

- Study design acceptable
- Include one and two spray placebo group for blinding
- _____
- Will need a clinical safety program to support application
- November 30, 2005, Teleconference
 - Clarification of need for clinical safety program – long term clinical safety data required because sucralose is novel excipient for IN use
 - VMR or PMR patients acceptable for long-term study
- February 17, 2006 - Approval of Astelin one spray per nostril
- June 29, 2006, Pre-NDA communication
 - Reminder of tox study requirements
 - ISE not required – full CSR for Study MP430 is sufficient
 - Agreement regarding ISS
 - Long term safety study of sweetened formulation and placebo for 6 months is acceptable
 - Labeling will be a review issue

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IV. Items required for filing and reviewer comments (21 CFR 314.50)

The following items were included in this submission:

- Form FDA 356h [Vol 1]
- Debarment certification [Vol 1, P 301]
- Financial disclosure statement [Vol 1, P 309-327]
- Statements of Good Clinical Practice [Vol 20, P 12 (MP430), _____ P30 (MP432)]
- Summary of Efficacy and Safety [Vol 20]
- Complete study report for MP430 (pivotal efficacy study) [Vol 21-37]
- Interim study report for MP432 (long-term safety study) [Vol 47]
- Complete study report for _____ [Vol 38-42]
- Complete study report for _____ [Vol 43-44]
- Review of the literature for safety information relevant to azelastine [Vol 20, P 42]
- Proposed labeling and annotated labeling [Vol 1, P16-280].
- Overdose and drug abuse information [Vol 20, P 43]
- Case report tabulations [Vol 121, 136, 140, and 141] and forms for patients with serious adverse events or discontinuing studies [Vol 163-168]
- Environmental assessment [Vol 5, P 233]
- Pediatric development plan [Vol 1, P331]

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Reviewer's comment: The submission does not include an Integrated Summaries of Efficacy, Safety, or Risks and Benefits as previously discussed during pre-NDA communication between the Applicant and the Division (June 29, 2006).

V. Clinical studies

A. MP429

- Title – Determination of the bioavailability of three intranasal formulations of azelastine hydrochloride in normal healthy male volunteers
- Design – Phase 1, open-label, single-center, randomized, parallel group study
- Duration: Single dose
- Patients – 54 healthy adult male volunteers
- Treatment groups – MP03-33 (137 mcg), Astelin (137 mcg), and MP03-36 (0.15% azelastine, 0.15% sucralose)
- Results – Per the Applicant, C_{max} and AUC_{0-t} were similar for Astelin and MP03-33 for both azelastine and its metabolite, desmethylazelastine. PK parameters were dose-proportional for MP03-36

Reviewer's comment: On May 3, 2005, the Division and the Applicant discussed the pharmacokinetic requirements for the MP03-33 program. At that time, Medpointe agreed to conduct a comparative study between MP03-33 and the marketed formulation, Astelin. Study MP429 is intended to meet this requirement. Of note, the study excluded female volunteers.

B. MP430

- Title – A randomized, double-blind, placebo-controlled trial of the safety and efficacy of MP03-33 in patients with seasonal allergic rhinitis
- Design – US multicenter, double-blind, placebo-controlled, 6-arm parallel study
- Duration – 2 weeks with 1 week placebo lead-in
- Patients – 835 moderate to severe seasonal allergic rhinitis
- Treatment groups – 1 or 2 sprays per each nostril twice daily of MP03-33 (137 mcg), Astelin (137 mcg), or placebo for MP03-33
- Results
 - Primary efficacy endpoint: Change from baseline to Day 14 in combined (AM and PM) 12-h reflective TNSS (Table 3)
 - Statistically significant difference from placebo with higher dose (2 sprays) only of both MP03-33 and Astelin
 - Secondary endpoints
 - Change from baseline to Day 14 in combined iTNSS statistically significant for MP03-33 compared to placebo for both 1 spray (p=0.003) and 2 sprays (p=0.025). Note that the iTNSS was not significant for Astelin for one or two sprays, p=0.055 and p=0.73, respectively.
 - Onset of action: statistically significant and durable separation from placebo at 30 minutes for MP03-33 (2 spray dose only) and at 45 minutes for Astelin (2 spray dose only)
 - Individual combined TNSS component symptoms (Table 4)

Treatment	LS Mean baseline	Change from baseline	P (vs placebo)	% change from baseline	P (vs placebo)
1 spray BID					
Astelin	18.14 (3.358)	-4.00 (4.560)	0.4	-21.12 (25.888)	0.469
MP03-33	18.16 (3.119)	-4.23 (4.605)	0.199	-22.92 (25.743)	0.186
Placebo	17.96 (2.854)	-3.55 (4.572)		-18.95 (24.017)	
2 sprays BID					
Astelin	18.15 (3.189)	-4.24 (4.456)	0.008	-23.46 (25.263)	0.008
MP03-33	18.00 (3.002)	-5.05 (4.958)	<0.001	-27.89 (26.917)	<0.001
Placebo	18.15 (2.802)	-2.84 (4.125)		-15.43 (23.047)	

Individual symptom score	1 spray BID	Change from baseline	P (vs placebo)	2 sprays BID	Change from baseline	P (vs placebo)
Itchy nose	MP03-33	-1.07 (1.399)	0.154	MP03-33	-1.28 (1.447)	<0.001
	Astelin	-1.00 (1.406)	0.312	Astelin	-1.02 (1.436)	0.046
	Placebo	-0.84 (1.318)		Placebo	-0.70 (1.310)	
Runny nose	MP03-33	-0.93 (1.339)	0.573	MP03-33	-1.29 (1.489)	<0.001
	Astelin	-0.99 (1.265)	0.324	Astelin	-1.06 (1.278)	0.013
	Placebo	-0.84 (1.285)		Placebo	-0.69 (1.161)	
Sneezing	MP03-33	-1.36 (1.322)	0.033	MP03-33	-1.39 (1.342)	<0.001
	Astelin	-1.17 (1.347)	0.400	Astelin	-1.25 (1.408)	0.004
	Placebo	-1.04 (1.390)		Placebo	-0.81	
Nasal congestion	MP03-33	-0.88 (1.287)	0.666	MP03-33	-1.10 (1.446)	<0.001
	Astelin	-0.83 (1.231)	0.925	Astelin	-0.92 (1.125)	0.040
	Placebo	-0.82 (1.231)		Placebo	-0.63 (1.132)	

* Data not adjusted for multiplicity

Reviewer's comment: Based on the summary data and study report provided, MP03-33 and Astelin appear comparable in Study MP430. However, the study fails to demonstrate statistically significant difference between the 1-spray dose of MP03-33 and 1-spray placebo (p=0.199). The Applicant has included additional post hoc analysis with pooling of the 1-spray and 2-spray placebo groups. When the 1-spray dose of MP03-33 is compared to the pooled placebo, the p-value equals 0.023. These data do not show convincing evidence of efficacy for the 1-spray dose of either MP03-33 or Astelin. Other data supporting the 1-spray dose of Astelin was previously submitted as a supplement to NDA 20-114, approved in 2006.

In addition, the submission does not include any efficacy data in VMR patients, even though the Applicant intends to carry over both the SAR and VMR indication from the currently approved, unsweetened product. At the May 3, 2005, the Division stated that a separate VMR study may not be required. More recently, however, the Division stated that VMR pathophysiology is distinct and the addition of any excipients that alter the sensorial profile of the product may affect efficacy in VMR or even exacerbate the condition (August 26, 2006, Discussion of Applicant's other sweetened formulation, MP03-36).

The protocol was subject to a Special Protocol Assessment review (September 20, 2005, Dr. Tejashri Purohit-Sheth's medical officer review). At that time, the Division objected to the proposed blinding strategy, recommending inclusion of a placebo for Astelin in addition to placebo for MP03-33.

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C. MP432

- Title – Active-controlled trial of the safety and tolerability of MP03-33 in patients with chronic allergic or nonallergic rhinitis
- Design – European multicenter, open-label, parallel study
- Duration – 6 month interim report. Ongoing 1-year study.
- Patients – 559 patients 12 years of age and older with perennial allergic rhinitis and non-allergic or vasomotor rhinitis
- Treatments – 2 sprays per nostril twice daily of MP03-33 (137 mcg) or Astelin (137 mcg)
- Results
 - SAEs and discontinuation due to AEs – Per the Applicant, MP03-33 and Astelin has similar safety profiles. Fourteen patients discontinued due to an AE in the MP03-33 arm; 18 patients discontinued due to AE in the Astelin arm. The most common reasons for discontinuation due to AE included headache, epistaxis, nasal congestion, as well as rhinitis in the MP03-33 group and somnolence in the Astelin group. One SAE was reported in the MP03-33 group, rectal bleeding and rectal carcinoma, which did not appear to be treatment-related.
 - Common AEs – Overall, headache (9% and 8%, respectively), dysgeusia (8.2 and 8.3%, respectively), and epistaxis (7.5% and 8.7%, respectively) were the most commonly reported adverse events. Somnolence was reported in 1.4% and 1.8% of subjects.
 - In addition to safety endpoints, the Applicant reports a significant improvement from baseline in quality of life measures for both MP03-33 and Astelin.

Reviewer's comment: Based on an initial, brief review of the data provided, the safety and tolerability of MP03-33 and Astelin appear comparable. Of note, the study included subjects with both VMR and PAR. PAR is not an approved indication for azelastine in the United States. The breakdown of subjects who had VMR versus PAR is not presented in the study report and will be requested from the Applicant. The issue of whether to include PAR or VMR patients in a long-term safety study was previously discussed in a teleconference regarding a SPA for MP430 (November 30, 2005, Teleconference meeting minutes). At that time, Division suggested that the study be conducted in patients who would "show a benefit from this drug." The Applicant will be requested to provide a breakdown of adverse events by PAR versus VMR diagnosis. Besides providing safety information, this additional data may provide potential support for a VMR indication in the absence of efficacy data with the sweetened formulation.

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2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

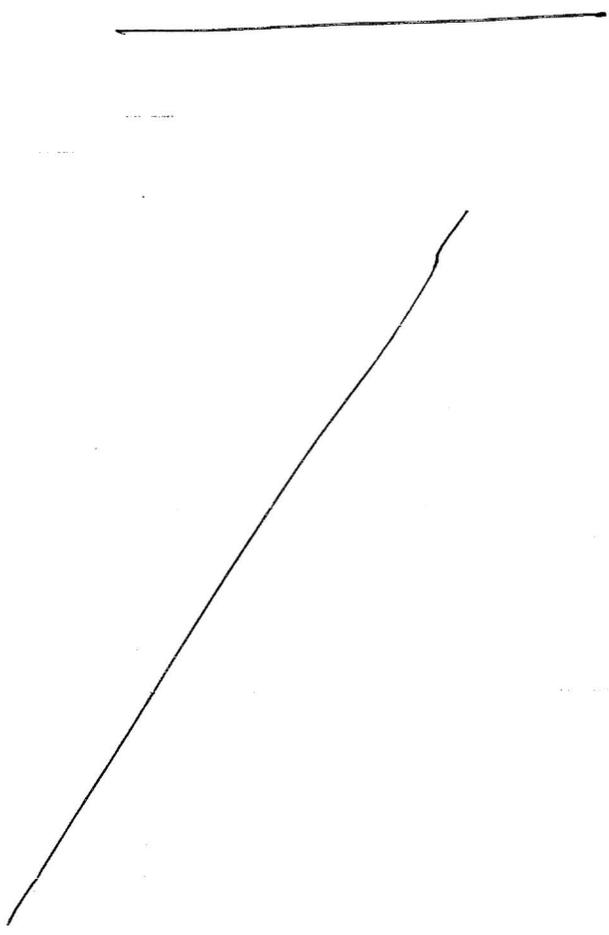
Draft Labeling (b5)

Deliberative Process (b5)

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- Carton and container label: Both the carton and container label contain a graphic that obscures the proprietary name and distracts from the established name.

Figure 3 Proposed container and carton label



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VII. DSI review/audit

Initial review of the application does not raise any data integrity concerns There were _____ investigators with financial interests/arrangements _____; however, none of these investigators enrolled a significant number of subjects (each enrolled _____ patients). In addition, Azelastine is a known drug substance with extensive post-marketing experience. Because of these reasons, no DSI review is recommended at this time.

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VIII. Pediatric development plan

As previously discussed with the Division following the February 17, 2006, approval of the lower 1 spray dose in patients 5 years of age and older, _____

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_____ The Applicant requests a waiver from PREA requirements in children under the age of 2 years based on the following reasons:

- The existence and diagnosis of SAR in this age group is questionable,
- Systemic therapy for atopic disease is more desirable in this age group, who most frequently manifest dermatologic and lower airway signs of atopy.
- Oral medications, such as cetirizine which is approved down to age of 6 months, have a more reliable route of administration in this age group compared to intranasal inhalation.

Reviewer's comment: Studies in children under the age of 2 years were previously waived at the time of approval for the 1-spray dose of Astelin for SAR (June 2006). As this application does not include a new indication or formulation, it does not trigger PREA requirements.

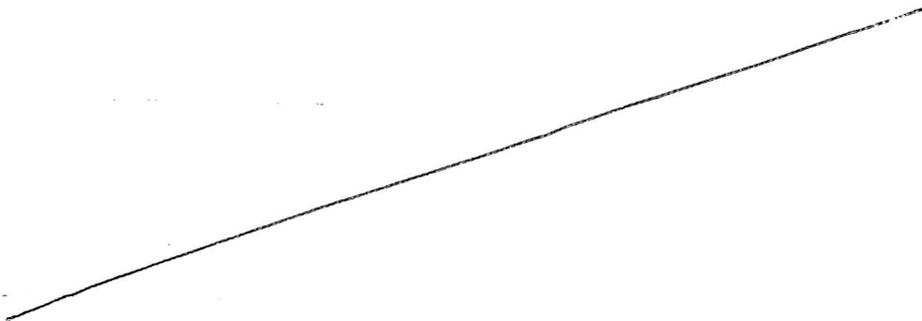
IX. Recommendation

The application is fileable.

X. Comments for the Sponsor

The following comments are to be communicated to the Sponsor.

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- On the carton and container labels, remove the graphic ' _____ ' above the proprietary name as it obscures and crowds the proprietary name. In addition, by increasing the prominence of the proprietary name, the presence of the graphic decreases the relative prominence of the established name. Also remove the graphic ' _____ ' in the proprietary name. See 21 CFR 201.15(a)(6) and 21 CFR 201.10(g)(2).

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XI. Time line for review

September 6, 2007	Filing and planning meeting
November 12, 2007	Midcycle meeting
February 25, 2008	Labeling meeting
March 10, 2008	Wrap-up meeting
March 12, 2008	Labeling TCON
March 18, 2007	Primary reviews due

Reviewed by:

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/s/

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Sally Seymour
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I concur.