

Patients entered the individual symptom scores in their diary cards in 12-hour interval both reflectively and instantaneously. Scores for the four individual symptoms were measured on a 4-point scale:

- 0=no symptoms
- 1=mild symptoms
- 2=moderate symptoms
- 3=severe symptoms

As defined, TNSS ranges from 0 to 24.

The secondary efficacy endpoints included:

1. Onset-of-action (change from baseline in instantaneous TNSS over the first 4-hour treatment).
2. Change from baseline in instantaneous TNSS for the 14-day treatment period.
3. Change from baseline in 12-hour sum of AM and PM reflective individual symptom scores.
4. Change from baseline in reflective TNSS to the end of first 12-hour dosing interval as observed on the AM of Day 2.
5. Change from baseline in sum of AM and PM reflective TNSS to the end of first 12-hour dosing interval at Day 2.
6. Change from baseline in sum of AM and PM reflective TNSS to the end of first 12-hour dosing interval at Day 14 or last day in study.
7. Change from baseline to Day 14 in RQLQ based on overall score of RQLQ.

The descriptions of the secondary efficacy variables 1-7, above, and other exploratory outcome variables can be found on page 25 of the study report.

### ***Analysis Patient Populations***

Male and female patients, 12 years of age and older, with a minimum 2-years history of SAR who met all study inclusion/exclusion criteria were randomized. Efficacy analyses were done in intent-to-treat (ITT) population consisting of all randomized patients with at least one post baseline observation. A total of 834 patients who met the entrance criteria were randomized to double-blind treatments. Among these patients, 815 completed the study. The disposition of the patients can be found in Table 1 page 40 of the study report. An image of this table is shown below.

**Table 4 Raw means and standard deviations of 14-day AM+PM reflective TNSS by treatment (Study 430)**

Treatment	#Patients	Mean of Baseline Combined (AM+PM) TNSS	Mean of Day 14 Combined (AM+PM) 12-Hr Reflective TNSS	SD of Day 14 Combined (AM+PM) 12-Hr Reflective TNSS
Astelin x1	137	18.18	14.27	4.81
MP03-33 x1	139	18.20	13.95	4.91
MP03-33p x1	137	17.97	14.56	4.64
Astelin x2	137	18.16	13.98	5.02
MP03-33 x2	146	18.04	13.18	5.30
MP03-33p x2	138	18.14	15.34	4.65

Source: D\_tnss\_analysis3

**Table 5 LS-Mean change from baseline to 14-day AM+PM reflective TNSS by treatment (Study 430)**

Treatment	#Patients	LS-Mean	StdErr	Lower CL	Upper CL
Astelin x1	137	-3.94	0.38	-4.68	-3.20
MP03-33 x1	139	-4.20	0.37	-4.94	-3.47
MP03-33p x1	137	-3.51	0.38	-4.25	-2.76
Astelin x2	137	-4.23	0.38	-4.98	-3.49
MP03-33 x2	146	-5.04	0.36	-5.76	-4.33
MP03-33p x2	138	-2.83	0.38	-3.57	-2.09

Source: D\_tnss\_analysis3

**Table 6 Mean change from baseline in reflective TNSS over 14 days in patients 12 years of age and older with SAR (Study 430)**

Treatment	#Patients	Baseline LS Mean	Change from Baseline	Difference From Placebo		
				LS Mean	95% CI	P value
ASTELIN (1 spray)	137	18.10	-3.94	-0.44	-1.46, 0.59	0.4045
MP03-33 (1 spray)	139	18.14	-4.20	-0.70	-1.72, 0.32	0.1810
Placebo (1 spray)	137	17.93	-3.51			
ASTELIN (2 sprays)	137	18.13	-4.22	-1.39	-2.41, -0.36	0.0079
MP03-33 (2 sprays)	146	17.95	-5.04	-2.20	-3.21, -1.20	<0.0001
Placebo (2 sprays)	138	18.12	-2.83			

Source: D\_tnss\_analysis3

This analysis confirmed that MP03-33 and Astelin administered 2 sprays per nostril bid were superior to placebo statistically. MP03-33 and Astelin administered 1 spray per nostril bid did not show statistically significant superiority to placebo.

**Analyses of secondary efficacy variables****Analysis of onset-of-action**

The onset-of-action was analyzed by the sponsor based on data from the first 4 hours following the first dose of study medication. The onset-of-action measurement was defined as change from baseline in instantaneous TNSS. The baseline was the instantaneous TNSS measurement before the study medication was taken. The change in instantaneous TNSS from baseline was analyzed at Minutes 15, 30, 45, 60, 90, 120, 150, 180, and 240.

The following tables show the means and standard deviations of the changes in TNSS from baseline by time point and treatment. A negative number indicates improvement on the TNSS.

**Table 7 Means and standard deviations of the changes in TNSS from baseline (Study 430)**

Time point in minutes	Astelin x1		MP03-33 x1		MP03-33p x1		Astelin x2		MP03-33 x2		MP03-33p x2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
15	-1.40	2.24	-1.32	2.14	-0.79	1.61	-1.42	2.24	-1.10	2.03	-1.12	1.77
30	-2.04	2.51	-2.22	2.20	-1.48	1.74	-2.23	2.40	-2.33	2.27	-1.75	2.00
45	-2.65	2.52	-3.04	2.30	-2.26	2.10	-3.01	2.52	-3.08	2.52	-2.36	2.18
60	-3.12	2.64	-3.44	2.55	-2.76	2.27	-3.70	2.83	-3.66	2.64	-2.79	2.37
90	-3.58	2.79	-3.83	2.53	-3.10	2.43	-4.21	2.64	-3.96	2.71	-3.29	2.60
120	-3.96	2.83	-4.14	2.65	-3.44	2.72	-4.59	2.72	-4.38	2.78	-3.57	2.66
150	-4.40	2.76	-4.53	2.69	-3.55	2.73	-4.74	2.75	-4.54	2.95	-3.66	2.80
180	-4.58	2.92	-4.71	2.68	-4.04	2.88	-4.99	2.93	-4.95	3.06	-3.73	2.86
210	-4.74	3.03	-4.88	2.65	-4.05	2.92	-5.13	2.92	-5.00	3.12	-3.86	2.91
240	-4.61	2.95	-4.84	2.71	-4.12	3.06	-5.30	2.83	-5.10	3.09	-4.01	2.96

Source: d\_tnss\_onset

By-time statistical comparisons represented by p-values between active treatments and placebo are displayed in the following table.

**Table 8 Comparisons between active treatments and placebo in p-values (Study 430)**

Time point in minutes	MP03-33 x2 vs. Placebo	AzNS x2 vs. Placebo	MP03-33 x1 vs. Placebo	AzNS x1 vs. Placebo
15	0.9593	0.2443	0.0333*	0.0179*
30	0.0238*	0.0763	0.0064*	0.0526*
45	0.0073*	0.0219*	0.0067*	0.2061
60	0.0030*	0.0029*	0.0310*	0.3027
90	0.0238*	0.0034*	0.0221*	0.1735
120	0.0088*	0.0019*	0.0414*	0.1749
150	0.0049*	0.0012*	0.0032*	0.0161*
180	0.0002*	0.0003*	0.0542	0.1842

Time point in minutes	MP03-33 x2 vs. Placebo	AzNS x2 vs. Placebo	MP03-33 x1 vs. Placebo	AzNS x1 vs. Placebo
210	0.0004*	0.0002*	0.0173*	0.0714
240	0.0010*	0.0003*	0.0374*	0.2079

Source: d\_tnss\_onset

\*: P-value<0.05

The findings in Table 8 are consistent with the sponsor's report (Sponsor's Table 4, page 50, MedPointe Protocol 430). The sponsor claimed in the label, "In patients with seasonal allergic rhinitis, onset was demonstrated within 30 minutes." The sponsor's such claim appears to be justified.

#### Analysis of RQLQ

The sponsor claimed that the overall mean RQLQ scores were statistically improved at Day 14 compared with placebo with the 2 spray per nostril bid dosages of Astelin and MP03-33 with p-values of 0.042 and <0.001, respectively. There were no statistical improvements in the overall RQLQ scores compared with placebo with the 1 spray per nostril bid dosages of Astelin and MP03-33 with p-values of 0.093 and 0.648, respectively.

I verify the sponsor's findings based on the sponsor's data file, D\_RQLQ. There were 834 patients at the time of randomization. At Visit 4 (14 days), there were 825 patients remaining in the RQLQ data file.

The following table shows the results of the RQLQ analysis based on the change from baseline in overall RQLQ scores. The analysis was performed using an ANCOVA model. It included fixed effects of treatment and center. The baseline RQLQ score served as the covariate.

**Table 9 Mean change from baseline in overall RQLQ over 14 days (Study 430)**

Treatment	N	Baseline	Change from baseline	Difference from placebo	95% Lower CL	95% Upper CL	P Value
Astelin x1	135	3.81	-1.20	-0.27	-0.58	0.04	0.0832
MP03-33 x1	138	3.49	-1.01	-0.09	-0.39	0.22	0.5801
MP03-33p x1	136	3.61	-0.93				
Astelin x2	136	3.72	-1.17	-0.31	-0.61	-0.01	0.0417
MP03-33 x2	143	3.74	-1.43	-0.57	-0.87	-0.27	0.0002
MP03-33p x2	137	3.65	-0.86				

Source: D\_RQLQ

I compared the numbers of patients based on the sponsor’s data (D\_RQLQ) and the sponsor’s report (Table 10). There were fewer patients reported in the sponsor’s Table 14.2.11 than existed in the data. The number of patients the sponsor showed represented the number of patients with non-missing data of change from baseline in overall RQLQ.

My p-values for the comparisons between the 1 spray dose regimens and placebo are different from the sponsor’s p-values. However, my results are consistent with the sponsor’s findings.

**Table 10 Discrepancy in the number of patients**

Treatment	# Patients in data file D_RQLQ for Visit=4 (Day 14s)	Sponsor’s ITT patients with available data in Table 14.2.11, page 66, vol 73 of the study report
Astelin x1	135	111
MP03-33 x1	138	113
MP03-33p x1	136	105
Astelin x2	136	113
MP03-33 x2	143	110
MP03-33p x2	137	116
<b>Total</b>	<b>825</b>	<b>668</b>

Other re-analyses of the sponsor’s data for the remaining secondary efficacy variables were not performed for this report.

### Evaluation of Safety

I evaluated the number of adverse events occurring in patients who took at least one dose of study drug during the double-blind safety treatment period.

Table 11 provides the numbers and percentages of AEs using MedDRA preferred terms. Table 12 shows the numbers and percentages of AEs using MedDRA system organ class terms.

Note that AEs marked “\*” are the ones listed in the “adverse reactions” section of the proposed label. The most frequent AE, dysgeusia (unusual taste), was reported less often from patients treated with MP03-33 (1 or 2 sprays) than from patients treated with Astelin.

**Table 11 AE reactions based on MedDRA preferred terms (Study 430)**

AEs presented as: AEPTTXX; Group totals: 137,139,137,137,146,138	Treatment											
	Astelin x1		MP03-33 x1		MP03-33p x1		Astelin x2		MP03-33 x2		MP03-33p x2	
	N	%	N	%	N	%	N	%	N	%	N	%
<b>**NO AE**</b>	95	69.34	102	73.38	110	80.29	95	69.34	99	67.81	107	77.54
<b>DYSGEUSIA</b>	17	12.41	9	6.47	2	1.46	14	10.22	10	6.85	6	4.35
<b>HEADACHE</b>	5	3.65	4	2.88	3	2.19	4	2.92	8	5.48	1	0.72
<b>EPISTAXIS</b>	8	5.84	3	2.16	3	2.19	4	2.92	4	2.74		
<b>NASAL DISCOMFORT</b>	3	2.19			1	0.73	6	4.38	2	1.37		

AEs presented as: AEP TTX T; Group totals: 137,139,137,137,146,138	Treatment											
	Astelin x1		MP03-33 x1		MP03-33p x1		Astelin x2		MP03-33 x2		MP03-33p x2	
	N	%	N	%	N	%	N	%	N	%	N	%
FATIGUE	1	0.73			1	0.73	3	2.19	3	2.05	1	0.72
SOMNOLENCE	2	1.46	2	1.44			2	1.46	3	2.05		
PHARYNGOLARYNGEAL PAIN	2	1.46	2	1.44					2	1.37	2	1.45
DIZZINESS	1	0.73	1	0.72	1	0.73	1	0.73	2	1.37		
DRY MOUTH	1	0.73	1	0.72	1	0.73			2	1.37	1	0.72
SINUS HEADACHE	2	1.46	1	0.72	1	0.73					2	1.45
UPPER RESPIRATORY TRACT INFECTION			2	1.44			2	1.46	1	0.68	1	0.72
DYSPHONIA	1	0.73			1	0.73	1	0.73	2	1.37		
EXCORIATION	1	0.73	1	0.72			2	1.46			1	0.72
SINUSITIS			1	0.72	2	1.46			1	0.68	1	0.72
ABDOMINAL DISCOMFORT					1	0.73	1	0.73			2	1.45
CONTUSION			1	0.72			3	2.19				
MYALGIA					2	1.46			1	0.68	1	0.72
COUGH					1	0.73			2	1.37		
INSOMNIA					2	1.46			1	0.68		
NASOPHARYNGITIS			1	0.72	1	0.73					1	0.72
NAUSEA	1	0.73					2	1.46				
PYREXIA	1	0.73							1	0.68	1	0.72
ABDOMINAL PAIN UPPER			1	0.72			1	0.73				
BACK PAIN									1	0.68	1	0.72
DERMATITIS CONTACT									2	1.37		
DIARRHOEA					1	0.73			1	0.68		
DRY THROAT	1	0.73							1	0.68		
DYSPNOEA	1	0.73			1	0.73						
EAR PAIN									1	0.68	1	0.72
FLATULENCE	1	0.73							1	0.68		
NASAL DRYNESS	1	0.73					1	0.73				
NASAL SEPTUM ULCERATION	1	0.73					1	0.73				
PAIN IN EXTREMITY	1	0.73							1	0.68		
RASH					1	0.73			1	0.68		
SCAB							2	1.46				
THIRST			1	0.72					1	0.68		
URTICARIA	1	0.73							1	0.68		
VOMITING					1	0.73			1	0.68		
ABDOMINAL PAIN LOWER									1	0.68		
ACNE											1	0.72
ARTHRALGIA							1	0.73				
ARTHROPOD BITE			1	0.72								
ASTHMA									1	0.68		
AURICULAR SWELLING							1	0.73				
BACK INJURY			1	0.72								
CONJUNCTIVITIS ALLERGIC									1	0.68		
CONSTIPATION											1	0.72
DECREASED APPETITE			1	0.72								
DERMATITIS ALLERGIC			1	0.72								
DRY SKIN									1	0.68		
DYSPEPSIA					1	0.73						

AEs presented as: AEPTT; Group totals: 137,139,137,137,146,138	Treatment											
	Astelin x1		MP03-33 x1		MP03-33p x1		Astelin x2		MP03-33 x2		MP03-33p x2	
	N	%	N	%	N	%	N	%	N	%	N	%
DYSPNOEA EXERTIONAL							1	0.73				
EAR INJURY							1	0.73				
ECZEMA									1	0.68		
EYE INFECTION							1	0.73				
FACE INJURY	1	0.73										
FLANK PAIN									1	0.68		
FOREIGN BODY SENSATION IN EYES	1	0.73										
FUNGAL INFECTION									1	0.68		
GASTROENTERITIS					1	0.73						
HORDEOLUM			1	0.72								
HYPERSENSITIVITY			1	0.72								
IRRITABILITY			1	0.72								
IRRITABLE BOWEL SYNDROME									1	0.68		
JOINT DISLOCATION							1	0.73				
JOINT SPRAIN			1	0.72								
LACRIMATION INCREASED							1	0.73				
LIMB INJURY	1	0.73										
LYMPHADENITIS			1	0.72								
MUSCLE SPASMS					1	0.73						
MUSCULOSKELETAL STIFFNESS	1	0.73										
NASAL CONGESTION							1	0.73				
NASAL ULCER							1	0.73				
NECK PAIN					1	0.73						
OCULAR HYPERAEMIA											1	0.72
ORAL PAIN	1	0.73										
PALPITATIONS									1	0.68		
PHOTOSENSITIVITY REACTION	1	0.73										
POOR QUALITY SLEEP									1	0.68		
PROCEDURAL PAIN			1	0.72								
RHINALGIA											1	0.72
RHINITIS											1	0.72
RHINITIS ALLERGIC	1	0.73										
SCAR							1	0.73				
SEDATION											1	0.72
SNEEZING											1	0.72
STRESS	1	0.73										
SUNBURN											1	0.72
TENDONITIS											1	0.72
THERMAL BURN	1	0.73										
THROAT IRRITATION									1	0.68		
TONSILLAR NEOPLASM BENIGN											1	0.72
TOOTH DISORDER			1	0.72								
TOOTH INFECTION											1	0.72
TOOTHACHE											1	0.72
TRIGGER FINGER									1	0.68		
VITREOUS FLOATERS							1	0.73				

Source: AE\_ANA

**Table 12 AE reactions based on MedDRA system organ class terms**

AEs presented as: AESOCTXT; Group totals: 137,139,137,137,146,138	Treatment											
	Astelin x1		MP03-33 x1		MP03-33p x1		Astelin x2		MP03-33 x2		MP03-33p x2	
	N	%	N	%	N	%	N	%	N	%	N	%
<b>**NO AE**</b>	95	69.34	102	73.38	110	80.29	95	69.34	99	67.81	107	77.54
NERVOUS SYSTEM DISORDERS	19	13.87	11	7.91	7	5.11	13	9.49	15	10.27	7	5.07
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	14	10.22	5	3.60	7	5.11	15	10.95	14	9.59	4	2.90
GASTROINTESTINAL DISORDERS	11	8.03	9	6.47	5	3.65	12	8.76	13	8.90	8	5.80
INFECTIONS AND INFESTATIONS			5	3.60	4	2.92	3	2.19	3	2.05	5	3.62
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4	2.92	6	4.32			6	4.38			2	1.45
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2	1.46	2	1.44	1	0.73	3	2.19	5	3.42	2	1.45
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2	1.46			4	2.92	1	0.73	5	3.42	3	2.17
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2	1.46	1	0.72	1	0.73	3	2.19	5	3.42	1	0.72
EYE DISORDERS	1	0.73					2	1.46	1	0.68	1	0.72
PSYCHIATRIC DISORDERS	1	0.73			2	1.46			1	0.68		
EAR AND LABYRINTH DISORDERS							1	0.73	1	0.68	1	0.72
BLOOD AND LYMPHATIC SYSTEM DISORDERS			1	0.72								
CARDIAC DISORDERS									1	0.68		
IMMUNE SYSTEM DISORDERS			1	0.72								
METABOLISM AND NUTRITION DISORDERS			1	0.72								
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)											1	0.72

Source: AE\_ANA

(4)

b(4)

1   Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

## Summary and Conclusions

### Statistical issues and Collective Evidence

#### Efficacy evaluation

Based on the analysis of the efficacy data from Study 430, I confirmed that MP03-33 and Astelin administered 2 sprays per nostril bid are statistically superior to placebo. MP03-33 and Astelin administered 1 spray per nostril bid did not show statistical superiority to placebo. The sponsor argued that the lack of statistically significant difference from placebo was due to a placebo effect that was not anticipated. The sponsor also argued that the superiority of Astelin 1 spray was successfully demonstrated that lead to the approval. More over, the comparability between Astelin and MP03-33 has been demonstrated. I recognize the sponsor's rationale. Therefore, I consider the approvability of MP03-33 at 1 spray per nostril bid to be a regulatory decision rather than a statistical one.

In Study 430, the sponsor also claimed that the onset-of-action was established at 30 minutes for MP03-33. Based on the analysis using the change from baseline (instantaneous TNSS measurement before the study medication was taken on Day 1 of the treatment) in instantaneous TNSS, onset-of-action was demonstrated within 30 minutes.

---

b(4)

Based on the data of Study 430, the overall mean RQLQ scores were statistically significantly improved at Day 14 compared with placebo with the 2 spray per nostril bid dosages of Astelin and MP03-33. Note, only the difference between MP03-33 and placebo achieved the minimum important difference criterion of 0.5. There were no statistical improvements in the overall RQLQ scores compared with placebo with the 1 spray per nostril bid dosages of Astelin and MP03-33.

#### Safety evaluation based on AE findings

The most frequent AE, dysgeusia (unusual taste), was reported less often from patients treated with MP03-33 (1 or 2 sprays) than from patients treated with Astelin.

### Conclusions and Recommendations

MP03-33 and Astelin administered 2 sprays per nostril bid were statistically significantly superior to placebo. MP03-33 and Astelin administered 1 spray per nostril bid did not show statistical superiority to placebo. Taking evidence from previous clinical trials into

consideration, the approvability of MP03-33 at 1 spray per nostril bid should be a regulatory decision.

The onset-of-action time of MP03-33 showed to be 30 minutes postdose.

The most frequent AEs included dysgeusia, headache, epistaxis, nasal discomfort, fatigue, pharyngolaryngeal pain, and somnolence, most of which were included in the proposed label.

## COMMENTS ON LABELING

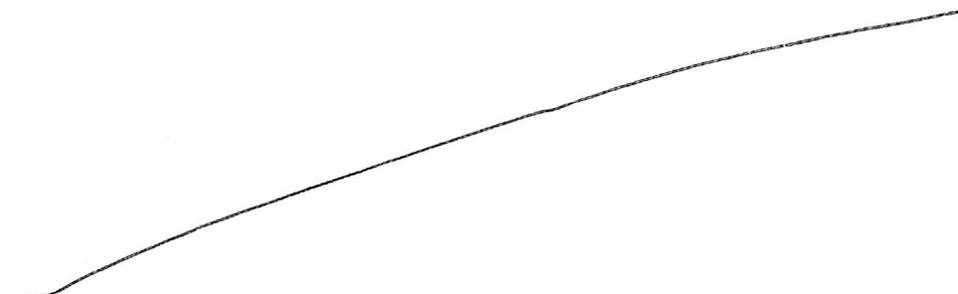
### *Clinical Studies*

The sponsor's table, below, is based on a *post-hoc* analysis using pooled placebo arm rather than the primary efficacy analysis pre-specified in the protocol (See Table 14, below).



b(4)

My analysis confirmed that MP03-33 and Astelin administered 2 sprays per nostril bid were statistically superior to placebo. However, MP03-33 and Astelin administered 1 spray per nostril bid did not show statistical superiority to placebo (See Table 15).



b(4)

b(4)

*Adverse Reactions*

Reported AEs from Study 430 included dysgeusia, headache, epistaxis, nasal discomfort, fatigue, pharyngolaryngeal pain, and somnolence. I suggest that all these AEs are considered to be included in the label.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Ted Guo  
3/28/2008 01:39:07 PM  
BIOMETRICS

Qian Li  
3/28/2008 01:45:27 PM  
BIOEQUIVALENCE STATISTICIAN  
I Concur.