by Dr. Carr in his own paper (EX1037) reporting the Dymista® clinical trials. Dr. Carr's paper utilizes a 24-point rTNSS scale rather than the 12-point scale used in Drouin. When normalized to Dr. Carr's 24-point scale by multiplying by 2, the difference is 1 full point. In Dr. Carr's paper, in Table II (reproduced below) he presents a meta-analysis of the three individual trials reported and shows only a 0.8 point difference between the reduction of TNSS for Dymista® versus fluticasone propionate alone.

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<sup>2</sup> Based on the baseline TNSS scores for each arm of the study, I calculated the difference in TNSS scores as follows: (baseline TNSS) x ((% reduction in TNSS in Table 2)/100) = (the number of points reduction in symptoms). For BDP + placebo, the reduction is  $8.6 \times (0.48) = 4.1$ . For BDP + loratadine, the reduction is  $8.4 \times (0.55) = 4.6$ . The difference between the two arms is  $4.6 - 4.1 = 0.5$  points.

**TABLE II.** Total nasal symptom scores (baseline and change from baseline) for 3 randomized trials and the meta-analysis results (ITT population)

Treatment	No.	Baseline	Change from baseline	Difference	LS mean	95% CI	P value
Study MP4002							
MP29-02	207	18.3 (3.0)	-5.5 (5.2)	—	—	—	—
FP	207	18.2 (3.2)	-5.0 (4.7)	MP29-02, FP	-0.9	-1.74 to -0.07	.034
AZE	208	18.2 (3.5)	-4.1 (4.6)	MP29-02, AZE	-1.4	-2.22 to -0.54	.002
Placebo	209	18.6 (3.2)	-2.6 (3.9)	MP29-02, PLA	-2.7	-3.48 to -1.91	<.001
				FP, PLA	-1.8	-2.50 to -1.09	<.001
				AZE, PLA	-1.3	-2.04 to -0.60	.001
Study MP4004							
MP29-02	193	18.2 (3.3)	-5.6 (5.2)	—	—	—	—
FP	189	18.6 (2.9)	-5.0 (5.2)	MP29-02, FP	-1.0	-1.91 to -0.05	.038
AZE	194	18.5 (3.1)	-4.4 (4.6)	MP29-02, AZE	-1.0	-1.90 to -0.09	.032
Placebo	200	18.2 (3.1)	-2.8 (3.9)	MP29-02, PLA	-2.5	-3.33 to -1.67	<.001
				FP, PLA	-1.5	-2.34 to -0.69	.001
				AZE, PLA	-1.5	-2.31 to -0.71	.001
Study MP4006							
MP29-02	448	19.4 (2.4)	-5.6 (5.2)	—	—	—	—
FP	450	19.4 (2.4)	-5.1 (4.7)	MP29-02, FP	-0.6	-1.22 to -0.07	.029
AZE	445	19.5 (2.5)	-4.5 (4.8)	MP29-02, AZE	-0.7	-1.30 to -0.13	.016
Placebo	448	19.5 (2.4)	-3.2 (4.3)	MP29-02, PLA	-2.1	-2.70 to -1.57	<.001
				FP, PLA	-1.5	-2.03 to -0.95	<.001
				AZE, PLA	-1.4	-1.96 to -0.87	<.001
Meta-analysis (studies MP4002, MP4004, and MP4006)							
MP29-02	848	18.8 (2.9)	-5.7 (5.3)	—	—	—	—
FP	846	18.9 (2.8)	-5.1 (4.9)	MP29-02, FP	-0.8	-1.18 to -0.34	.001
AZE	847	18.9 (3.0)	-4.4 (4.8)	MP29-02, AZE	-0.9	-1.37 to -0.52	<.001
Placebo	857	19.0 (2.8)	-3.0 (4.2)	MP29-02, PLA	-2.3	-2.75 to -1.95	<.001
				FP, PLA	-1.6	-1.97 to -1.21	<.001
				AZE, PLA	-1.4	-1.78 to -1.02	<.001

Data are expressed as means (SDs). Difference from active treatment is given as LS mean treatment difference with associated 95% CIs and *P* values.

AZE, Azelastine (137 µg per nostril twice daily); FP, fluticasone propionate (50 µg per nostril twice daily); LS, least squares; MP29-02, azelastine/FP (137/50 µg/nostril twice daily); PLA, placebo.

17. Likewise, his comment that the improvement of 0.4 points is typically less than shown by placebo is also misleading. Large placebo effects are routinely observed in the treatment of AR, as can be seen in Table II of Dr. Carr's Dymista® paper: the meta-analysis of 3498 patients shows that the net improvement Dymista® produced over placebo is less than the improvement placebo produced over baseline by itself (compare the -3.0 point reduction obtained with placebo versus the -2.3 point reduction that Dymista® shows over placebo).

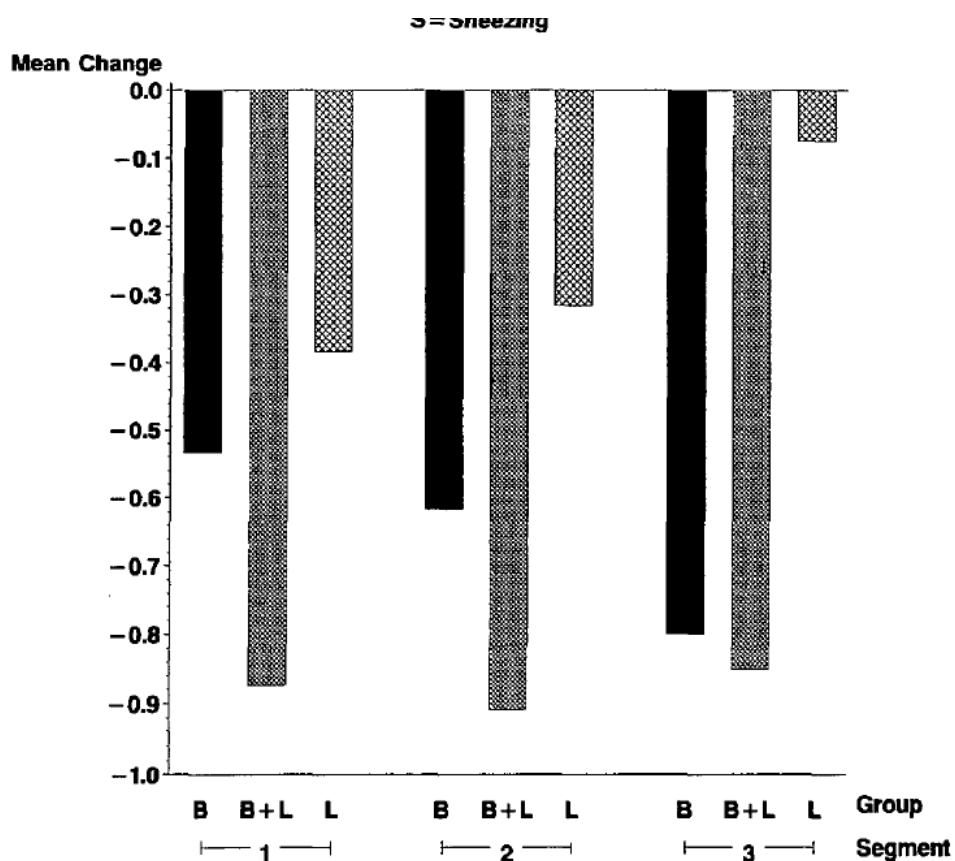
18. Furthermore, Drouin's 3-day nasal itching and sneezing scores show, respectively, a 1 point and 0.8 point reduction in symptoms (on a 12 point scale). The clinical significance of these and the TNSS results are supported by Drouin's

report that 39% of patients and 34% of physicians whose global evaluation at the endpoint of the study found the combination to be excellent compared to only 19% and 17%, respectively who found BDP plus placebo to be excellent. EX1035, 346 (Figs. 2-3).

19. Similar trends may be observed in the other short studies or in the early parts of longer studies. Brooks (EX1038), a two-week study of the combination of beclomethasone dipropionate (BDP) and loratadine for treatment of hay fever during ragweed season, is a good example of how complementarity between the two types of drugs works. In fact, this study was prompted by the authors' observation that "low dose corticosteroid primarily benefitted congestion, drainage, and eye symptoms, whereas antihistamine affected primarily itching and sneezing." *Id.*, 198. They postulated that the combination would at least treat more symptoms, but found "additive symptom suppression almost across the board." *Id.*

20. In this study, patients were divided between three groups: (1) BDP + a loratadine placebo, (2) loratadine + a BDP inhaler placebo, and (3) BDP + loratadine. *Id.*, 194. Congestion, runny nose, sneezing and itching were assessed twice a day and the effects examined in 3-day intervals. *Id.*, 195. Pretreatment days (-3 to -1) provided a baseline of symptoms, and the drug effects were examined in segments 1 (treatment days 2-4), 2 (treatment days 5-7) and 3 (treatment days 8-10). *Id.*

21. The combination showed superior control of itching and sneezing as shown in Figures 4 and 5. Figure 5 in particular shows how early on (days 2-4) the combination of antihistamine and steroid was clearly superior to the monotherapies in decreasing sneezing, but that the effect of the steroid alone increases over the next two segments until, in segment 3, it appears to account for the bulk of the response observed for the combination.



**Figure 5.** Sneezing Mean Change by Treatment Group and Study Segment. Group and Segment as in Figure 1.

22. Dr. Carr makes no serious attempt to analyze and rebut these findings, but focuses on the fact that although overall at the end of the study, patients in the monotherapy arms preferred beclomethasone to loratadine, this preference did not

reach statistical significance. According to him, because a POSA would have known that a steroid should be substantially better than antihistamine (based merely on general statements concerning efficacy in EX1019 and EX1024), a POSA would interpret the steroid-arm as somehow not working. Yet the POSA would attribute the improvement observed in the combination-arm to the steroid working properly in the co-administration population. EX2147 ¶60. A POSA would have recognized this statement is not true for all steroids over all time periods, and is sheer speculation by Dr. Carr, unsupported by any other evidence in Brooks. Even a cursory review of Figures 1-5 in Brooks comparing the performance of the steroid arm to the antihistamine arm and the combination indicate that the steroid arm is working properly. The study's authors conclude that for each symptom examined, "antihistamine produced a relatively modest benefit, almost always less than that produced by the topical corticosteroid." EX 1038, 195.

23. The symptoms examined in Figures 1-3 are known to be mitigated by corticosteroids and that is what is observed in the Brooks study. EX1038, 198. For example, Fig. 1 shows that, as expected, BDP alone reduces congestion two to three times better than loratadine, and is not statistically different than the combination treatment. EX1038, 196, 198. Likewise, although the reduction in eye symptoms is modest, again as expected, BDP shows from about 3 to 10 times



better symptom reduction than loratadine. Finally, Fig. 3 shows that the antihistamine had almost no effect on runny nose, but BDP had over 10 times better symptom reduction. Far from being flawed, Brooks just shows that in a small two-week study designed to take advantage of the complementary actions of steroids and antihistamines, where the steroid's full effects on all symptoms had not yet had time to develop, the clear preference for steroid alone (15) over antihistamine alone (9) did not quite reach statistical significance. That does not mean it was not clinically meaningful.

24. In my previous declaration, I also discussed Simpson (EX1036), a 21-day study of the steroid budesonide, the antihistamine terfenadine and a combination of both in the treatment of AR. The primary efficacy data were reported at week 3 for overall effectiveness (Figure 1) and for nasal symptoms (blocked nose, runny nose, itch nose, sneezing) (Figure 2), respectively. Simpson showed a statistically significant improvement in sneezing with the combined therapy versus both monotherapies. EX1003, 86. Figure 3 (reproduced below) shows changes in mean total nasal symptom scores in each treatment group over the first week of treatment. The latter graph shows that between the first and seventh day, the mean nasal scores of all arms of the study decreased, and those of the budesonide arm and the combination arm had almost converged, reflecting the expected increasing effectiveness of the steroid over time.

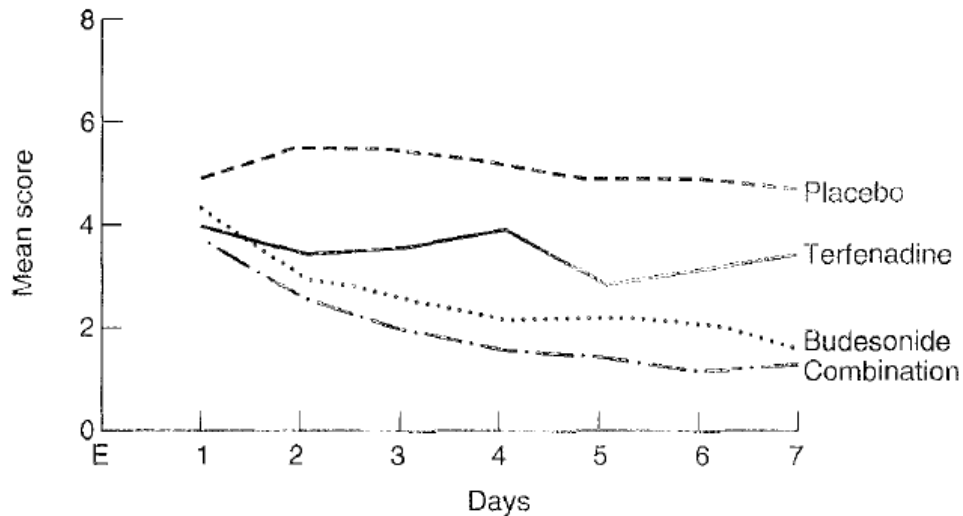


Figure 3. Changes in mean total nasal symptom scores in each treatment group during the first week of treatment.

25. While Dr. Carr relies on the authors' comment that budesonide was shown to be effective alone, and that budesonide is stated to be a highly effective treatment for hay fever (EX2147, 55), the article takes no position on the clinical relevance of the combination. These statements do not negate the fact that the combination controlled one of the four cardinal symptoms of AR better than the steroid alone. Data provided in the lower right panel of Figure 2 (reproduced below) clearly show a statistically significantly higher reduction in sneezing score compared to either monotherapy. Notably, Simpson does not conclude that the combination is less effective than budesonide or that it offers no meaningful benefit over budesonide alone. Indeed, the authors conclude that "[b]udesonide alone or in combination with terfenadine, was perceived by patients as being

significantly more effective in alleviating symptoms than terfenadine alone.”

EX1038, 501.

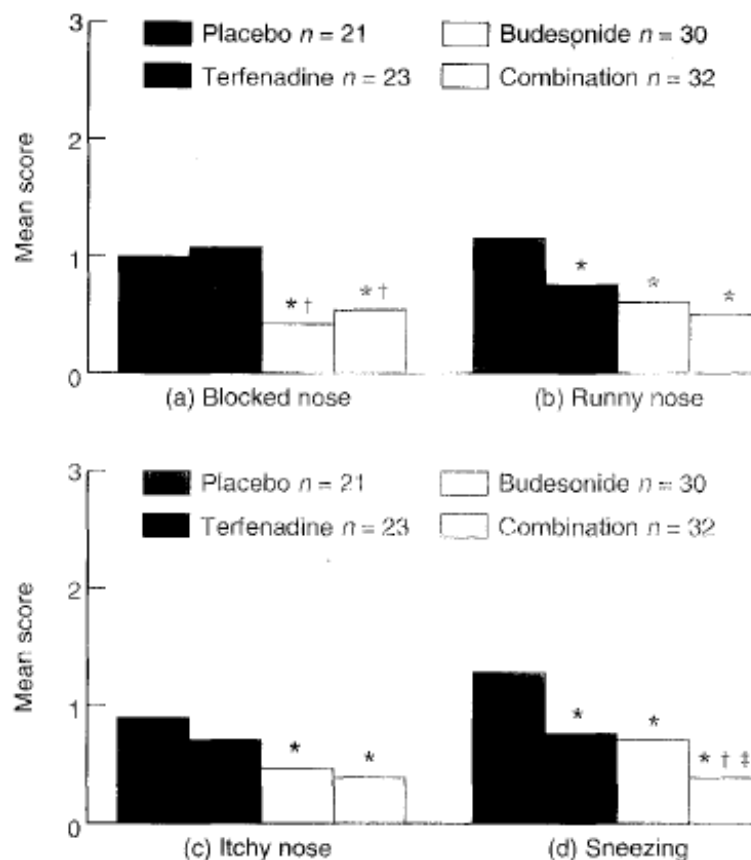


Figure 2. Assessment of nasal symptom scores at week 3 as derived from patients' diary booklets. \* Statistically significant difference versus placebo ( $P < .05$ ). † Statistically significant difference versus terfenadine ( $P < .05$ ). ‡ Statistically significant difference versus budesonide ( $P < .05$ ).

26. In my first declaration, I pointed out that Ratner'98 (EX1034), a two-week AR treatment study of fluticasone propionate aqueous nasal spray (FP ANS), loratadine, and the combination of the two, showed a statistically significant difference for patient rated TNSS. EX1003 ¶90. However, the authors of this study also stated that addition of loratadine to FP ANS did not “confer meaningful additional benefit.” This conclusion may be based on the clinician ratings of

symptoms, which did not find a statistically significant difference in the ratings between FP ANS and the combination with loratadine. EX1043, 121-122. In revisiting this paper, I note that at the end of the timeframe of the study (two weeks), loratadine alone did no better than placebo in alleviating any symptom of AR, and so it is not surprising that the additive effects observed by clinicians for the combination (shown in Fig. 1) did not reach statistical significance. By contrast, in Simpson, where an additive effect was observed for sneezing at the end of three weeks, the antihistamine did provide a statistically significant reduction in that same symptom compared to placebo.

27. Consistent with Drouin, Brooks, and Simpson, the later Ratner 2008 (EX1045) study demonstrates nicely how the complementarity of antihistamine and INS works during the period that the steroid has not yet achieved its full anti-inflammatory effects. Azelastine and fluticasone propionate—the combination of ingredients in Dymista®—were tested as the individual monotherapies and as the combination by sequential concurrent administration. Fig. 2 from this paper is a graph showing the effects on TNSS by each monotherapy and the concurrent combination for each day of the study. While the first 11 days showed statistical significance of the combination over fluticasone, the last three days did not, as the improvement in the effects of fluticasone rose. This is the same sort of behavior I pointed out in Brooks, Figure 5 (*supra*).

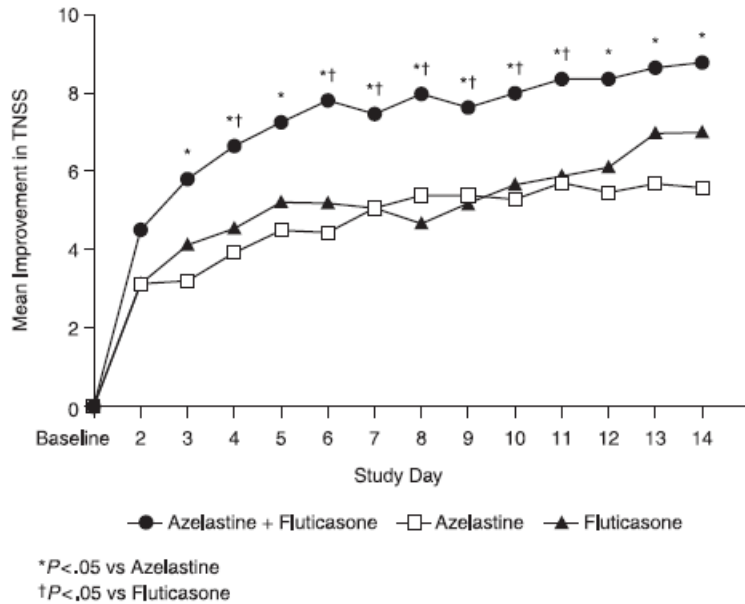


Figure 2. Total nasal symptom score (TNSS) daily improvements. The asterisk indicates  $P < .05$  for azelastine hydrochloride plus fluticasone propionate vs azelastine alone; dagger,  $P < .05$  for azelastine plus fluticasone vs fluticasone alone.

28. Dr. Carr, who makes much ado about how clinical practice is more important to this case than “laboratory experiments,” appears to run away from this position in his criticism of Juniper ’97 (EX1031). The investigators of this study wanted their study “to be as close to real life as possible and to provide practical information for clinicians” about how patients can use INS and antihistamines alone and in combination to better control their hay fever. Id., 1129, 1124. This study measured whether health related quality of life (HRQL) of patients suffering from AR could be improved by starting with antihistamine (terfenadine) and adding INS (fluticasone propionate, FP) or by starting with FP and adding terfenadine. Id., 1124. Hence the starting premise was that some patients would need both medications to properly control their symptoms. It found no difference

in outcomes for the two regimes, but concluded that “at least 50% of patients will need to take both types of medication [nasal corticosteroids and oral antihistamines] in combination to adequately control symptoms.” EX1003 ¶¶89; EX1031, 1123.

29. Alleging that I took this statement out of context, Dr. Carr argues that the study does not show a benefit to using both drugs together, and that only a need for better control was shown. CIP2147 ¶¶68. This complaint is beside the point. Juniper ‘97 was not an efficacy study but rather represents clinical practice then and now. It simply illustrates my contention that before 2002 it was known that some patients would need a combination of antihistamines and INS to control AR symptoms and that physicians acted on this knowledge by prescribing such combinations. The study is consistent with the Guidelines in recommending the use of the two types of drugs together for difficult cases. Contrary to Dr. Carr’s rigid interpretation of the Guidelines, the authors of Juniper ‘97 conclude that treatment should be based on patient preference, *convenience* and cost. There is no mandate here requiring the sole use of antihistamines and INS as monotherapies. Juniper's conclusion that “at least 50% of patients will need to take both types of medication to adequately control symptoms” emphasizes that it would have been convenient and obvious to combine these medications.

30. Dr. Carr cites two other clinical studies for the proposition that these studies found no meaningful additional benefit when adding (oral) antihistamine to INS, including Juniper '89 (EX1039) (beclomethasone, astemizole) and Benincasa (EX1040) (FP, cetirizine). In his analysis, Dr. Carr fails to consider the context of these studies and the differences from studies that found additive effects for the combination of INS and antihistamine.

31. Juniper '89 was a 6-week prophylactic study of beclomethasone and astemizole, alone and in combination. The authors explained that “the pharmacologic profile for nasal steroids suggests that the most effective approach to treatment is regular prophylactic use.” *Id.*, 627. Hence, medication was begun one week before hay fever season started and for a week after it ended. EX1039, 629. Benincasa was structured similarly; it was an 8-week trial of fluticasone propionate and cetirizine in which “treatment was commenced before the beginning of the expected hayfever season in the U.K.” EX1040, 227. A POSA would have been aware that these studies were designed to provide a lead-in time for the steroid to reach its maximal effects by or shortly after the hay fever season has begun. Thus, from the start there were fewer AR symptoms to be controlled and less need either for antihistamines’ generally faster onset of action or ability to control EPR symptoms such as itching and sneezing. Nevertheless, despite the lead-in time, Juniper '89 still showed transiently that the combination performed

better than FP alone in reducing sneezing (Figure 1, where baseline is after 1-week treatment) and the use of eye drops (Figure 2). As the effects of FP ramped up, the advantage faded. Juniper '89 and Benincasa stand in contrast to shorter studies such as Drouin, Brooks and Simpson which found significant additional beneficial effects of the combination as described above. Consideration of the timing or window of complementarity is able to explain the seeming discrepancy between studies which showed advantages to the combination of antihistamine and steroid and those which did not.

32. Dr. Carr's characterization of several review articles is misleading. He quotes Howarth (CIP2041) out of context, ignoring a key aspect of Howarth's conclusion. The Howarth paper is concerned with assessing whether antihistamines have anti-inflammatory activity apart from their antihistaminic activity and whether they may be used in prophylactic treatment, *i.e.*, **long-term** treatment to prevent AR symptoms:

While H<sub>1</sub>-antihistamines are clearly effective in relieving symptoms, particularly those associated with sensory neural stimulation, it has been proposed that many drugs within this class have more extensive actions, modifying the inflammatory process in addition to inhibiting the H<sub>1</sub>-receptor-mediated end-organ effects of histamine. As such, ***H<sub>1</sub>-antihistamines*** might be potentially considered



an alternative *prophylactic* therapy to topical corticosteroids in rhinitis. **IP2040**, 6, emphasis added.

33. As described by Howarth, “by acting very early in the inflammatory pathway, corticosteroids can prevent the cascade of events associated with cell recruitment and activation and, ultimately, clinical disease expression.” *Id.*, 7. While Howarth mentions the antihistaminic symptom relief of antihistamines, he makes clear that he is discussing the potential antiallergic activity of antihistamines:

With short-term therapy, H<sub>1</sub>-antihistamines are most effective at reducing the neurally mediated symptoms of itch, sneeze, and rhinorrhea. This can be attributed to end-organ receptor blockade. There is, however, an indication that a number of these agents also have the *potential for anti-allergic activity* that, theoretically, may increase their spectrum of clinical effectiveness. *Id.*, 8

34. The hypothesis being considered by Howarth was not complementary mechanisms of activity with respect to EPR and LPR symptom relief—which was an important point of emphasis (EX1003, ¶¶53-58)—but the ability of antihistamines to act like steroids, *e.g.*, to inhibit some portion of the inflammatory cascade. CIP2041, 9. Specifically, Howarth discusses studies suggesting that antihistamine may inhibit release of histamine (*e.g.*, via mast cell degranulation)

and to inhibit recruitment of some cells. *Id.*, 8-9. While I also discussed this aspect of antihistamines' activity and especially of azelastine (EX1003 ¶¶56, 66-67), that was not my sole point. My discussion focused on why antihistamines offer complementarity of relief from EPR and LPR symptoms during the 1-2 week window that the full anti-inflammatory effects of an INS have yet to develop. *Id.*, 53-58. Howarth has nothing to say about this kind of complementarity, and does not cite any *in vivo* studies involving azelastine itself.

35. With respect to complementary anti-inflammatory effects of antihistamines and INS, Dr. Howarth made clear that his conclusion of no superior effect was based on the ***limited studies*** available; his paper did not actually contain citations to any *in vivo* studies, as references 52 and 53 are missing. CIP2041, 9-10. He did not cite or discuss Brooks, Drouin, or Simpson, none of which relate to the anti-inflammatory activity of antihistamines, but all of which speak to complementarity as I discussed above. He further qualified this preliminary conclusion as being confined to “***long-term regular therapy*** with the combination compared to topical steroid alone,” which is not at issue in this proceeding. *Id.*

36. A POSA reading Howarth as a whole would have understood first that the complementarity mentioned by Howarth referred to complementary anti-inflammatory effects of antihistamines and INS—not the complementary symptom relief provided in the EPR by antihistamines and in the LPR by INS that was also

known. Thus, Howarth only alleges that the anti-inflammatory effects of antihistamines and INS are redundant *in vivo*<sup>3</sup> and makes no statement about any other complementary effects the two drug classes possess. Second, a POSA would have understood that Howarth's conclusion is based on limited data and that he did not consider the Drouin, Brooks, and Simpson studies. Third, a POSA would have understood that Howarth considered only long-term prophylactic studies and reached no conclusion about benefits of combined antihistamine and INS therapy in the context of shorter 1-3 week studies such as Drouin, Brooks and Simpson.

37. The thrust of the Nielsen review (CIP2042) cited by Dr. Carr (CIP2147 ¶62) differs greatly from the Howarth paper. Whereas Howarth was concerned with whether antihistamines exhibited anti-inflammatory effects *in vivo* that could be complementary to those of corticosteroids in long-term prophylactic treatment (*supra*), Nielsen reviewed clinical data on treating AR with

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<sup>3</sup> Howarth states "The 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 the corticosteroids overlap those of the H<sub>1</sub>-antihistamines, making the action of the latter redundant. ... Thus, first-line therapy for rhinitis based on ***anti-inflammatory activity*** is a topical corticosteroid such as fluticasone propionate." *Id.*, 10.

antihistamines and INS in order to provide recommendations on first line therapy. CIP2042, 1564. While I agree that as of June 2002, intranasal corticosteroids represented a first-line therapy for patients with moderate to severe AR, as a result of the demonstrated complementarity of INS and antihistamines during, e.g., the first week of combined use (vide supra), I must disagree with the authors when they state “[t]he common clinical practice of combining INCS and oral antihistamines in the treatment of AR has no support in clinical evidence” (*Id.*, 1573).

38. Nielsen’s review of combination studies is perfunctory, incomplete and ignores the one study it cites that contradicted its conclusion about no support in clinical evidence.<sup>4</sup> Nielsen’s review includes Juniper ’89, Ratner ’98, Simpson, Brooks and Juniper ’97. However, the two paragraphs and accompanying Table III give only the basics about the nature, size, and scope of the studies. It does not consider Drouin, does not mention the significant reduction in sneezing observed in Simpson, nor why Brooks’ results were at odds with Juniper ’89 and Ratner ’98.

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<sup>4</sup> Dr. Carr also cites a 1-page communication (EX2162) that published after the priority date claimed for the ‘620 patent. CIP2147 ¶63. It is even more perfunctory than Nielsen and freely admits that the ARIA Guidelines (EX1022) recommend the combination of INS and antihistamine is clinically useful. EX2162, 1.

Further, the negative comment about Juniper '97 (“unable to demonstrate any difference in quality of life measures”) is misleading as the same steroid/antihistamine combination was being compared by starting the patient on steroid and adding antihistamine or vice versa (supra). During the late 90s, there was considerable competition between makers of INS and makers of antihistamines to capture the AR market. The authors of this study—Nielsen, Mygind and Dahl, as well as Howarth— were well known to be single minded advocates of the use of INS at the time. In my view, a POSA would have been skeptical of the dogmatic stance they have taken that combined use of these drugs was not indicated, not only because of the studies that I have outlined that contradict this view but also because of the prevailing wisdom of physicians and patients that were effectively using this combination to manage disease at that time. Finally, despite one of Nielsen’s coauthors (Mygind) also being an author of one of the Guidelines (EX 1019, 1022, EX1024), the fact that the Guidelines still recommended addition of INS to antihistamine and did not recommend discontinuing antihistamine indicates that overall, the Guidelines authors did not agree with Nielsen either.

39. Another person who did not agree with Howarth and Nielsen was one of Cipla’s own medical experts at the *Apotex* trial, Dr. Kaliner. As shown in the trial transcript that Cipla submitted in this proceeding, Dr. Kaliner clearly admitted

that he testified at his deposition as saying: “Okay, in my clinical practice and at that period of time [2001], my impression was that the combination of a nasal steroid and an antihistamine was the best treatment I can give.” CIP2021, 498:4-7. As the trial transcript also shows, Dr. Kaliner admitted that he told a symposium of allergists in May 2002 that “symptoms typical of allergic rhinitis; primarily sneezing, nasal itching, and rhinorrhea; benefit most from an intranasal corticosteroid, combined with an oral antihistamine, to which topical antihistamine can be added for additional symptomatic control.” *Id.*, 490:1-7, *see also* 488:12 - 490:1. I agree with Dr. Kaliner that in 2001 the combination of a nasal steroid and an antihistamine were for many patients with severe AR, the best treatment available.

**IX. The Guidelines reflect clinical practice as of June of 2002 and would have encouraged a POSA to develop a single formulation of azelastine and fluticasone propionate**

40. Dr. Carr’s assertion (CIP2147 ¶) that the Dykewicz (EX1019), van Cauwenberge (EX1022) and ARIA (EX1024) papers (“the Guidelines”) would not motivate a POSA to develop a fixed-dose combination is not well founded in my opinion. As I explained in my first declaration (EX1003, ¶¶71-77), the Guidelines reflect the considered opinion of the leading AR medical community at the time that, for patients whose AR is not controlled by first-line INS therapy, an antihistamine may be added (or *vice versa*). EX1022, 120; EX 1024, S251;

EX1019, 478, 517; *see also* EX1021, 540. The Guidelines discourage certain practices and note when proposed therapies require more study. EX1019, 506 (parenteral steroid use discouraged), 510 (oral anti-leukotriene agents). No such warnings are attached to the use of antihistamines combined with INS, including azelastine and INS. Notwithstanding Dr. Carr's and Cipla's portrayal of the Guidelines as *mandating* intermittent use of antihistamines and INS (CIP2147 65-67; Patent Owner Response, Paper 21, 11), the Guidelines still demonstrate routine conjunctive use of antihistamines with INS such as azelastine with fluticasone propionate.

41. This is consistent with Dr. Carr's own clinical practice and those of other physicians. Two of those physicians were Apotex's experts, Dr. Wedner and Dr. Accetta. Copies of ten of Dr. Accetta's patient notes were presented at trial (about which Cipla cross-examined him) and established that he had practiced co-prescription of fluticasone propionate and azelastine prior to 2002. I clearly heard Dr. Carr—as well as Drs. Kaliner (Cipla), Wedner and Accetta—testify that each prescribed both Flonase and Astelin to individual patients before the priority date of the '620 patent at the *Apotex* trial. *See* CIP2018 46:12 – 47:21 (Wedner), 48:11 – 55:6 (Accetta); CIP2021, 496:23 – 497:12 (Kaliner), 571:15 – 572:14 (Carr). During his deposition in this proceeding, after a drawn out back and forth with

counsel, Dr. Carr eventually confirmed his co-prescribing of Flonase and Astelin. EX1142, 6:8-11:15. His initial unwillingness to do so is just baffling to me.

42. Other prior art also demonstrates conjunctive use of azelastine and fluticasone propionate or similar antihistamine/INS combinations for treatment of AR prior to June 2002. Berger notes that “for those patients whose symptoms are not adequately controlled by either treatment often a combination of both an antihistamine with an intranasal corticosteroid is prescribed”; EX1021, 536. Juniper ’97 tested whether it was better to start AR treatment with an antihistamine and add nasal steroid or the reverse; EX1031, 1124. Nielsen discloses that for treatment of AR, “[a] combination of antihistamine and INCS is often used in clinical practice.” EX2042, 1572. Even Ratner 2008—published by MedPointe<sup>5</sup> and coauthors of Dr. Carr—notes “anecdotal reports of the use of these agents [azelastine and fluticasone propionate] in combination are common.” EX1045, 74. EX1045, 74.

43. Dr. Carr alleges that because the Guidelines recommend using step-up/down and on-demand approaches when treating patients with a combination of drugs to treat AR, *e.g.*, a steroid and azelastine, that 1) the drugs had to be kept separate, and 2) a fixed dose regimen would prevent both step-up/down and on-

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<sup>5</sup> Forerunner of Cipla’s U.S. licensee, Meda Pharmaceuticals, Inc. Several authors also appear on Dr. Carr’s Dymista paper, EX1037.



demand practice. CIP2147 ¶¶67. In my opinion, a POSA would not treat the Guidelines so inflexibly.

44. First, as Dr. Carr states “a POSA is aware of all pertinent art.” CIP2147 ¶¶18. So, a POSA would not have read the Guidelines in isolation. A POSA would have been aware of studies such as Drouin, Brooks, Simpson that showed a definite advantage in conjunctive use of an INS and an antihistamine to treat AR. Supra.

45. A POSA would also have been aware that patient compliance would have been expected to improve for the reasons I previously gave: 1) faster and more complete relief due to the additive effects of having both drugs, rather than only one or the other; and 2) the convenience of fewer sprays for the combined product. CIP1003 ¶¶81-2. While Dr. Carr cites Shenfield (CIP2043) as allegedly showing that the number of doses, not the number of pills, is what matters for compliance (CIP2147 ¶¶86), it is not evident to me on what basis Dr. Carr argues that this statement applies equally to all drugs under all conditions or that it applies in particular to intranasal drugs for the treatment of AR. Dr. Carr’s colleagues at Meda Pharmaceuticals appear to agree with me. In a 2008 meeting with the FDA, Meda (Cipla’s partner in developing Dymista® at that time), argued to the FDA:

that the combination product [fluticasone propionate and azelastine hydrochloride] would be better than the individual ingredients because **patients would not have to take four sprays** of medication at one

time. With the individual components, compliance becomes an issue; thus leading to treatment failures and unmet needs. Meda suggested that the patient population would be those that have failed common treatment regimens and those **inconvenienced** by taking two products. CIP2165, 7.

46. I pointed out in my first declaration that complementary mechanisms of action had been taken advantage of before in the Advair product (fluticasone and salmeterol) for the treatment of asthma. EX1003, ¶¶83-84. Dr. Carr's complaint (EX2147 ¶72, n. 6) that Advair is not relevant because it is an inhaler for asthma treatment misses the point of this example. Asthma, like AR, is an inflammatory disease that can be treated with fluticasone propionate. The faster onset of salmeterol is analogous to the faster onset of antihistamines, and demonstrates to a POSA that the combination of a faster-acting drug with fluticasone was known to be useful and increased compliance.

47. In view of the considerations discussed above, I believe a POSA would still have been motivated to develop the combination of INS and antihistamine. Doubtless, developing the combination would have involved recognized compromises. In this case, the choice is one between convenience and flexibility. A POSA would have been motivated to combine these two intranasal drugs - intranasal fluticasone propionate, which was the most popular intranasal steroid at the time, and intranasal azelastine, which was the most popular intranasal

antihistamine at the time - for the obvious benefits of simplicity of use, improved compliance (with one spray vs two) and for the complementarity of their actions that I have discussed. All three of these benefits; simplified ease of use, improved compliance and complementary actions, would be expected by a POSA at the time of invention. A POSA would have also been aware that making this combination involved some sacrifice in flexibility. However, patients and physicians already had the option to use these two intranasal drugs separately and were doing so in large numbers. The choice to use monotherapies was still available should the combination have been too limiting of flexibility in a given patient.

48. In summary, and contrary to Dr. Carr's testimony, a POSA would not have been discouraged from developing a single formulation containing antihistamine and corticosteroid. In fact, the prior art as a whole recognized the clinical usefulness of this combination and a POSA would have been motivated to develop a combined nasal formulation of azelastine and fluticasone propionate for the reasons set forth in my first declaration.

**X. Dr. Carr's side effects analysis is scientifically unsound; topically applied drugs such as azelastine are generally safer than the same drug administered orally**

49. Dr. Carr's analysis of azelastine's side effects (CIP2147 ¶¶74-79) contradict sound scientific practice and is at odds with the warning on Dymista®'s own label. I agree with Dymista®'s prescribing information which states:

“[b]ecause clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.” CIP2066, 5. I would add that in cases where the trials are for the same drug but under sufficiently different conditions, say two trials run at different drug dosages or for widely differing time periods such as 1 week versus 8, adverse reaction rates will vary significantly. Yet in paragraphs 75-78 of Dr. Carr’s Second Declaration (CIP2147), he compares side effects listed on azelastine’s label to those for four oral antihistamines. In doing so, he deliberately misinterprets my statement about intranasal antihistamines possessing fewer side effects than their oral counterparts, by which I meant the same drug compared after nasal delivery versus oral delivery. *Id.* ¶75.

50. Dr. Carr’s analysis more generally appears to call into question a fundamental advantage that topical drugs have in general compared to the same drug delivered systemically. Topical delivery of a drug to its site of action results in a higher drug concentration at the site of action, lower systemic distribution and therefore lower side effects. This is well illustrated by the widespread use of INS as a first-line treatment for AR rather than oral steroid. EX1024, S230 (“The rationale for using intranasal glucocorticosteroids in the treatment of allergic rhinitis is that high drug concentrations can be achieved at receptor sites in the

nasal mucosa, with a minimal risk of systemic adverse effects”). While oral steroid such as prednisone can cause significant side effects such as osteoporosis, glaucoma, hypertension and HPA suppression, these are for the most part avoided when steroids are used topically, *e.g.*, via intranasal administration. *Id.* ; EX1042, 641. Further, as Dr. Carr’s own colleagues (who published the Dymista® trial paper with him) acknowledge, “[i]n contrast to oral antihistamines, intranasal delivery targets the nasal mucosa, the site of allergic inflammation; reduces the risk of systemic adverse effects and drug interactions; and possibly enhances antiallergic and anti-inflammatory effects by increasing local tissue concentrations.” EX1045, 80.

51. Notably, Dr. Carr fails to mention that the adverse effects observed for azelastine have consistently been considered to be mild and transient. EX1021, 536; EX1050, 823; EX1015, 392. He cites no study to the contrary, but improperly compares side effects across studies and does not mention that the Astelin label states “the incidence of discontinuation due to adverse reactions in patients receiving Astelin Nasal Spray was not significantly different from vehicle placebo (2.2% vs. 2.8%, respectively).” EX1008, 3. In fact, the Astelin label shows the majority of adverse events in Figure 1 are indistinguishable from placebo. *Id.* For example, his Figure 1 represents headache as a problem at 14.8%, but the label shows that 12.7% of the placebo group experienced headache

as well and that this difference was not statistically significant. *Id.* While azelastine does show a temporary bad taste if it runs down the back of the throat, it is not noticed by the majority of patients, and it is temporary. EX1015, 392. Dr. Carr has not cited a single study showing that anyone missed doses because of bad taste. As shown below in Section XI.C, when the side effects of Dymista® and azelastine are compared in the same trial, there is virtually no difference between adverse reaction rates.

**XI. Dymista® shows no unexpected results compared to the closest prior art**

52. As described in my first declaration, during prosecution of the '620 patent, Cipla failed to establish any surprising or unexpected results for the claimed formulations because it did not compare them to the closest prior art. EX1003, ¶¶105-16. Dr. Carr makes the same mistake. He asserts the closest prior art is the combination of INS with oral antihistamines, rather than with azelastine. CIP2147 ¶101. Dr. Carr went on to compare Dymista® to azelastine monotherapy, and fluticasone monotherapy, which are also not the closest prior art.

53. Among the references the present trial is concerned with, the closest prior art is Segal and Cramer because both disclose nasal pharmaceutical formulations including the combination of fluticasone propionate and azelastine hydrochloride, the claimed combination of the '620 patent. EX1003 ¶¶102-103; *supra*. Similarly, the clinical art suggested conjunctive use of azelastine

hydrochloride (*e.g.*, Astelin®) and fluticasone propionate (*e.g.*, Flonase®) as I previously discussed. *Supra*; see also EX1003 ¶¶52-58. Conjunctive use of a fluticasone propionate nasal spray and an azelastine hydrochloride nasal spray was confirmed in the prior *Apotex* trial concerning the ‘620 patent as discussed above. *Supra*; EX1055.

54. Upon reviewing Dr. Accetta’s RX in his deposition, Dr. Carr misinterpreted Dr. Accetta’s note stating the patient’s physical exam was normal as meaning the patient had no allergic disease. EX1142, 6:8-9:19. In the RX, Dr. Accetta stated the patient had mild persistent nasal congestion that was worse in the spring, and diagnosed the patient with allergic rhinitis and chronic rhinitis. EX1055. My interpretation of the RX is that the patient had normal height, weight, blood pressure, temperature, and other vital signs (*i.e.*, normal physical exam), but had allergic rhinitis and chronic rhinitis for which he/she was prescribed Flonase® with the addition of Astelin®. Dr. Accetta was certainly not the only doctor before 2002 prescribing the conjunctive use of a fluticasone propionate nasal spray and an azelastine hydrochloride nasal spray. As already mentioned, I heard Dr. Carr clearly admit during the *Apotex* trial that he co-prescribed fluticasone and azelastine to individual patients before 2002. *Supra*; CIP2021, 110:8-13.

55. Dr. Carr avoids all mention of Segal and Cramer in his discussion of Dymista®’s alleged unexpected efficacy results. CIP2147 ¶¶99-112. Instead, he

asserts that the closest art from “a clinical perspective” are the studies he cites showing no added benefit to combining an antihistamine and an INS. *Id.*, ¶101.

Dr. Carr is well aware that the Guidelines reflect the considered opinion of the AR medical community and the Guidelines prior to 2002, and still today, clearly teach the standard of care for patients whose AR is not controlled by first-line INS therapy may add an antihistamine (or vice versa). *Supra*. I would be quite surprised if Dr. Carr’s refusal to acknowledge this fact stemmed from his unfamiliarity with the Guidelines. EX1142, 25:17-26:2.

56. Dr. Carr acknowledges that none of the studies he reviewed included azelastine or any other intranasal antihistamine formulation. *Id.*, ¶108 (“These studies included fluticasone, but never azelastine”). He provides no reasoning for selecting these studies and not even considering Segal and Cramer, which actually disclose the same combination of drugs in a nasal spray as in Dymista®.

57. Instead he asserts three reasons that fail to take into account the issues I raise in this and my previous declaration. First, he alleges that because clinical efficacy of azelastine was the same as oral antihistamines and because clinical efficacy of fluticasone propionate was equal to other steroids, there was no reason to choose these particular drugs. *Id.* ¶¶102-103. Even if that were true, it ignores the clinical practice that he himself engaged in, and which was well-known to have



occurred prior to 2002, namely co-prescribing azelastine and fluticasone propionate for conjunctive use. *Supra.*

58. Second, he cites the Benincasa and Ratner '98 studies as not showing any advantage to the combination of fluticasone propionate with two different oral antihistamines. CIP2147 ¶104. As discussed above, a POSA would have understood that the Benincasa study was a long-term prophylactic study which was not designed to detect the complementarity that would have been observed in the first week or two. *Supra.* The Ratner '98 study did in fact show a statistically significant advantage for the combination of steroid and antihistamine as judged by the patients themselves; however the study is suspect because the antihistamine only arm did not show a statistically significant reduction in AR symptoms. *Supra.*

59. Third, he argues that it is not possible to extrapolate the results of Drouin and Brooks to the combination of azelastine and fluticasone propionate. CIP2147 ¶105. While it is true that there is some risk extrapolating results with one drug to expectations for the activity of a different drug, such projections had little risk with regard to the INS component of the treatment. As Dr. Carr himself states, there were no important differences among the various INS drugs available in clinical effectiveness (CIP 2147 ¶103), so it is perfectly reasonable to expect that fluticasone would work as well as beclomethasone in a combination. As to the antihistamine, a POSA would have had good reason to expect that the use of

azelastine would have been as good or better, with respect to nasal symptoms, as loratadine for the reasons given in my first declaration. EX1003 ¶¶56, 62; *see also*, EX1021.

60. It therefore remains my opinion that in view of Segal, Cramer and the clinical art, a POSA would not have viewed studies lacking azelastine as the closest art, and would not have considered monotherapies as the appropriate comparison to assess whether Dymista® showed unexpected efficacy, faster onset of action, or reduced side effects. The appropriate comparison in view of the closest prior art is conjunctive use of the monotherapies.

**A. The efficacy of Dymista® in treating AR is essentially the same or worse than the active ingredients co-administered separately**

61. When the activity of Dymista® is properly compared to conjunctive use of a fluticasone propionate nasal spray and an azelastine hydrochloride nasal spray, it shows essentially the same efficacy. The Ratner 2008 study (EX1045), which I extensively discussed in my first declaration (EX1003 ¶¶110-111), provides the necessary data for comparing the conjunctive use of a fluticasone propionate nasal spray and an azelastine hydrochloride nasal spray to the published Dymista® clinical trial studies, Hampel (CIP2045) and Carr (EX1037). The groups used in the three studies are summarized in the Table below. The Ratner 2008 study and the Hampel study were conducted at the same site with the same

patient cohort by the same research group during the allergy season of two separate years and are therefore very comparable.

	<b>Astelina®/Flonase® vs. monotherapies</b>		<b>Dymista® vs. monotherapies</b>		<b>Dymista® vs. reformulated monotherapies (Dymista® excipients)</b>	
	Ratner 2008 (EX1045)		Hampel (CIP2045)		Carr (EX1037)	
<b>Group 1</b>	Astelina®	1.1 mg azelastine 200 µg fluticasone	Dymista®	0.55 mg azelastine 200 µg fluticasone	Dymista®	0.55 mg azelastine 200 µg fluticasone
<b>Group 2</b>	Astelina®	1.1 mg azelastine	Astelina®	0.55 mg azelastine <sup>+</sup>	Azelastine - Dymista® formulation	0.55 mg azelastine <sup>+</sup>
<b>Group 3</b>	Flonase®	200 µg fluticasone	Flonase®	200 µg fluticasone	Fluticasone - Dymista® formulation	200 µg fluticasone

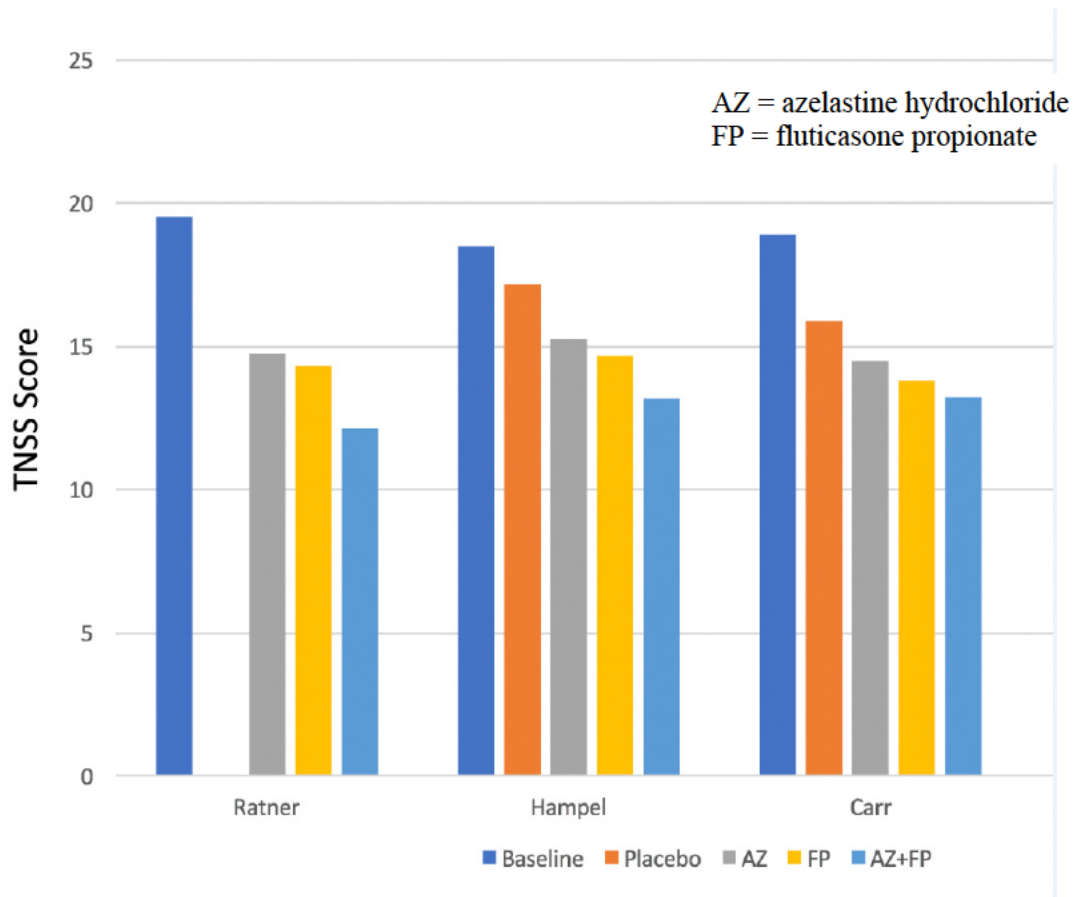
<sup>+</sup>UK approved dosing for Astelina® equivalent (EX1150)

62. I have prepared Figures A, B, and C to compare the results of these studies. Figure A shows the efficacy based on the raw Total Nasal Symptom Score (“TNSS”). EX1045; CIP20145; EX1037. In the three studies, the baseline raw TNSSs in Figure A were very similar (19.53, 18.48, and 18.9<sup>6</sup>), the net effect of each drug delivered as a monotherapy was similar, and the combination of fluticasone and azelastine showed additive effects that were similar (whether administered as two separate sprays (Ratner 2008) or a single spray (Hampel and Carr). *Id.* When the correct comparison is made to the closest prior art, it is readily apparent that Dymista®’s activity is no better than the co-administration of the monotherapies.

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<sup>6</sup> Averaged from meta-analysis base lines of 18.8, 18.9, 18.9, and 19.0. EX1037, Table II.

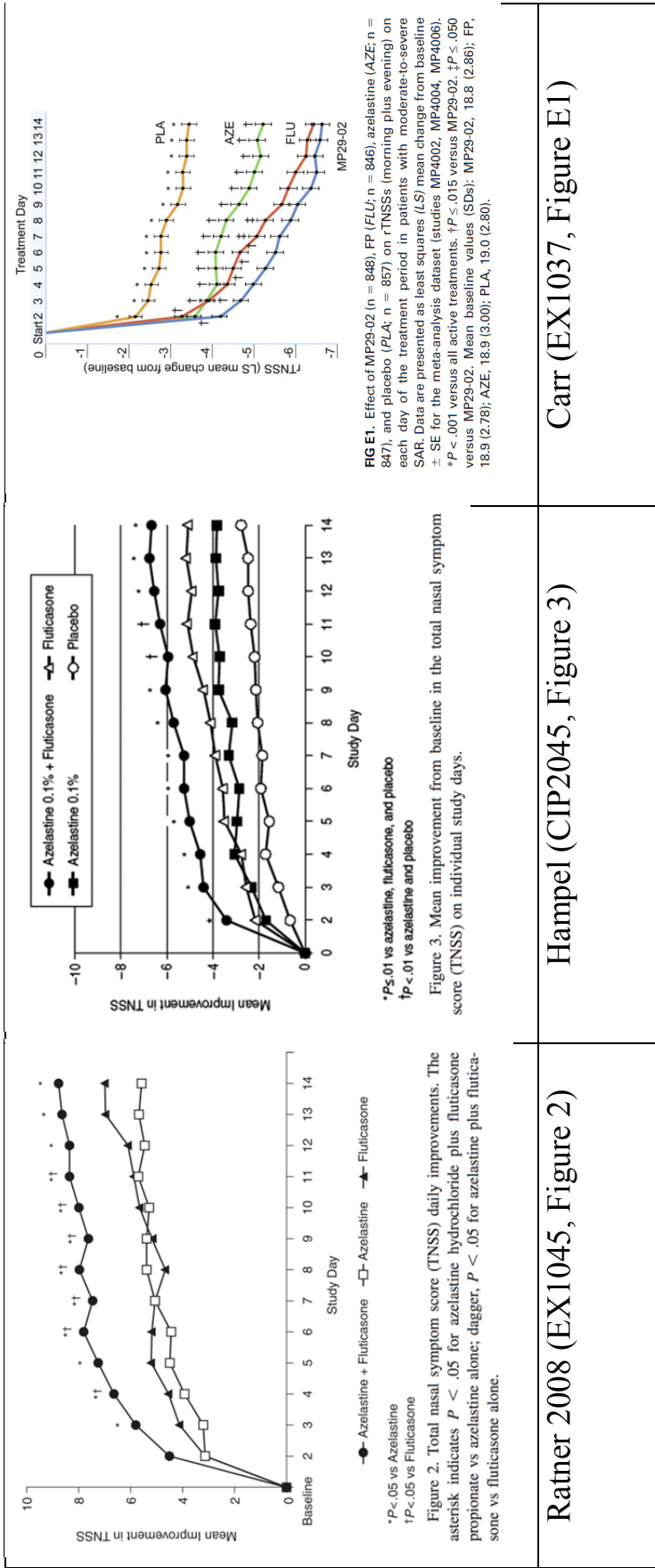
**Figure A: Comparison of raw TNSS in Ratner 2008, Hampel, and Carr**



63. Figure B shows the time course efficacy for the monotherapies of azelastine and fluticasone in the three studies, the conjunctive use with separate sprays (Ratner 2008), and the Dymista® co-formulation of azelastine and fluticasone (Hampel and Carr). *Id.* With the exception of the lack of a placebo group in Ratner 2008, the results of the studies are remarkably similar. Similar to Figure A, Figure B shows all three studies had an improvement in the combination group compared to the monotherapies and, the efficacy was as good or slightly better (lower TNSS) when administering the combination via two separate nasal

sprays (Ratner 2008) compared to Dymista® (Hampel and Carr). It is also evident during the second week of the time-course, the fluticasone monotherapy group is slowly overtaking the azelastine monotherapy group and approaching the efficacy of the combination group. This first two-week period is the "window" of time that I have previously explained is the time period in which the two drugs show the most complementarity. *Supra.*; EX1003, ¶¶ 52-58.

**Figure B: Time Course of TNSS improvement in Ratner 2008, Hampel, and Carr**



Ratner 2008 (EX1045, Figure 2)

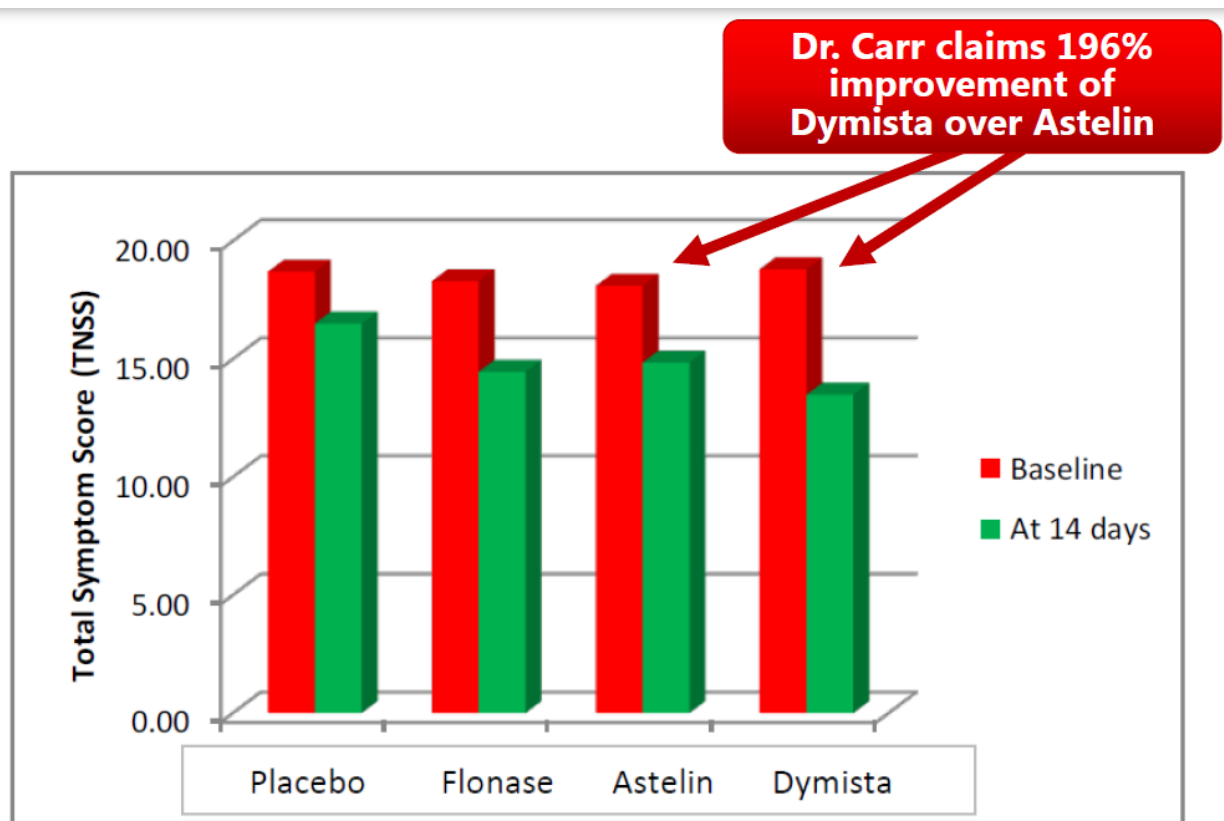
Hampel (CIP2045, Figure 3)

Carr (EX1037, Figure E1)



64. Figure C shows the baseline and two week TNSS for each study group recreated from Hampel's data (CIP2045). It is readily apparent that Dymista® does not have an improvement of 196% over Astelin as asserted by Dr. Carr. CIP2147 ¶109. By failing to show the baseline TNSS and the efficacy of placebo, Dr. Carr misrepresents the efficacy of Dymista® compared to the monotherapies.

**Figure C: Baseline and 14-day TNSS in Hampel**



65. Several points are clear from Figures A, B, and C:
- the baseline raw TNSSs were very similar in the three studies (just under 20 on a 24 point scale in each study);

- ii.) the fluticasone monotherapy and the azelastine monotherapy were roughly equally effective in these two-week studies;
- iii.) the combination of fluticasone and azelastine was close to the sum of the effect of the two monotherapies in all three studies;
- iv.) all of the results are nearly identical across all three studies.

66. Importantly, the combination of fluticasone and azelastine showed additive effects that were similar across all three studies, despite the fact that the drugs were combined in a single device in Hampel and Carr (CIP2045; EX1037) but in separate devices in Ratner 2008 (EX1045). These results suggest that the combination of the two drugs worked just as well whether they were administered in the same container or whether they were administered separately. This continues to confirm my opinion that no superior efficacy of Dymista® over the closest prior art has been demonstrated.

67. Even if the closest prior art was the monotherapy of azelastine or the monotherapy of fluticasone (which it is not), Dymista® provides nothing more than a difference in degree. Dymista® fails to provide a difference in kind, because, as explained above, before 2002 several studies established intranasal steroids (*e.g.*, fluticasone) and intranasal antihistamines (*e.g.*, azelastine) were known and clinically shown to have significant effect in the treatment of AR. *Supra.*; see also EX1003 ¶¶52-67. When evaluating the data as a whole it is clear,

at most, Dymista® provides nothing more than the expected added effects of azelastine (*e.g.*, Astelin®) and fluticasone (*e.g.*, Flonase®).

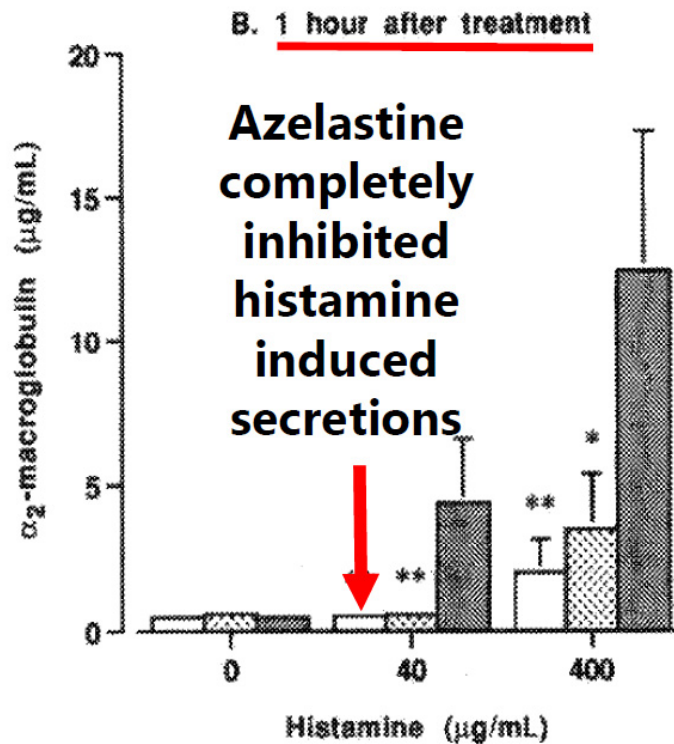
**B. Dymista® does not have an unexpectedly faster onset of action**

68. Dr. Carr wrongly asserts that Dymista®’s 30-minute onset of action was unexpected compared to the closest prior art. CIP2147 ¶¶113-116. First, Dr. Carr cites to three co-administration studies, none of which included azelastine: EX1036 (comparison of budesonide and terfenadine), EX1039 (comparison of beclomethasone dipropionate and astemizole), and EX1040 (comparison of fluticasone propionate and cetirizine). *Id.*, ¶113. The only study Dr. Carr cites that includes azelastine is Ratner 2008 (EX1045). *Id.* However, that study did not evaluate the early onset of action of azelastine or the early onset of action of conjunctive use of azelastine and fluticasone. Since, a POSA would have expected the clinical onset of the combination to be the same as the onset time of the quicker acting drug in the combination, the correct comparison is with azelastine.

69. Dr. Carr however relies on his previous *Apotex* trial testimony that “azelastine was known to have an onset of action of three hours.” CIP2147 ¶114 (emphasis added) (citing CIP2021, 94:23-95:17). This is inaccurate. The prescribing information for Astelin® (azelastine hydrochloride) states “Astelin® Nasal Spray administration resulted in a decrease in symptoms, which reached statistical significance from saline placebo within 3 hours after initial dosing and

persisted over the 12-hour dosing interval.” EX1008, 3 (emphasis added). A POSA would have been aware that azelastine was reported to have an onset time that was much less than 3 hours, and in fact was the same as that of Dymista<sup>®</sup>.

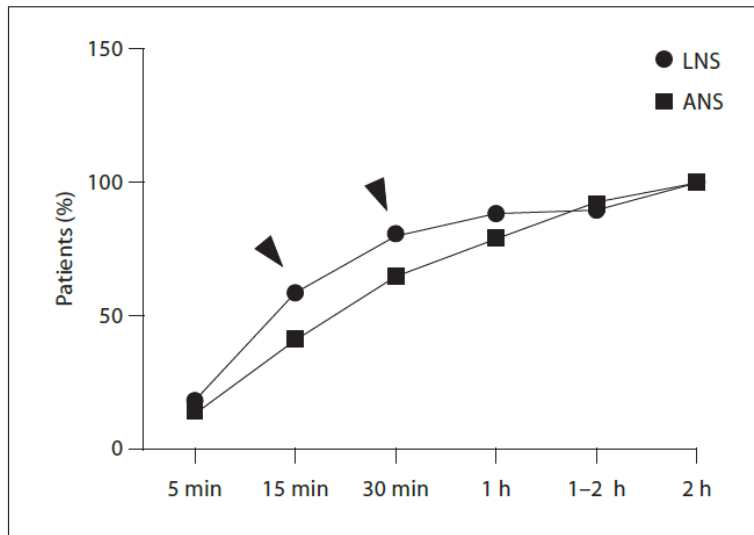
70. One such study by Greiff was published in 1997 and evaluated the rapidity of azelastine’s ability to inhibit both sneezing and vascular leak (a component of nasal secretions) caused by histamine in human volunteers. EX1147; *see also* CIP2012, 39-40. This study found that azelastine inhibited both parameters profoundly within one hour of treatment, suggesting an impact within minutes. *Id.* Figure 2B, reproduced below, illustrates the effects on  $\alpha$ -2 macroglobulin, a measure of blood vessel leakage, one hour after administration of azelastine. *Id.* The histamine-induced leak is completely blocked by azelastine when a low dose of histamine was used in the challenge (40  $\mu$ g/mL) and nearly completely blocked using a higher dose of histamine to cause the response (400  $\mu$ g/mL):



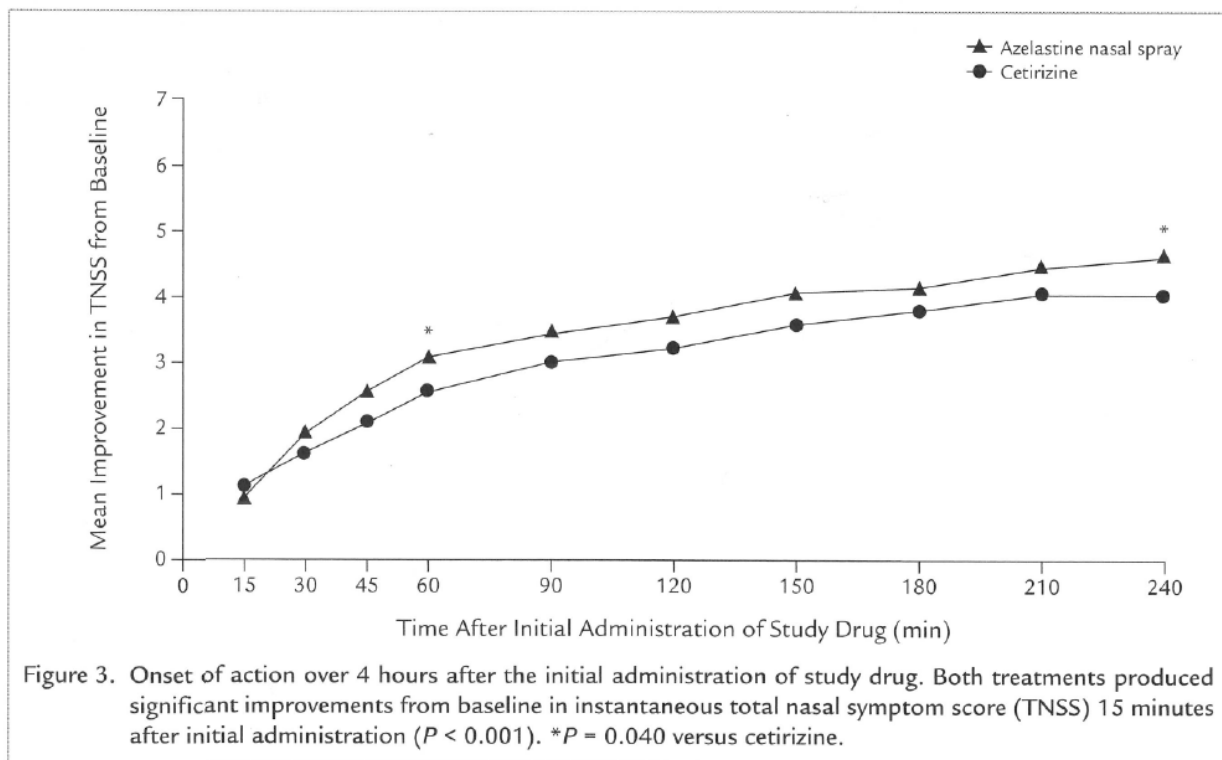
**Fig 2.** Effects of topical azelastine, oral cetirizine and placebo on histamine challenge-induced mucosal exudation of bulk plasma ( $\alpha_2$ -macroglobulin). Treatments were given at time point zero and challenges with control saline histamine (40 and 400  $\mu\text{g/mL}$ ) were given 1 h before treatment and 1–24 h after each treatment. (Comparisons between each treatment and placebo. \* $P < 0.05$ , \*\* $P < 0.01$ ). □ = azelastine; ▨ = cetirizine; ▩ = placebo.

71. This figure shows that both cetirizine (middle bar) and azelastine (left bar) reduced the presence of  $\alpha$ -2 macroglobulin significantly compared to placebo (right bar) created by a histamine challenge. *Id.* Not only did azelastine reduce the presence of  $\alpha$ -2 macroglobulin more than did cetirizine, it almost completely eliminated the presence of  $\alpha$ -2 macroglobulin *within* one hour. *Id.* This result demonstrates that azelastine acts within minutes and certainly within 60 minutes; it does not require “an onset of action of three hours.” *Id.*; CIP2147 ¶114 (emphasis added) (citing CIP2021, 94:23-95:17).

72. Other studies have confirmed the onset of action of azelastine is within minutes, not hours. Han *et al.* evaluated the onset of action, efficacy, and safety of azelastine and levocabastine in the treatment of AR. EX1148. As replicated below in Figure 2, the study found that 41% of the patients reported an onset of action at 15 minutes and 65% at 30 minutes when receiving the same daily dose of azelastine hydrochloride (abbreviated ANS in the figure) as in Dymista® (one spray in each nostril twice daily of 0.1% azelastine hydrochloride). *Id.*, 1-4. Similarly, Corren *et al.* also found azelastine's onset of action to be 15 minutes. EX1160. As replicated below in Figure 3, the study found azelastine nasal spray “produced significant improvements from baseline in instantaneous total nasal symptom score (TNSS) 15 minutes after administration.” *Id.*, 9. Thus, azelastine has a very rapid onset of action, whether it is formulated alone or in combination with fluticasone. A POSA would have expected this to be the case.



**Fig. 2.** Comparison of symptom control by LNS and ANS at different time points. Ratio of cases with improved TNSS at scheduled time points (from 5 min to 2 h) are shown. LNS was more effective than ANS at 15 and 30 min after the first dosage ( $p < 0.05$ ), but both sprays were similar after 1 h.



**Figure 3.** Onset of action over 4 hours after the initial administration of study drug. Both treatments produced significant improvements from baseline in instantaneous total nasal symptom score (TNSS) 15 minutes after initial administration ( $P < 0.001$ ). \* $P = 0.040$  versus cetirizine.

73. Accordingly, Dr. Carr's conclusion that a POSA would find it unexpected for Dymista® to have "a much faster onset of 30 minutes" is simply false. EX2147 ¶114. The azelastine in Dymista® is the ingredient that has an "onset of 30 minutes" and azelastine was known to act within minutes. This rapid onset time for azelastine monotherapy was also mentioned in both the ARIA and Dykewicz guidelines for AR care (EX1024, S222; EX1019, 28), in McNeely (EX1164, 21), as well as in Nielsen, an article relied upon by Dr. Carr (CIP2042, 1565 ("They [azelastine and levocabastine] have a faster onset of action than oral antihistamines and act within 15-30 minutes"))).

**C. Dymista® does not have reduced side effects compared to the closest prior art**

74. Again, Dr. Carr failed to compare the closest prior art to Dymista® in determining the side effects. Rather, Dr. Carr compared Dymista® "to either azelastine or fluticasone monotherapies." EX2147 ¶122 (title). If Dr. Carr had compared Dymista® to the closest prior art, he would have found that the side effects are similar and expected.

75. Dr. Carr's selective citation of data is scientifically unsound and ignores the comparative data in Dymista®'s own prescribing label. Dr. Carr picked data from the Astelin® label (azelastine hydrochloride) (EX1008) and Flonase® label (fluticasone propionate) (EX1010), which are from separate studies with different protocols, parameters, research groups, and patient cohort to



compare the side effects of Dymista®. CIP2147 ¶¶123-128. But Dymista® expresses in their own prescribing label that clinical trials from different studies should not be compared. CIP2066, 5 (“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.”). I can only assume Dr. Carr did this because the comparative studies in Dymista®’s prescribing label contradict his conclusions. In fact, Dr. Carr has admitted to having patients experience side effects and telling them to decrease their intake of Dymista®. EX1142, 196:22-198:14.

76. The studies provided in Dymista®’s prescribing label demonstrate that the side effects associated with Dymista® were slightly worse than the monotherapies of azelastine hydrochloride and fluticasone propionate (comparators using the same vehicle and device as Dymista®). CIP2066, 5-7. The first study from the label concluded the “[o]verall, adverse reactions were 16% in the DYMISTA treatment groups, 15% in the azelastine hydrochloride nasal spray groups, 13% in the fluticasone propionate nasal spray groups, and 12% in the placebo groups.” *Id.*, 5. Similarly, two other studies included in the label compared Dymista® to fluticasone propionate and concluded the “[o]verall, adverse reactions were 47% in the DYMISTA treatment group and 44% in the

fluticasone propionate nasal spray group” and “[o]verall, adverse reactions were 40% in the DYMISTA treatment group and 36% in the fluticasone propionate nasal spray group.” *Id.*, 7.

77. When the side effects of Dymista® are properly compared to the conjunctive use of a fluticasone propionate nasal spray and an azelastine hydrochloride nasal spray, essentially the same side effects and side effect frequencies are observed for both. Again, Ratner 2008 (EX1045) and the published Dymista® clinical trials, Hampel (CIP2045) and Carr (EX1037), which I discussed above, provide the necessary data and are presented in the Table below. *Supra*; EX1045, 5; CIP2045, 5; EX1037, 3-4 and E7. I also note that as I explained above, the Ratner 2008 study and the Hampel study were conducted at the same site with the same patient cohort by the same research group during the allergy season of two separate years and are therefore very comparable. *Supra*.

	Astelin®/Flonase® vs. monotherapies	Dymista® vs. monotherapies	Dymista® vs. reformulated monotherapies (Dymista® excipients)
	Ratner 2008 (EX1045)	Hampel (CIP2045)	Carr (EX1037)
<b>Bitter Taste</b>	Combination therapy (13.5%) Astelin® (8.2%) Flonase® (2.0%)	Dymista® (7.2%) Astelin® (4.1%) Flonase® (0%)	Dymista® (2.1-4.7%) Azelastine (3.4-7.2%) Fluticasone (0.2-1.0%)
<b>Headache</b>	Combination therapy (5.8%) Astelin® (4.1%) Flonase® (4.0%)	Dymista® (2.6%) Astelin® (1.3%) Flonase® (3.9%)	Dymista® (0.5-2.6%) Azelastine (0.5-2.0%) Fluticasone (1.3-2.4%)
<b>Combination therapy/Dymista® other adverse events</b>	“No other adverse event was reported by more than 1 patient.”	Epistaxis (3.9%) Pharyngolaryngeal pain (1.3%) Nasal discomfort (1.3%) Nausea (0.7%) Mucosal erosion (0.7%) Somnolence (0.7%)	Epistaxis (1.0-1.8%) Oropharyngeal pain (0.5%) Nasal discomfort (0.5-1.0%) Nausea (0.5%) Mucosal erosion (0.4-1.0%) Somnolence (1.1%)

78. The most common side effect associated with the conjunctive use of Astelin® (azelastine) and Flonase® (fluticasone) (EX1045) and Dymista® (azelastine + fluticasone) was bitter taste (CIP2045; EX1037). EX1045, 5; CIP2045, 5; EX1037, 3-4 and E7. As I previously explained, the most common side effect associated with azelastine is bitter taste with about 20% of patients reporting a bitter taste after using azelastine. EX1003 ¶65 (citing EX1019, 505). Later studies found the bitter taste reporting percent ranged from 3.3% to 11% (EX1159; EX1160; EX1161; EX1162), so it is not surprising that it was also the most common side effect for the conjunctive use of Astelin® (azelastine) and Flonase® (fluticasone) and Dymista® (azelastine + fluticasone). EX1045, 5; CIP2045, 5; EX1037, 3-4 and E7. Although the most commonly reported side effect, the bitter taste is transient and Dr. Carr has not cited any reference showing it affects patient compliance.

79. It is important to note that the monotherapies alone and Dymista® are all quite safe medicines. EX1008; EX1010; EX2066; EX1050, 823; EX1024, S234. Nonetheless, the second most common side effect associated with the conjunctive use of Astelin® (azelastine) and Flonase® (fluticasone) (EX1045) and Dymista® (azelastine + fluticasone) was headache (CIP2045; EX1037). EX1045, 5; CIP2045, 5; EX1037, 3-4 and E7. I agree with Dr. Carr that the most common

side effect associated with Flonase® (fluticasone) and the second most common side effect associated with Astelin® (azelastine) is headache. CIP2147 ¶127. So again, it is not surprising that headache was the second most common side effect for the conjunctive use of Astelin® (azelastine) and Flonase® (fluticasone) (EX1045) and Dymista® (azelastine + fluticasone) (CIP2045; EX1037). EX1045, 5; CIP2045, 5; EX1037, 3-4 and E7.

80. Ratner 2008 used twice the amount of Astelin® (azelastine) compared to the Cipla studies, so the slightly higher incidence of bitter taste and headache in Ratner 2008 is expected given that the two most common side effects associated with azelastine are bitter taste and headache. EX1008; EX1160. In Ratner 2008 the conjunctive use therapy and the Astelin® monotherapy had a dosing of 1.1 mg azelastine compared to the Cipla studies which used 0.55 mg<sup>7</sup>. *Supra*.

81. The consistency of the most common side effects and frequency of side effects continues to confirm my opinion that no reduced side effects of Dymista® over the closest prior art has been demonstrated. Thus, when considering the results from the studies looking at each therapy in the same clinical trial (as Dymista®'s own label says must be done), Dymista® exhibits a worse, and certainly no better, side effect profile as compared to the monotherapies. Dr. Carr's assertions to the contrary are scientifically unsound and highly misleading.

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<sup>7</sup> UK approved dosing for Astelin® equivalent (EX1150)

82. Even if the closest prior art was the monotherapy of azelastine or the monotherapy of fluticasone (which it is not), Dymista® fails to have reduced side effects. Instead, in Cipla's studies Dymista® had a higher frequency of bitter taste (Hampel) and similar frequency of headache (Hampel and Carr) compared to the monotherapies. CIP2045, 5; EX1037, 3-4 and E7.

**D. There are no surprising or unexpected results associated with Dymista's® formulation**

83. Dr. Carr additionally asserted that when azelastine and fluticasone were reformulated with the excipients found in Dymista®, and not in their commercial forms as the monotherapies substantially reduced side effects were exhibited. CIP2147 ¶125; EX1142, 92:3-94:21. As shown by Cipla's own studies, this is not true. CIP2045; EX1037. Hampel compared (1) commercially available Astelin® (azelastine hydrochloride), (2) commercially available Flonase® (fluticasone propionate), and (3) Dymista® (azelastine hydrochloride + fluticasone propionate). CIP2045. Carr compared (1) azelastine hydrochloride reformulated using Dymista®'s formulation (*e.g.*, same excipients), (2) fluticasone propionate reformulated using Dymista®'s formulation, and (3) Dymista®. EX1037. If Dymista®'s formulation exhibited reduced side effects or any other surprising result, this would be apparent by comparing the data in Hampel and Carr.

84. There is no difference in the side effects between Hampel and Carr. As can be seen from the table above, Astelin® had a 4.1% frequency of bitter taste compared to reformulated azelastine hydrochloride with a 3.4-7.2% frequency of bitter taste. CIP2045; EX1037. Similarly, Astelin® had a 1.3% frequency of headache compared to reformulated azelastine hydrochloride with a 0.5-2.0% frequency of headache. *Id.* Flonase® had a 0% frequency of bitter taste compared to reformulated fluticasone propionate with a 0.2-1.0% frequency of bitter taste. *Id.* Similarly, Flonase® had a 3.9% frequency of headache compared to reformulated fluticasone propionate with a 1.3-2.4% frequency of headache. *Id.*

85. There is no difference in any other result between Hampel and Carr. Figures A and B discussed above clearly show that Astelin® and Flonase® (Hampel) have very similar efficacy to azelastine and fluticasone reformulated using Dymista®'s formulation (Carr). *Supra.*

86. Accordingly, Dr. Carr's conclusion that Dymista®'s formulation (*e.g.*, excipients) surprisingly reduced side effects or produced any other surprising result is discredited by Cipla's own studies.

## **XII. There was no long-felt, but unmet need for Dymista®**

87. I disagree with Dr. Carr's contention that there was a long-felt, but unmet need for a more effective, faster, and safer treatment of AR and that Dymista® satisfied the need. CIP2147 ¶¶136-141. Any such need was already

met by doctors—including Dr. Carr—who were prescribing fluticasone and azelastine for conjunctive use prior to 2002. *Supra*. The common place practice of conjunctive use was also recognized by Ratner 2008. EX1045, 1 (“To our knowledge, there are no published studies that evaluated the efficacy of azelastine hydrochloride nasal spray in combination with an intranasal corticosteroid, **although anecdotal reports of the use of these agents in combination are common**”).

### **XIII. The discussion of the skepticism by the FDA is unconvincing**

88. The absence of an FDA procedure in place to approve a combination nasal spray is not evidence that the FDA was skeptical of Dymista®. While Dr. Carr argues that the FDA was “skeptical” (CIP2147 ¶¶142-147), in reality the FDA was merely doing its job to ensure Meda had created clinical studies with appropriate experimental parameters, including the appropriate patient populations to be tested. CIP2164, 2-3. This is apparent from the FDA’s statements to Meda on two separate occasions:

In addition, according to 21CFR300.50, the combination should be safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Therefore, you need to identify a patient population that requires such a combination product. Your clinical development program should evaluate the proposed combination



product in the proposed patient population that requires the concurrent therapy with both azelastine and fluticasone propionate. CIP2164, 3.

With the proposed program, MEDA would use the same endpoint, total nasal symptom score (TNSS), to evaluate the efficacy of the combination product and each component. This is problematic because some patients may not respond to one component, but yet respond to the combination; and use of the same endpoints will not discriminate. CIP2165, 7.

A POSA would appreciate that these statements are nothing more than the FDA's concern that Meda produce an experimental design with the appropriate patient population that discriminates different possible outcomes such as where a patient does not respond to one of the component drugs in the combination, but would respond to the combination. Most notably, the combination rule does not require that the combination work better than the drugs co-administered separately.

89. Likewise, any concerns the FDA had regarding reduced flexibility and dosage titration of the combination were tied to Meda creating appropriate experimental parameters. The FDA's particular concern was that Meda had not identified the appropriate patient population in need of the combination product over the commercially available monotherapies. CIP2164, 3. This is not skepticism—every drug study must identify the proper patient population or risk

being unable to show clinical efficacy for the drug(s) being tested. Furthermore, Dr. Carr misses the point that a combination product does not eliminate the possibility of downward titration, because as soon as a patient in need of the combination experiences AR symptom relief, a doctor could prescribe either Astelin® or Flonase® alone. CIP2147 ¶145. Such options were not important to the FDA, because the approval being sought was only for the combination product. Another option for downward titration is for a patient to reduce their Dymista® intake. Dr. Carr even admits to sometimes suggesting that a patient take half the dose of Dymista in cases that warrant it, demonstrating that some flexibility still remains, even with use of the fixed combination. EX1142, 196:22-197:8.

#### **XIV. The few instances of industry praise are unpersuasive**

90. Dr. Carr and Cipla cite exactly two instances of industry praise for the conclusion that “Dymista® has been widely praised in the industry as the new gold standard for the treatment of AR.” CIP2147 ¶¶148-149 (citing CIP2052). The first instance does not amount to independent praise of Dymista®, but rather a direct quote from Dr. Carr’s own paper presented as an “Editor’s Choice” in the same volume of the journal. CIP2052 (citing EX1037). The excerpt relied on by Dr. Carr states “[g]iven these findings, MP29-02 can be considered the drug of choice for the treatment of AR.” CIP2052 (emphasis added). In comparison, the final sentence of Dr. Carr’s own paper states “these results show that MP29-02 can be

considered the drug of choice for AR...” EX1037, 7 (emphasis added). I also note that Dr. Carr’s own paper discloses that he has a potential conflict of interest. *Id.*, 1.

**Leung (2012)**

Given these findings, MP29-02 can be considered the drug of choice for the treatment of AR.

**Carr (2012)**

Taken together, these results show that MP29-02 can be considered the drug of choice for AR therapy because it offers additional benefit to patients with AR, in particular with moderate-to-severe disease.

Disclosure of potential conflict of interest: W. Carr has consulted for and received research support from MEDA

**Dr. Carr is a Meda consultant.  
Both papers are in the same edition of the same journal.**

91. My own experience with this journal has been that when one of my articles is selected as the “Editor’s Choice,” I am asked to write the “independent review” referred to by Dr. Carr. In the *Apotex* trial, Dr. Carr denied writing the review. Nonetheless, I find it highly unlikely that the editors wrote the review he discusses, and if they did, they simply paraphrased the abstract of the paper.

92. Cipla asserts a second alleged instance of industry praise, stating that GlobalData praised Dymista® as the “gold standard of AR therapy.” POR, 60

(citing CIP2053, 133). Nowhere does the reference make such a statement.

Instead the reference states intranasal corticosteroids (“INCS”) “are currently the gold-standard treatment for AR therapy.” CIP2053, 133. Additionally, Cipla altogether ignores the other statements on the same page of the reference including a list of weaknesses and threats. *Id.*

Weaknesses	Is more expensive than prescribing each therapy individually, and considerably more expensive than the cheaper formulary-preferred generic versions of the two individual components.
	Mechanism of action has not been fully-determined.
	ARIA guidelines support the use of oral over intranasal AHs in adults with seasonal or perennial/persistent AR.
	Clinical trials compared monotherapy with each agent with Dymista rather than against taking the two agents concurrently.
	Despite a statistically significant reduction in nasal symptoms in patients treated with Dymista compared with placebo and monotherapy ( $p < 0.001$ ), the absolute difference between the treatment arms was small, and might not be clinically relevant enough to warrant the higher price associated with the FDC drug for payers.
	Carries a safety warning stating that patients cannot consume alcohol while taking Dymista.

For example, in the weaknesses section and again repeated in italics on the side of the page, the reference states:

Despite a statistically significant reduction in nasal symptoms in patients treated with Dymista® compared with placebo and monotherapy ( $p < 0.001$ ), *the absolute difference between the treatment arms was small, and might not be clinically relevant enough to warrant the higher price associated with the FDC drug for payers. Id.* (emphasis added).

Several other weaknesses were also listed including that it is more expensive than prescribing each therapy individually and the “[c]linical trials compared the monotherapy with each agent with Dymista® rather than against taking the two agents concurrently.” *Id.* The latter is exactly the same point I made above in discussing the lack of unexpected results exhibited by Dymista®. *Supra.*

93. Indeed, it is clear from the *Apotex* trial testimony by Drs. Accetta and Wedner, and Dr. Carr's unwillingness at his deposition to reveal the percentage of his AR patients that ultimately receive Dymista<sup>®</sup>, that it is not considered the drug of choice for most doctors and patients. CIP2018, 54:20-56:17; 91:2-93:13; EX1142, 109:7-115:4. I recently polled my clinical colleagues at Northwestern University and they all stated their drug of first choice is intranasal steroid monotherapy. Most of them said they avoid Dymista<sup>®</sup> altogether, because the majority of insurance companies do not cover it. Dr. Accetta also testified to not prescribing Dymista<sup>®</sup> for the same reason. CIP2018, 55:20-56:2. My colleagues said in some cases, they will give a patient a free sample of Dymista<sup>®</sup> that will last two weeks and suggest that the patient purchase an over-the-counter intranasal steroid for use after the two weeks. Dr. Carr also acknowledged that he has had patients with and without insurance who have difficulty with the cost of Dymista<sup>®</sup>. EX1142, 114:16-121:20. He admitted that pharmacies often substitute Dymista<sup>®</sup> and provide his patients with an azelastine nasal spray and fluticasone nasal spray. *Id.*, 128:11-18. This substitution is common, because (1) as I've discussed above use of the two separate nasal sprays provides similar efficacy and (2) the cost of generic azelastine nasal spray and generic fluticasone nasal spray are substantially less than Dymista<sup>®</sup>. Dr. Accetta also testified to this common substitution during the *Apotex* trial. CIP2018, 56:3-17. Dr. Accetta, who served on the pharmacy

committee for a major insurance plan in Massachusetts, testified that he did not try to get Dymista® covered by insurance in the state, since the use of fluticasone and azelastine monotherapies in conjunction is just as effective. *Id.*

## Conclusion

94. In signing this declaration, I recognize that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

95. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated:

3/6/18

Robert P. Schleimer, Ph.D.

A handwritten signature in blue ink that reads "Robert Schleimer". The signature is written in a cursive style with a large, stylized 'R' and 'S'.