

Table 20 Study MP430: Change from baseline in combined (AM plus PM) instantaneous TNSS over 14-day treatment period

Treatment	Baseline (SD) ^a	Change from baseline	P-value (vs placebo) ^b
1 spray BID			
Astelin	16.98 (4.225)	-3.81 (4.708)	0.055
MP03-33	16.98 (3.902)	-3.98 (4.784)	0.025
Placebo	17.10 (3.393)	-2.80 (4.652)	
2 sprays BID			
Astelin	17.00 (3.837)	-4.24 (4.456)	0.073
MP03-33	17.12 (3.553)	-5.05 (4.958)	0.003
Placebo	16.93 (3.637)	-2.84 (4.125)	

^a Least-square mean and standard deviation

^b P-value calculated from repeated measures ANCOVA model containing study day as the within-patient effect, treatment group and site as between-patient effects, treatment-by-study day interaction, and baseline as a covariate.

Source: Vol 21, Section 14.0, Table 14.2.4.2

Reviewer's comment: The iTNSS scores support the efficacy of the proposed BID dosing regimen (iTNSS) for both the lower and higher doses of MP03-33. Results appear comparable to those presented for Astelin.

10.1.2.6.2.3 Change from baseline rTNSS for individual symptom scores for the 14-day treatment period

Table 21 Study MP430: Change from baseline in combined 12-hour rTNSS individual symptom scores over 14-day treatment period

Individual symptom	Treatment	Baseline (SD) ^a	Change from baseline	P-value (vs placebo) ^b
Itchy Nose	1 spray BID			
	Astelin	4.50 (1.215)	-1.00 (1.406)	0.312
	MP03-33	4.56 (1.047)	-1.07 (1.399)	0.154
	Placebo	4.35 (1.104)	-0.84 (1.318)	
	2 sprays BID			
	Astelin	4.51 (1.105)	-1.02 (1.436)	0.046
MP03-33	4.52 (1.065)	-1.28 (1.447)	<0.001	
Placebo	4.58 (1.128)	-0.70 (1.310)		
Runny nose	1 spray BID			
	Astelin	4.62 (1.087)	-0.99 (1.265)	0.324
	MP03-33	4.54 (0.970)	-0.93 (1.339)	0.573
	Placebo	4.64 (0.925)	-0.84 (1.285)	
	2 sprays BID			
	Astelin	4.67 (1.129)	-1.06 (1.278)	0.013
MP03-33	4.66 (0.966)	-1.29 (1.489)	<0.001	
Placebo	4.68 (1.007)	-0.69 (1.161)		
Sneezing	1 spray BID			
	Astelin	3.85 (1.368)	-1.17 (1.347)	0.400
	MP03-33	3.95 (1.290)	-1.36 (1.322)	0.033
	Placebo	3.85 (1.276)	-1.04 (1.390)	
	2 sprays BID			
	Astelin	3.88 (1.235)	-1.25 (1.408)	0.004
MP03-33	3.89 (1.359)	-1.39 (1.342)	<0.001	
Placebo	3.86 (1.247)	-0.81 (1.223)		
Congestion	1 spray BID			
	Astelin	5.17 (0.724)	-0.83 (1.231)	0.925
	MP03-33	5.11 (0.832)	-0.88 (1.287)	0.666
	Placebo	5.12 (0.787)	-0.82 (1.298)	
	2 sprays BID			
	Astelin	5.10 (0.798)	-0.92 (1.125)	0.040
MP03-33	4.93 (0.794)	-1.10 (1.446)	<0.001	
Placebo	5.04 (0.754)	-0.63 (1.132)		

^a Least-square mean and standard deviation

^b P-value calculated from repeated measures ANCOVA model containing study day as the within-patient effect, treatment group and site as between-patient effects, treatment-by-study day interaction, and baseline as a covariate.

Source: Vol 21, Section 11.4.1.2, Text Table 11

Reviewer's comment: The individual symptom scores support the efficacy of MP03-33 over placebo at the 2-spray dose. For the 1-spray dose, the results are not as consistent. Although numerically favorable, MP03-33 did not show a statistically significant improvement over placebo for the symptoms of itchy nose, runny nose, or congestion. Overall, MP03-33 compared favorably to Astelin, as was observed for the composite rTNSS.

10.1.2.6.2.4 Change in rTNSS from baseline to end of the first 12-hour dosing interval

The change in TNSS from baseline (which includes Day 1 AM) to the morning of Day 2 is presented as the change at the end of the first 12 hour dosing interval. All groups improved numerically during this time period; only the 2-spray MP03-33 dose was statistically superior to placebo during this time frame (p=0.012). Results are summarized in Table 22.

Table 22 Study MP430: Change in rTNSS from baseline to end of the first 12-hour dosing interval			
Treatment	Baseline (SD)^a	Change from baseline	P-value (vs placebo)^b
1 spray BID			
Astelin	9.08 (1.674)	-1.59	0.336
MP03-33	9.06 (1.509)	-1.78	0.104
Placebo	8.88 (1.506)	-1.32	
2 sprays BID			
Astelin	9.05 (1.601)	-1.59	0.330
MP03-33	8.96 (1.495)	-2.02	0.012
Placebo	9.01 (1.459)	-1.31	

^a Baseline includes the rTNSS scores over the 7-day lead-in period, including Day 1 AM. Presented as least-mean square with standard deviation.

^b P-value calculated from repeated measures ANCOVA model containing study day as the within-patient effect, treatment group and site as between-patient effects, treatment-by-study day interaction, and baseline as a covariate.

Source: Vol 21, Section 14.1, Table 14.2.5.1

10.1.2.6.2.5 Change from baseline combined rTNSS to end of the first 24-hour dosing interval

The change in TNSS from baseline (which includes Day 1 AM) to the morning of Day 2 is presented as the change at the end of the first 12 hour dosing interval. All groups improved numerically during this time period; only the 2-spray MP03-33 dose was statistically superior to placebo during this time frame (p<0.001). Results are summarized in Table 23.

Table 23 Study MP430: Change from baseline combined rTNSS to end of the first 24-hours dosing interval			
Treatment	Baseline (SD)^a	Change from baseline	P-value (vs placebo)^b
1 spray BID			
Astelin	18.14 (3.358)	-3.29	0.275
MP03-33	18.16 (3.119)	-3.60	0.096
Placebo	17.96 (2.854)	-2.68	
2 sprays BID			
Astelin	18.15 (3.189)	-3.37	0.063
MP03-33	18.00 (3.002)	-4.24	<0.001
Placebo	18.15 (2.802)	-2.35	

^a Baseline includes the rTNSS scores over the 7-day lead-in period, including Day 1 AM. Presented as least-mean square with standard deviation.

^b P-value calculated from repeated measures ANCOVA model containing study day as the within-patient effect, treatment group and site as between-patient effects, treatment-by-study day interaction, and baseline as a covariate.

Source: Vol 21, Section 14.1, Table 14.2.1.3.1

10.1.2.6.2.6 Change from baseline 12-hour rTNSS to endpoint (Day 14 or last day of study)

The change from baseline to the last day of the study is presented in Table 24. All groups improved numerically between these two timepoints. Only the 2-spray MP03-33 and Astelin were statistically superior over placebo. MP03-33 and Astelin appeared to perform comparably.

Table 24 Study MP430: Change from baseline combined rTNSS to last day of study

Treatment	Baseline (SD) ^a	Change from baseline	P-value (vs placebo) ^b
1 spray BID			
Astelin	18.14 (3.358)	-4.75	0.659
MP03-33	18.16 (3.119)	-4.75	0.657
Placebo	17.96 (2.854)	-4.46	
2 sprays BID			
Astelin	18.15 (3.189)	-4.97	0.015
MP03-33	18.00 (3.002)	-5.66	<0.001
Placebo	18.15 (2.802)	-3.38	

^a Baseline includes the rTNSS scores over the 7-day lead-in period, including Day 1 AM. Presented as least-mean square with standard deviation.

^b P-value calculated from repeated measures ANCOVA model containing study day as the within-patient effect, treatment group and site as between-patient effects, treatment-by-study day interaction, and baseline as a covariate.

Source: Vol 21, Section 14.1, Table 14.2.1.3.1

10.1.2.6.2.7 RQLQ

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is a validated instrument for assessing the impact of rhinitis on activities of daily living and overall well-being. It is a 28-item, disease-specific instrument designed to measure the seven domains of functional impairment that are most important to patients with SAR: sleep impairment, non-nasal symptoms (e.g., headache and fatigue), practical problems, nasal symptoms, eye symptoms, activity limitations, and emotional function. There is also an overall quality of life score for the RQLQ that is expressed as the mean of the seven individual domains. Patients are asked to consider their experiences over the previous seven days and to score their degree of impairment on a seven-point scale (0 = not bothered, 6 = extremely bothered). A minimally important difference (MID) in the RQLQ is considered to be the smallest difference in score that is considered to be of clinical significance. The MID for the RQLQ has been determined to be 0.5.

The overall mean RQLQ score was statistically improved at Day 14 compared to placebo with the 2 spray MP03-33 dose (1.43 v. 0.88; p<0.001). The 2-spray Astelin dose was also statistically superior to placebo (1.19 v. 0.88; p=0.042). No statistically significant improvements were noted for the lower dose MP03-33 (p=0.093) or Astelin (p=0.648) groups.

Reviewer's comment: The RQLQ results support the efficacy of the 2-spray dose of MP03-33 over placebo; the results for the 1 spray dose are not statistically significant and the RQLQ difference is less than the established MID of 0.5, but the numerical trend favors MP03-33 over placebo. The treatment difference in both the 1-spray and 2-spray Astelin arms also falls short of the MID. The RQLQ results are not replicated in a second study. Study MP432, the long-term safety study, uses a shorter version of the RQLQ, the 14-item Mini-RQLQ.

10.1.2.7 Safety assessments

10.1.2.7.1 Adverse events

10.1.2.7.2 Serious adverse events

No serious adverse events or deaths were reported during the course of the study.

10.1.2.7.3 Discontinuations from the study due to adverse events

Eight patients discontinued prematurely from the study due to adverse events. Reasons for discontinuation are summarized below.

	Treatment group	N	Reason for discontinuation
1 spray BID	Astelin	1	Allergic rhinitis
	MP03-33	0	
	Placebo	1	Rash
2 sprays BID	Astelin	1	Sinus infection
		1	Dizziness
	MP03-33	1	Upper respiratory tract infection
		1	Severe allergic conjunctivitis
		1	Heart palpitations
Placebo	1	Sinus infection requiring antibiotics	

Source: Vol 22, Table 14.3.2.3

Reviewer's comment: Few early discontinuations were attributed to adverse events. No new safety signals are identified upon review of the listed events. Of note, Table 7 indicates that only 6 patients discontinued due to AEs, rather than 8. In a December 10, 2007 information update, the Applicant clarified this discrepancy as follows: 1) Patient 01-0356 reported dizziness earlier in the study and later withdrew consent, but the withdrawal of consent was found not to be related to the dizziness; 2) Patient 29-015 was initially reported as withdrawing for a sinus infection, but was later noted to be discontinued due to non-compliance.

10.1.2.7.4 Common adverse events

The most common adverse event reported for both MP03-33 and Astelin was dysgeusia. Common adverse events are summarized in Table 11 and were consistent with adverse events noted in the clinical trials to support the approval for Astelin. The most common adverse events for patients receiving MP03-33 that occurred at a rate greater than placebo included dysgeusia, epistaxis (for the 2 spray dose only), headache, nasal discomfort (2-spray dose only), fatigue (2-spray dose only), and somnolence.

Preferred Term [N(%)]	1 Spray BID			2 Sprays BID			Total (N=835)
	Astelin (N=137)	MP03-33 (N=139)	Placebo (N=137)	Astelin (N=137)	MP03-33 (N=146)	Placebo (N=138)	
Any AE	37 (27.0)	29 (20.9)	22 (16.1)	34 (24.6)	41 (28.1)	27 (19.6)	190 (22.8)
Dysgeusia	13 (9.5)	8 (5.8)	2 (1.5)	11 (8.0)	10 (6.8)	3 (2.2)	47 (5.6)
Epistaxis	8 (5.8)	3 (2.2)	3 (2.2)	3 (2.2)	4 (2.7)	0 (0.0)	21 (2.5)
Headache	5 (3.6)	2 (1.4)	1 (0.7)	3 (2.2)	4 (2.7)	1 (0.7)	16 (1.9)
Nasal discomfort	3 (2.2)	0 (0.0)	1 (0.7)	6 (4.3)	2 (1.4)	0 (0.0)	12 (1.4)
Fatigue	1 (0.7)	0 (0.0)	1 (0.7)	3 (2.2)	3 (2.1)	1 (0.7)	9 (1.1)
Somnolence	2 (1.5)	2 (1.4)	0 (0.0)	2 (1.4)	3 (2.1)	0 (0.0)	9 (1.1)

Source: Vol 21, Section 12.2.2, Text Table 13

Reviewer's comment: The types of adverse events reported for MP03-33 in Study MP430 are consistent with the known safety profile of intranasal azelastine. MP03-33 compared favorably to Astelin in terms of dysgeusia. In general, the frequency of adverse events was lower than the rates observed in the controlled clinical trials supporting approval of Astelin 2 spray BID for treatment of SAR. For comparison, as noted in the Astelin product label, dysgeusia/bitter taste was reported in 19.7%, headache in 14.8%, somnolence in 11.5%, nasal burning in 4.1%, and epistaxis in 2.0%. For the Astelin 1 spray BID dosing regimen, dysgeusia was reported in 8.3% and somnolence in 0.4%.

10.1.2.7.5 Vital signs

No notable derangements in vital signs were noted in any of the treatment groups during the 14-day treatment period (Source Vol 22, Section 14.0, Table 14.3.5).

10.1.2.7.6 Physical examinations

General physical examinations were performed at Screening. Focused nasal exams were performed at Screening, Randomization, Day 7, and Day 14/Termination Day. No significant changes in the focused nasal exam were recorded in any of the treatment groups for the 14-day treatment period. The most common observations were physical findings consistent with allergic rhinitis (e.g. boggy turbinates, pale mucosa, watery mucosa, etc.).

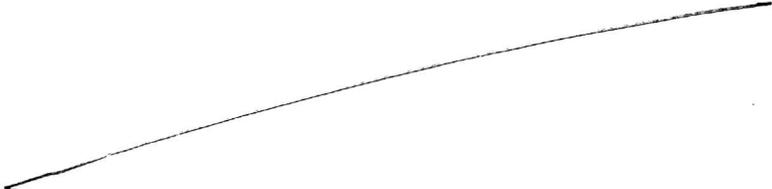
10.1.2.8 Clinical laboratory evaluations

Not applicable.

10.1.3 Study summary and conclusions

The results of Study MP430 provide support for dose-related efficacy of MP03-33 over placebo in the treatment of the symptoms of SAR, although these results were statistically significant only for the higher, 2-spray dose. The active comparator, the commercially available unsweetened formulation (Astelin), showed similar efficacy against placebo, supporting the clinical comparability of the proposed sweetened azelastine formulation, MP03-33, with the currently marketed product. The proposed BID regimen is the same as the dosing regimen for the currently marketed product, and is supported by the data provided. Secondary efficacy variables were also supportive of the higher dose of MP03-33 over placebo; results for the lower dose of MP03-33 were also generally favorable if not statistically significant.

Review of the safety data does not identify any new safety signals. The most common adverse events observed – primarily dysgeusia, headache, epistaxis, and local irritation – are consistent with the safety profile of the approved commercial product, Astelin.



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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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10.3 Individual Study Report: Study MP432

10.3.1 Study Protocol: Study MP432, Active-controlled trial of the safety and tolerability of MP03-33 in patients with chronic allergic or nonallergic rhinitis

10.3.1.1 Study administrative information

- Study initiation date: July 24, 2006
- Study completion date: Ongoing (interim report included in NDA submission)
- Location: 48 sites from 5 countries (Australia, Bulgaria, France, Slovakia, United Kingdom)

10.3.1.2 Study objectives/rationale

- Evaluate the safety and tolerability of MP03-33 with chronic use over a 1-year period in patients with chronic allergic or non-allergic rhinitis compared to commercially available azelastine hydrochloride (Astelin)

10.3.1.3 Study design and overview

The study is an ongoing 1-year randomized, open-label, active-controlled, parallel-group study in patients with chronic allergic or non-allergic rhinitis. Interim analysis was performed once 200 patients had completed 6 months of the study. Patients meeting screening criteria were randomized to receive MP03-33 or Astelin, 2 sprays to each nostril BID. To date, safety and tolerability assessments were made at Months 1, 3, and 5 along with phone contact at Months 2, 4, and 5. Efficacy in patients 18 years and older was assessed using the mini-RQLQ. No efficacy assessments were made in patients 12 to 17 years of age.

10.3.1.4 Patient Population

A total of 800 patients 12 years of age and older with chronic allergic or non-allergic rhinitis are expected to be enrolled in the study. The interim analysis is based on 559 patients (281 in MP03-33 treatment group and 278 in the Astelin treatment group).

Inclusion criteria

- 12 years of age and older
- ≥ 1 year history of rhinitis due to perennial allergies, non-allergic triggers, or vasomotor rhinitis (VMR). Diagnosis must have been made on the basis of medical history, physical exam, rhinitis symptoms, skin testing or RASTs, and may have also included nasal smears. Patients with seasonal allergies were included provided that they had significant symptoms outside the allergy seasons.
- General good health
- If on immunotherapy, on stable maintenance regimen for at least 30 days prior to the first study visit

Exclusion criteria

- Use of investigational drug 30 days prior to screening
- Hypersensitivity to azelastine, sorbitol, or sucralose
- Pregnancy or nursing mothers
- Women of childbearing potential who are not abstinent and do not practice a medically acceptable method of contraception
- Nasal disease which may interfere with deposition of intranasal medication
- Asthma (except mild intermittent) or other significant pulmonary disease
- Known history of alcohol or drug abuse
- Any significant surgical or medical condition

10.3.1.5 Treatments

- MP03-33 2 sprays to each nostril BID (137 mcg azelastine/actuation)
- Astelin 2 sprays to each nostril BID (137 mcg azelastine/actuation)

10.3.1.6 Study procedures

10.3.5.6.1 Blinding

The study is open-label.

10.3.5.6.2 Prior and concomitant therapy

The following medications were prohibited during the course of the study: antihistamines, oral and intranasal anticholinergic agents, topical and oral decongestants, intranasal or inhaled corticosteroids, systemic corticosteroids, omalizumab, leukotriene inhibitors, nasal saline, and other intranasal medications.

An exception was made for certain rescue medications, such as oral decongestants for upper respiratory infection, if their use was limited to no more than 5 consecutive days and no more than 2 courses per month. No intranasal products were permitted for rescue.

10.3.5.6.3 Schedule of assessments

Table 32 presents the schedule of assessments for Study MP432. In addition to the scheduled clinic visits, study staff contacted patients by telephone at Months 2, 4, 5, 7, 8, 10, and 11 for additional assessment of compliance, concomitant medication use, and adverse events.

Procedure	Screening Day -7	V2	V3 Month1	V4 Month3	V5 Month6	V6 Month9	V7 Month12
Medical history	X						
Physical exam	X						
Nasal exam†	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory tests*	X						
ECG	X						
Urine pregnancy test	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Dispense treatment diary		X	X	X	X	X	X
Mini-RQLQ		X	X	X	X	X	X
Dispense study medication		X	X	X	X	X	
Collect used study medication			X	X	X	X	X
Collect treatment diary		X	X	X	X	X	X
Assess compliance		X	X	X	X	X	X
Adverse events assessment		X	X	X	X	X	X

† Focused exam of the head and neck and graded on numeric scale of 0 to 3 from mild to severe.

* Includes hematology, chemistry, and urinalysis.

Source: Volume 47, Section 9.1.5.3, Table 2

Nasal exam

Focused exam of the head and neck was performed at each study visit. Investigators graded any of the following positive findings on a scale of 0 to 3 from mild to severe: mucosal edema, nasal discharge, mucosal bleeding, mucosal ulceration, and crusting of mucosa. Mucosal bleeding or ulceration was recorded as adverse events. Patients who developed mucosal bleeding or ulceration severe enough to prevent daily activity or who developed a nasal perforation were

referred to an otorhinolaryngologist and followed until resolution of the lesion. Additional examination of the conjunctiva, tympanic membranes, and lymph nodes of the head and neck was performed and abnormalities recorded.

Mini RQLQ

An abbreviated 14-item version of the Rhinitis Quality of Life Questionnaire (Mini-RQLQ) was completed by patients at each study visit. The Mini-RQLQ consists of 5 domains (Activities, Practical Problems, Nose Symptoms, Eye Symptoms, and Other Symptoms), each rated on a 7-point scale with 0 = no trouble from rhinitis symptoms to 6 = extremely troubled. The Domain score was calculated from the mean score of all items in the domain. The Overall score was calculated from the mean score of all items. The Mini-RQLQ was administered only in patients 18 years of age and older.

10.3.5.6.4 Treatment compliance

Patients recorded each dose of study medication in the patient diary, which was reviewed at each study visit and reconciled with bottle weights. Any discrepancy was to be resolved prior to the end of the visit and recorded in the comment section of the CRF. If more than 50% of required doses were missing in the diary, discontinuation from the study was considered.

10.3.1.7 Efficacy parameters

10.3.1.8 Primary efficacy variable

Study MP432 is intended primarily as a long-term safety study. In terms of efficacy, patients completed an abbreviated 14-item version of the Rhinitis Quality of Life Questionnaire (Mini-RQLQ) at each study visit. Change from baseline to each clinical visit up to 6 months (1, 3, and 6 months) was calculated for the overall score and individual domain scores. The Mini-RQLQ was administered only in patients 18 years of age and older; no formal efficacy assessments were made in patients 12 to 17 years of age.

10.3.1.9 Secondary efficacy variables

Additional efficacy assessments were not made.

10.3.1.10 Safety parameters

- Frequency of patient-reported AEs, coded using MedDRA
 - If the onset date of an AE was incomplete or missing, the AE was assumed to have started after the first date of study medication.
 - Events with missing severity were assumed mild if the event started prior to the first dose of study medication. If started after the first dose, the event was assumed to be severe.
 - Events with missing relationship to study drug were assumed to be unrelated if started prior to the first dose of study drug.
- Serial nasal examinations

10.3.1.11 PK parameters

No PK assessments were made.