

#### 10.3.1.12 Statistical plan

Descriptive statistics were used for patient demographics, treatment, disposition, and description of adverse events. ANCOVA with baseline as covariate was used for comparison of treatment groups for the Mini-RQLQ. No adjustments for multiplicity were made as efficacy was not the primary objective of the study. For missing RQLQ data, the following rules were applied:

- If one score was missing, the change in domain score was calculated from scores of matching questions.
- If the score for more than one question in the domain was missing, then the domain score was set to missing.
- If any domain score was missing, the overall score was set to missing.

Sample size was calculated to ensure an adequate safety databases according to ICH Guideline E1, assuming an attrition rate of 25% at the 6-month time point and 50% at the 1-year time point.

#### 10.3.2 Results

##### 10.3.2.1 Protocol amendments

- Amendment 1 – May 11, 2006
  - Deleted HIV and hepatitis screening
  - Changed from the full RQLQ to the mini-RQLQ
  - Mini-RQLQ administered only to patients 18 years of age and older
- Amendment 2 – January 2, 2007
  - Extension of visit window for Months 6 to 12 from 7 days to 14 days
  - Added vital signs, height, and weight at screening
  - Added weight check at Months 6 and 12
  - Added formal otolaryngology evaluation for new cases of nasal mucosal ulceration or septum perforation
  - Day 1 changed to date of randomization

##### 10.3.2.2 Protocol deviations

The most common protocol deviation reported was <75% compliance with study medication in both treatment groups (27 patients in MP03-33 arm and 26 in the Astelin arm). Seven patients (3 in the MP03-33 group and 4 in the Astelin group) took prohibited medications during the study. Three patients who were randomized to one treatment group incorrectly received the other. A full listing of protocol deviations is located in Section 10 Individual Study Reviews 16.2.2 of the Applicant's submission.

*Reviewer's comment: The protocol deviations listed are minor and were unlikely to have impacted study results.*

##### 10.3.2.3 Datasets analyzed

- Safety population: Includes all patients who were randomized with documentation of having received at least 1 dose of study drug. All analyses were performed on the safety population unless otherwise indicated. The interim analysis covers the time period for the first 200 patients who completed 6 months of treatment.

### 10.3.2.4 Patient disposition

As of May 2007, 860 patients have been randomized to treatment. The interim analysis included patients who enrolled in the study by November 17, 2006. Patients who enrolled after that date but discontinued prior to the time of the interim analysis were also included in the interim study report. Table 10 shows the patient disposition for Study MP432.

Disposition	MP03-33 (N=281) N (%)	Astelín (N=278) N (%)	Total (N=559) N(%)
Randomized*	281 (100.0)	278 (100.0)	559 (100.0)
Completed 6 months	218 (77.6)	224 (80.6)	442 (79.1)
Discontinued	61 (21.7)	52 (18.7)	113 (20.2)
Adverse event	18 (6.4)	14 (5.0)	32 (5.7)
Treatment failure	15 (5.3)	17 (6.1)	32 (5.7)
Non-compliance	2 (0.7)	3 (1.1)	5 (0.9)
Withdrew consent	18 (6.4)	11 (4.0)	29 (5.2)
Lost to follow-up	3 (1.1)	4 (1.4)	7 (1.3)
Administrative problems	0	0	0
Other	5 (1.8)	3 (1.1)	8 (1.4)
Total safety population	279 (99.3)	276 (99.3)	555 (99.3)

\*Includes 7 patients who were randomized and do not have disposition data at 6 months; these patients are assumed to be ongoing in the study. Also includes 3 patients who were randomized to one treatment and incorrectly received the other treatment.  
 Source: Volume 47, Section 10.1, Table 3

### 10.3.2.5 Study patients

#### 10.3.2.5.1 Patient demographics and baseline characteristics

Patient demographics and baseline characteristics are presented in Table 8.

Demographics	MP03-33 N=279	Astelín N=276	Total N=555	P
Age				
Mean	40.8	40.8	40.8	0.979
SD	15.31	24.87	15.08	
Median	40.0	39.5	40.0	
Range	12-78	12-82	12-82	
12 to <18 [N(%)]	9 (3.2)	5 (1.8)	14 (2.5)	0.455
18 to <65 [N(%)]	248 (88.9)	253 (91.7)	501 (90.3)	
65 or older [N(%)]	22 (7.9)	18 (6.5)	40 (7.2)	
Sex				
Male	141 (50.5)	127 (46.0)	268 (48.3)	0.286
Female	138 (49.5)	149 (54.0)	287 (51.7)	
Race				
American Indian or Alaska Native	0	0	0	0.424
Asian	5 (1.8)	11 (4.0)	16 (2.9)	
Black	6 (2.2)	4 (1.4)	10 (1.8)	
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.2)	
White	264 (94.6)	257 (93.1)	521 (93.9)	
Other	3 (1.1)	4 (1.4)	7 (1.3)	

Clinical Review  
 Susan Limb, MD  
 NDA 22-203, N000  
 TRADENAME (Azelastine hydrochloride intranasal inhalation solution, 137 mcg)

TNSS*				
Mean	9.64	10.00	9.82	0.270
SD	4.488	4.668	4.578	
Median	9.09	9.67	9.43	
Range	0.9-21.5	0.2-23.3	0.2-23.3	
Duration of rhinitis				
Mean	11.0	12.1	11.5	0.134
SD	11.10	11.21	11.16	
Median	7.0	7.8	7.1	
Range	1-74	1-68	1-74	

\* Mean baseline reflective TNSS over 7-day lead-in period, including Day 1 AM.  
 Source: Volume 47, Section 11.2.1, Table 4

*Reviewer's comment: The demographics and baseline characteristics appear comparable between treatment groups. At baseline, patients appeared to have ranged from disease with minimal symptoms to quite symptomatic. The Applicant does not distinguish between patients with chronic allergic and nonallergic rhinitis.*

#### 10.3.2.5.2 Medication compliance

According to the patient diaries, 250 (89.6%) patients in the MP03-33 arm and 245 (88.8%) in the Astelin group had >75% compliance with study drug. More detailed compliance records are presented in the Appendices 16.2.2.2 and 16.2.2.1 of the Applicant's NDA submission.

#### 10.3.2.6 Efficacy endpoints

#### 10.3.2.7 Primary efficacy endpoints

Changes from baseline Mini-RQLQ overall score and individual domains are presented in Table 35.

RQLQ Score	N <sup>a</sup>	Baseline <sup>b</sup>	N <sup>a</sup>	Change from baseline	P (treatment v. baseline)	P (MP03-33 v. Astelin)
Overall						
MP03-33	264	2.26 (1.113)	201	-0.98	<0.001	0.512
Astelin	267	2.22 (1.006)	214	-0.92	<0.001	
Activity						
MP03-33	271	2.38 (1.309)	208	-1.12	<0.001	0.982
Astelin	271	2.31 (1.246)	221	-1.12	<0.001	
Practical problems						
MP03-33	269	2.91 (1.411)	206	-1.39	<0.001	0.455
Astelin	272	2.92 (1.356)	221	-1.22	<0.001	
Nasal symptoms						
MP03-33	271	2.75 (1.248)	209	-1.22	<0.001	0.571
Astelin	269	2.82 (1.175)	218	-1.16	<0.001	
Eye symptoms						
MP03-33	266	1.61 (1.501)	205	-0.73	<0.001	0.292
Astelin	267	1.52 (1.375)	214	-0.62	<0.001	
Other						
MP03-33	269	1.88 (1.427)	207	-0.62	<0.001	0.999
Astelin	270	1.74 (1.343)	219	-0.62	<0.001	

<sup>a</sup> Based on number of patients in safety population with available data.

<sup>b</sup> Least-square mean (standard deviation)

Source: Volume 47, Section 11.4.1.1, Table 5

*Reviewer's comment: Although not planned as a formal efficacy comparison, MP03-33 and Astelin appear to have comparable efficacy as assessed by the Mini-RQLQ. The change in overall scores and individual RQLQ domains is comparable between treatment arms. Of note, these data are based on patients 18 years of age and older; no efficacy data was collected on patients 12 to 17 years of age. Also, no distinction was made between patients with chronic allergic versus non-allergic rhinitis and no conclusions can be made about the efficacy of MP03-33 in either of these rhinitis patient subpopulations.*

*Overall, Study MP432 provides supportive evidence for the efficacy of MP03-33 in this population of chronic allergic and nonallergic rhinitis patients. However the strength and reliability of these findings are limited by the study design (e.g. selection of RQLQ as opposed to TNSS as the efficacy parameter, no pre-specified adjustment for multiplicity, no placebo control, open label) and the lack of any efficacy data in patients 12 to 17 years. Furthermore, no distinction is made between chronic allergic and VMR patients. The latter may respond differently to sensorial triggers and may even have their rhinitis exacerbated by a formulation with added taste-masking agents.*

#### 10.3.2.8 Safety endpoints

##### 10.3.2.8.1 Extent of Exposure

The mean duration of exposure was 151.8 days for the MP03-33 group and 155.0 days for the Astelin group. The median duration was similar for both groups: 175.0 days for the MP03-33 arm and 174.0 days for the Astelin arm. Total number of doses taken was comparable as well: 273 doses for the MP03-33 group and 276 doses for the Astelin group. Four sprays (2 per each nostril) were counted as one dose.

##### 10.3.2.8.2 Adverse events

###### 10.3.6.8.2.1 Discontinuations due to adverse events

To date, 32 patients have withdrawn from the study due to a treatment-emergent AE. A wide range of adverse events were cited, although most of the terms were reported by no more than one patient. The following adverse events were cited by more than one individual in the MP03-33 group as a reason for discontinuation: rhinitis (n=2), headache (n=4), epistaxis (n=2), and nasal congestion (n=2). Patients could cite more than 1 AE if applicable.

*Reviewer's comment: The types of adverse events cited as reasons for discontinuation are consistent with safety profile described in the Astelin product label.*

###### 10.3.6.8.2.2 Serious adverse events or deaths

Four patients reported SAEs – 1 in the MP03-33 group and 3 in the Astelin group. The SAE in the MP03-33 group was a case of rectal bleeding related to rectal carcinoma, and the patient discontinued the study (Patient 502-008). The other 3 patients reported calculus bladder, chlamydial pneumonia, and syncope. According to the Applicant, the events were resolved and all three patients remained in the study. No deaths were reported.

*Reviewer's comment: The SAE, rectal bleeding secondary to rectal carcinoma, reported in the MP03-33 arm is unlikely to be related to the study drug.*

10.3.6.8.2.3 Common adverse events

Table 12 shows the adverse events reported in  $\geq 1\%$  of patients in the MP03-33 treatment arm. Adverse events are listed as preferred MedDRA terms.

<b>Table 36 Study MP432: Adverse events occurring in <math>\geq 1\%</math> of patients in the MP03-33 treatment arm</b>		
<b>Adverse event</b>	<b>MP03-33 (N=279) N(%)</b>	<b>Astelin (N=276) N(%)</b>
Any adverse event	139 (49.8)	132 (47.8)
Headache	25 (9.0)	22 (8.0)
Dysgeusia	23 (8.2)	23 (8.3)
Epistaxis	21 (7.5)	24 (8.7)
Nasopharyngitis	20 (7.2)	14 (5.1)
Viral infection	13 (4.7)	10 (3.6)
Pharyngolaryngeal pain	10 (3.6)	7 (2.5)
Cough	10 (3.6)	2 (0.7)
Rhinitis	10 (3.6)	2 (0.7)
Influenza	8 (2.9)	8 (2.9)
Bronchitis	8 (2.9)	6 (2.2)
Pharyngitis	8 (2.9)	5 (1.8)
Conjunctivitis	7 (2.5)	6 (2.2)
Nausea	7 (2.5)	6 (2.2)
Nasal mucosal disorder	7 (2.5)	5 (1.8)
Rhinalgia	7 (2.5)	5 (1.8)
Sneezing	7 (2.5)	4 (1.4)
Nasal discomfort	6 (2.2)	6 (2.2)
Upper respiratory tract infection	6 (2.2)	6 (2.2)
Back pain	5 (1.8)	10 (3.6)
Abdominal pain	5 (1.8)	0
Asthma	4 (1.4)	5 (1.8)
Somnolence	4 (1.4)	5 (1.8)
Vomiting	4 (1.4)	3 (1.1)
Gastroenteritis	4 (1.4)	3 (1.1)
Upper abdominal pain	4 (1.4)	1 (0.4)
Dizziness	3 (1.1)	5 (1.8)
Nasal dryness	3 (1.1)	4 (1.4)
Pruritus	3 (1.1)	4 (1.4)
Pyrexia	3 (1.1)	4 (1.4)
Vertigo	3 (1.1)	4 (1.4)
Dry eye	3 (1.1)	2 (0.7)
Eye pruritus	3 (1.1)	2 (0.7)
Sinusitis	3 (1.1)	2 (0.7)
Diarrhea	3 (1.1)	1 (0.4)
Ear infection	3 (1.1)	1 (0.4)
Respiratory tract infection	3 (1.1)	1 (0.4)
Gastroesophageal reflux	3 (1.1)	0

Source: Volume 47, Section 12.2.3.1, Table 8

*Reviewer's comment: In general, the adverse event profiles are similar between MP03-33 and Astelin. Of note, dysgeusia was reported with similar frequency despite the use of taste-masking agents in MP03-33. There is a small discrepancy in the frequency of rhinitis reported between MP03-33 and Astelin, 3.6 versus 0.7%. This discrepancy is most likely incidental, although the possibility remains that the sweetened formulation may exacerbate rhinitis symptoms in patients with VMR, who are prone to non-allergic, sensorial triggers. The rate of rhinitis reported in the current product label for Astelin is 2.3% for SAR trials, 5.6% in the VMR trials.*

#### 10.3.2.8.3 Focused nasal examinations

No nasal septal perforations were reported for either treatment groups. Other signs of nasal irritation were observed during focal nasal examinations as follows: epistaxis (3.6% in MP03-33 v. 5.1% in Astelin), pain (14.0% v. 14.5%, respectively), and ulceration (12.9% v. 11.9%, respectively), the two treatment groups were comparable. Other aspects of the head and neck exam, e.g conjunctival injection, tympanic membrane erythema, lymphadenopathy, etc., were comparable as well. A detailed table of exam findings is located in Volume 47, Section 12.5.2.2, Table 13 of the Applicants NDA submission.

*Reviewer's comment: The rate and severity of nasal irritation appeared comparable between the treatment groups.*

#### 10.3.3 Study summary and conclusions

In general, the adverse event profiles are similar between MP03-33 and Astelin in Study MP432 and with the adverse event profile described in the current product label for Astelin. The most common adverse events include headache, dysgeusia, epistaxis, nasopharyngitis, pharyngolaryngeal pain, cough, and rhinitis. Of note, dysgeusia was reported with similar frequency despite the use of taste-masking agents in MP03-33. A low rate of somnolence was reported in both treatment groups (1.4 and 1.8%, respectively), which is lower than the rate reported in the current Astelin product label (11.5% at the 2 spray BID dose). The addition of taste-masking agents in MP03-33 does not appear to increase the rate of local nasal irritation. However, there is a small discrepancy in the frequency of rhinitis reported between MP03-33 and Astelin, 3.6 versus 0.7%. The rate of rhinitis reported in the current product label for Astelin is 2.3% (5.6% in VMR trials). This discrepancy is most likely incidental, although the possibility remains that the sweetened formulation may exacerbate rhinitis symptoms in patients with VMR, who are prone to non-allergic, sensorial triggers. No new safety signals were identified upon review of this study.

In terms of efficacy data, Study MP432 provides supportive evidence for the efficacy of MP03-33 in this population of chronic allergic and nonallergic rhinitis patients 18 years of age and older. However, the strength and reliability of these findings are limited by the study design and the lack of any efficacy data in patients 12 to 17 years. Furthermore, no distinction is made between chronic allergic and nonallergic patients, who may respond differently to sensorial triggers as noted above.

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/s/

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Susan L Limb  
2/29/2008 04:35:39 PM  
MEDICAL OFFICER

Sally Seymour  
2/29/2008 06:59:02 PM  
MEDICAL OFFICER  
I concur.



NDA 22-203

**Response to Request for Formal Dispute Resolution**

Meda Pharmaceuticals  
Attention: Richard Fosko, RPh, MPH  
Director, Regulatory Affairs  
265 Davidson Avenue, Suite 300  
Somerset, NJ 08873-4120

Dear Mr. Fosko:

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for azelastine hydrochloride nasal spray.

Your July 1, 2008, request for formal dispute resolution (FDRR), received on July 2, 2008, concerned the not approvable action taken by the Division of Pulmonary and Allergy Products (DPAP, the Division) on this application. You requested that the agency rule that the data already submitted demonstrate substantial evidence of effectiveness for approval of NDA 22-203. You requested formal dispute resolution of the following issues:

- 1) Non-approval of the seasonal allergic rhinitis (SAR) indication in adults and adolescents (12 years and over)
- 2) Non-approval of the SAR indication in children (5-11 years)
- 3) Non-approval of the vasomotor rhinitis (VMR) indication in adults and adolescents (12 years and over)
- 4) Denial of an \_\_\_\_\_

b(4)

You also requested that a meeting be convened with me to discuss the issues set forth in your FDRR document. This meeting was granted and occurred on July 28, 2008.

In reaching my decision on your FDRR, I considered your FDRR package as well as the discussion at our July 28 meeting, information gathered from reference texts, pertinent internal documents generated during FDA's review of your application, pertinent draft guidances, a literature search, and communications with DPAP staff and other personnel within the Center for Drug Evaluation and Research (CDER).

My conclusion is that I support your request for approval of the SAR indication in patients 12 years and older with the caveat that appropriate labeling would need to be agreed upon. However, I support the Division's finding that your application is not approvable for 1) the SAR indication in patients 5-11 years and 2) the VMR indication in patients 12 years of age and older.

b(4)

I also agree with DPAP that your ' \_\_\_\_\_ ' is not supported by the data included in the NDA submission. I will expand upon my determination below.

I have included below a table of the chronology of events, with abbreviated pertinent points, to which I will refer in the discussion below.

Timeline Table

Date	Meeting/Interaction/Landmarks	Pertinent Points
5/3/2005	EOP2	<p>DPAP states two doses of old (Astelin) and new (MP03-33) formulation needed to establish comparability.</p> <p>DPAP states that convincing demonstration of comparability may be sufficient for carrying over the VMR indication.</p> <p>DPAP states that it is necessary to conduct studies down to the age where the disease exists.</p> <p>Pharm/tox reviewers comment that sucralose is a food additive for which safety of intranasal administration has not been established. Rats treated with 0.1% or 0.15% azelastine in the presence of 0.15% sucralose showed increased incidences of nasal lesions over those treated with vehicle, vehicle plus sucralose, or Astelin.</p>
8-10/2005		In a different application, DPAP discovers a differential safety signal for a topical nasal product based on age with the 5- to 11-year-old age group having increased findings compared to older age groups. This finding is based on an excipient.
11/4/2005	SPA Comments	<p>In response to whether two doses of new formulation in the same study will satisfy the requirement for an ' _____ ' instead of replication in two studies, DPAP responds that it will not.</p> <p>DPAP states that a separate clinical safety program will be required prior to submission of new drug application.</p>
12/27/2005	Teleconference	Sponsor asks for clarification regarding clinical safety program. DPAP responds that sucralose is the issue. No documentation of discussion regarding ages to be exposed.
6/29/2006	Pre-NDA Comments	Sponsor advised that the SAR indication for reformulated Astelin may be supported by one study; however, carrying over the VMR indication based on a single SAR study will be a significant review issue.
2006		Somewhere in this timeframe, DPAP becomes aware of an intranasal product with a similar active moiety to another existing product but with a different formulation which may have an impact on clinical efficacy results for SAR (perhaps better) that do not translate to successful treatment of VMR.
8/29/2006	IND 69,785 Meeting for higher strength dose of Azelastine HCL Nasal Spray (MP03-36)	<p>Sponsor asserts that efficacy established for Astelin in VMR and therefore does not need studies with MP03-36 if efficacy is shown for SAR and PAR.</p> <p>DPAP informed sponsor that VMR is a distinct condition with pathophysiology different from SAR and PAR and will need to study separately.</p> <p>DPAP argues that sucralose and sorbitol may be triggers for rhinitis.</p>
7/30/2007	NDA filed	
10/15/2007	74 Day Letter	<p>Sponsor reminded of comments from 8/29/2006 meeting</p> <p>DPAP requests data from VMR patients in long-term safety study as it may be supportive</p>

b(4)

10/23/2007	Pediatric Advisory Committee OTC Cough & Cold Products Pediatric Use	Although this meeting was held to discuss Over-the-Counter (OTC) cough and cold products, the committee voted against extrapolation of efficacy data from adults to children for the OTC cough/cold ingredients.
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As I have reviewed your briefing document and had the benefit of looking at these issues in retrospect, there are several points at which I do not think communication was optimal on either party's part. I will discuss this further below.

1. Non-approval of the SAR indication in adults and adolescents (12 years and over)

As your new formulation (MP03-33) is not qualitatively (Q1) or quantitatively (Q2) the same as Astelin, you sought a regulatory pathway utilizing a "comparability" approach. There is a draft guidance<sup>1</sup> giving recommendations that, while not binding, offers some insight into this approach. The MP03-33 development program was the first opportunity that DPAP had to apply these concepts to a topically inhaled nasal antihistamine. DPAP's suggestion was that your approach include two different doses of the new formulation compared to the same strength doses of the old formulation, and if both doses demonstrated greater efficacy than placebo and generated 'similar' dose response curves, which I interpret to mean slopes of a line generated from the point estimates since you will only generate two points for each formulation, then comparability of efficacy of the formulations would be established. This type of approach, comparison of dose-response curves, was used successfully for changing the propellant in metered-dose inhalers from chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) as demonstrated in the labels for drugs such as Pulmicort Flexhaler (budesonide inhalation powder) and Ventolin HFA (albuterol sulfate). Regarding Ventolin HFA, it should be noted that the original inhaler using CFC as the propellant had indications for both the treatment of bronchospasm in reversible obstructive airway disease and the prevention of exercise-induced bronchospasm (EIB). During the development program, in addition to the comparability study in the population with bronchospasm in reversible obstructive airway disease, the sponsor was required to also study the HFA-inhaler in a population with EIB. In other words, demonstrating comparability of efficacy between inhalers for treatment of bronchospasm in reversible obstructive airway disease did not gain the additional indication for EIB as EIB is considered to be a different disease. This principle was applied consistently throughout the CFC to HFA switches using a comparability approach as far as I can determine and will be relevant as it establishes a "prior" for when I discuss whether the VMR indication can be transferred to the new formulation of azelastine.

For your program, you conducted a study comparing 0.55 mg and 1.1 mg of your original product, Astelin, to MP03-33 (your sweetened azelastine product). Neither product demonstrated statistically significant efficacy compared to placebo at the 0.55 mg dose. I mention this as DPAP had informed you at the EOP2 meeting that if either the old or the new formulation appeared similar to placebo subsequent interpretation of the study results might be problematic. Since your 0.55 mg dosages for both formulations did not statistically separate from placebo, you did not generate "dose-ranging determinations" as the guidance recommends<sup>1</sup>. Therefore, to proceed with further comparability comparisons is problematic. Nevertheless, you

<sup>1</sup> Allergic Rhinitis: Clinical Development Programs for Drug Products. April 2000

did proceed by using all four point estimates to generate two straight lines for slope comparisons and comparability determinations between the two different formulations. Given the caveats stated above regarding the difficulty of interpretation of comparisons of these straight lines, these lines appear to have different slopes, which, had they been interpretable according to the guidance, would have required comparison of the slopes. Documentation available to me does not reveal that slope comparison had been discussed in any detail during the development program had you been able to generate legitimate lines. In any regard, due to the lower doses not separating from placebo, thus making comparison of the slopes inappropriate, I agree with DPAP that you have not demonstrated comparability. I also point out that the new formulation has greater point estimates of efficacy for both doses and a steeper slope of line compared to the old formulation, which one might interpret to be increased rate or extent (or both) of delivery of the active moiety to the site of action. \_\_\_\_\_

b(4)

With this information, DPAP then tried to determine whether you had sufficient evidence to show that your new formulation would not "lose" efficacy compared to the old formulation such that they could salvage your program and allow approval. DPAP felt that since both formulations are solutions with similar container/closure systems and in vitro characteristics, the original formulation, Astelin, had demonstrated efficacy in the past with the 0.55 mg dose (even though it did not when compared to placebo in your comparability study), your new formulation had point estimates that were similar (actually better) for both the 0.55 mg and the 1.1 mg dose, and the 1.1 mg doses of both formulations were superior to placebo, a single study was sufficient for approval and your product had adequately demonstrated efficacy for SAR. I agree with their assessment and believe that DPAP demonstrated adaptability and good faith in analyzing the data and not seeking strict comparability to determine efficacy. Since DPAP and I have determined that you have demonstrated efficacy for SAR for your new formulation, I think further contemplation of the comparability efficacy issue is a distraction and not applicable to your remaining points of contention.

Regarding your not being granted marketing approval for the indication of SAR in patients 12 years and older, while DPAP did not specifically cite a labeling impasse as the reason for their not approvable action for SAR in adults 12 and older, that is the apparent reason and is probably the result of miscommunication. Your March 26, 2008, correspondence to the division (in regard to the need for pediatric studies) stated, "Notifying us at this late juncture puts us in an untenable position of having a replacement product with a narrower indication than the legacy product." Despite this, it seems both parties were moving toward the goal of approving the product for the treatment of SAR in patients 12 years and older. I support this approval and feel that you should be able to resubmit your application as a Class 1 submission for the indication of SAR for ages 12 years and above and be approved if appropriate labeling can be agreed upon.

2. Non-approval of the SAR indication in children (5-11 years)

\_\_\_\_\_ b(4)

3 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)