

- The proposed tradename, _____, remains under review. Consultation from the Division of Medication Errors and Technical Support (DMETS) on the tradename is pending. b(4)
- Section 1, Indications and Usage: The recommended indication is the treatment of SAR in patients 12 years of age and older. The SAR indication in patients 5 to 11 years of age and the VMR indication for all ages are not recommended for approval.
- Section 5, Warnings and Precautions: In addition to the warning regarding concurrent use of CNS depressants with azelastine, a warning regarding fatigue and somnolence while performing activities requiring mental alertness is recommended.
- Section 6.1, Clinical Trials Experience
 - Inclusion of safety data for the Astelin active control arm in both the 2-week efficacy study and the 6-month safety study has been added to provide a link to the pre-existing safety database available for Astelin.
 - Statement that no pediatric safety information is available for the sweetened formulation added.
- Section 7, Drug Interactions: Information regarding ketoconazole and erythromycin has been separated into Section 7.2; information regarding cimetidine and ranitidine follows in Section 7.3. Section 7.1 will remain designated for discussion of CNS depressants.
- Section 8, Use in Specific Populations
 - Section 8.1, Pregnancy: Pre-clinical information on teratogenic effects has been reworded to maintain consistency with other labels in the new PLR format and according to recommendations made by the SEALD and Maternal and Child Health Teams.
 - Section 8.4, Pediatric Use: The limitations of data available for patients 5 to 11 years of age have been added. Discussion of efficacy in this age group should be removed as the SAR indication in this age group is not recommended.
- Section 13.2, Animal Toxicology and/or Pharmacology Reproductive Toxicology Studies: A new Section 13.2 has been added summarizing the preclinical information on azelastine and reproductive toxicology findings.
- Section 14, Clinical Studies
 - Section 14.1, Seasonal Allergic Rhinitis: The description of the clinical trial is modified to include the Astelin comparator arm, and data for both the 1- and 2-spray doses of MP03-33, Astelin, and placebo will be included in the table.
 - Placebo results should not be pooled, as initially proposed by the Applicant. An additional statement regarding the efficacy of the 1-spray dose of Astelin demonstrated in previous controlled clinical trials is recommended for inclusion.
 - Efficacy information on patients 5 to 11 years of age should be removed.

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this application.

10 Individual Study Reviews

10.1 Individual Study Report: Study MP430

10.1.1 Study protocol: MP430

10.1.1.1 Study administrative information

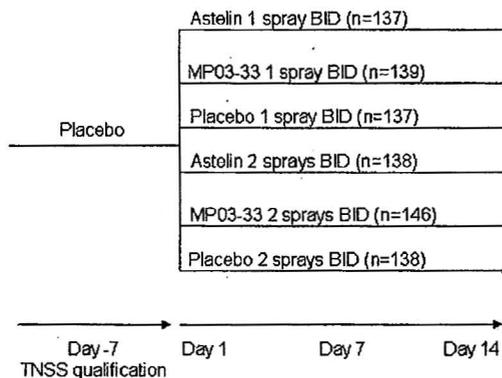
- Study initiation date: February 27, 2006
- Study completion date: June 21, 2006
- Location: 30 centers in the United States

10.1.1.2 Objectives/Rationale

- Determine if MP03-33 can demonstrate comparable efficacy to the commercial formulation of Astelin Nasal Spray
- Evaluate the dose-response relationship between the 1- and 2-spray dosage
- Determine onset of action
- Determine the tolerability of MP03-33 over a 2-week study period

10.1.1.3 Study design overview

MP430 was a 2-week, randomized, double-blind, parallel-group, placebo- and active-control study comparing MP03-33 1- and 2-sprays twice daily and the commercial formulation of azelastine (Astelin) 1 and 2-sprays twice daily with placebo (MP03-33 vehicle) in patients with seasonal allergic rhinitis.



10.1.1.4 Study population

780 patients with moderate to severe allergic rhinitis.

Inclusion criteria

- 12 years of age and older
- Written informed consent/pediatric assent

- Screening visit: Have a 12-hour rTNSS (AM or PM) ≥ 8 out of a possible 12 and a congestion score of 2 or 3 on Day -7
- Randomization visit:
 - Have a 12-hour rTNSS ≥ 8 on 3 separate days (1 of which was within 2 days of Day 1 and can include the morning of Day 1) during the Lead-in Period *AND*
 - AM or PM nasal congestion ≥ 2 on 3 separate days (1 of which was within 2 days of Day 1 and can include the morning of Day 1).
 - iTNSS ≥ 8 before beginning the onset of action assessment on Day 1
- Must have taken ≥ 10 doses of study medication during the Lead-in Period
- ≥ 2 year history of SAR during the spring pollen allergy season
- IgE-mediated hypersensitivity to local spring pollen confirmed by skin prick or intradermal testing within the last year.
 - ≥ 3 mm wheal larger than control on SPT *OR*
 - ≥ 7 mm wheal larger than control on IDT
- General good health
- Stable immunotherapy, if applicable, for at least 30 days before first study visit

Exclusion criteria

- Use of any investigational drug within 30 days prior to Day -7
- Hypersensitivity to drugs similar to azelastine, sorbitol, or sucralose
- Pregnancy or breastfeeding
- Women of childbearing potential who are not abstinent and not practicing a medically acceptable method of contraception
- Respiratory tract infection within 2 weeks prior to Day -7
- Respiratory tract infection requiring oral antibiotics within 2 weeks prior to Day -7
- Other nasal diseases which may affect deposition of intranasal medication
- Asthma (except mild, intermittent asthma) or other significant pulmonary disease
- Known history of drug or alcohol abuse
- Surgical or medical condition which may alter pharmacokinetics of study drug
- Clinically relevant abnormal physical findings within 1 week of randomization
- Planned travel outside the study area during the study period

10.1.1.5 Study treatments

10.1.1.5.1 Treatment groups

Group	Treatment	Total daily dose	Regimen
I	Astelin*	0.55 mg (137 mcg/spray)	1 spray BID
II	MP03-33	0.55 mg (137 mcg/spray)	1 spray BID
III	MP03-33 vehicle placebo	0 mg	1 spray BID
IV	Astelin*	1.1 mg (137 mcg/spray)	2 sprays BID
V	MP03-33	1.1 mg (137 mcg/spray)	2 sprays BID
VI	MP03-33 vehicle placebo	1.1 mg (137 mcg/spray)	2 sprays BID

* Commercially available, unsweetened azelastine nasal spray (Astelin)

10.1.1.5.2 Randomization

Randomization was performed by a third party biostatistical group that used an automated system for generating random assignment numbers. The system assigned random permutations of the treatment groups to consecutive groups of 6 patients. The lead statistician reviewed the randomization scheme prior to release.

10.1.1.5.3 Blinding

Nasal spray bottles were labeled with sponsor identification, protocol number, dosing instructions, storage conditions, and a caution statement, with additional space for site number, patient number, patient initials, and date dispensed. A blinded panel containing the product identity, quantity, and lot number was also attached to the bottles and was sealed. The blinded portion was only to be opened in an emergency.

Reviewer's note: Given the notable bitter aftertaste associated with azelastine, blinding of the study drug administered may not have been complete, particularly for patients with prior exposure to the drug.

10.1.1.5.4 Administration

On Day -7, patients received a 7-day supply of placebo nasal spray. Patients were observed taking the initial dose of placebo spray to ensure proper technique. Unused medication was returned on Day 1. On Day 1, patients received a 14-day supply of study drug nasal spray.

Reviewer's comment: The placebo nasal spray used during the run-in period was the MP03-33 vehicle, containing sucralose and sorbitol. Patients then randomized to the Astelin treatment group were most likely able to taste the difference from the sweetened placebo.

10.1.1.5.5 Treatment compliance

Patients were instructed to record each dose of study drug taken in the TNSS diary. On Day 1, 7, and 14, the study staff reviewed the amount of study medication returned and the amount recorded in the diaries, and assessed treatment compliance. Any discrepancies were to be resolved before the patient left the clinic site for that day.

10.1.1.6 Study procedures

10.1.1.6.1 Concomitant medications

The use of concomitant medications was discouraged but permitted at the discretion of the investigator. Intranasal saline, antibiotics to treat respiratory infections, and radiation therapy were prohibited. The following medications were not permitted during the study period and required the following washout periods prior to Day -7:

Medication/therapy	Time prior to Day -7
Loratadine	5 days
Desloratadine	5 days
Cetirizine	5 days
Fexofenadine	5 days
Azelastine nasal spray	5 days
Cromolyn compounds	14 days
Oral and intranasal anticholinergic agents	5 days
Leukotriene inhibitors	14 days
Antihistamines	5 days
Oral or other systemic corticosteroids	30 days
Intranasal corticosteroids	14 days
Ocular corticosteroids	7 days
All ocular mast cell stabilizers	14 days
Ephedrine or pseudoephedrine	5 days
Decongestants including cold preparations	5 days
Tricyclic antidepressants	30 days
Monoamine oxidase inhibitors	14 days
Immunosuppressives/immunomodulators	30 days
IgE antagonist	130 days

10.1.1.6.2 Assessments and evaluations

Table 15 shows the schedule of assessments and evaluations performed in Study MP430.

Procedure	Lead-in period	Treatment period		
	Day -7 Screening	Day 1 Randomization	Day 7	Day 14 or early termination
TNSS qualification				
Inclusion/exclusion criteria	X	X		
Skin test ^a	X	X		
Physical exam/history	X			
Nasal exam	X	X	X	X
Vital signs ^b	X	X	X	X
Urine pregnancy test	X			
Patient instruction	X	X	X	
Dispense placebo lead-in meds	X			
Dispense TNSS diary	X	X		
RQLQ ^c		X		X
Rhinitis questionnaire		X		
Dispense study medication		X		
Onset of action assessment		X		
AE assessment		X	X	X
Collect TNSS diary		X	X	X
Collect use study medication		X		X

^a May be omitted if patient had positive skin test for spring pollen during the last year.

^b Body weight, temperature, blood pressure, heart rate, and respiratory rate

^c Administered prior to first dose of study medication on Day 1

10.1.1.6.3 Efficacy parameters

10.1.1.6.3.1 Primary efficacy variables

The primary efficacy variable was the change from baseline in 12-hour combined (AM plus PM) reflective TNSS (rTNSS) over the 2-week, double-blind treatment period compared to placebo. Patients recorded symptoms in the diaries twice daily, AM and PM. The baseline score was defined as the average of the combined AM and PM TNSS during the 7-day placebo lead-in period. Patients evaluated 4 nasal symptoms on a 0-4 scale (none to severe): runny nose, sneezing, itchy nose, and nasal congestion. The highest possible combined score on this scale was 32 (maximum AM rTNSS of 16 + maximum PM rTNSS of 16).

10.1.1.6.3.2 Secondary efficacy variables

Secondary efficacy variables included the following:

- Onset of action (first timepoint after initiation of treatment when active drug demonstrated a statistically significant change from baseline iTNSS compared to placebo over the 4-hour post-dose period following initial administration of study drug)
 - Timepoints assessed: 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes
- Change from baseline iTNSS for the 14-day treatment period
- Change from baseline rTNSS for individual symptom scores for the 14-day treatment period
- Change in TNSS from baseline to end of the first 12-hour dosing interval
- Change from baseline 12-hour rTNSS to Day 2 (AM)
- Change from baseline 12-hour rTNSS to endpoint (Day 14 or last day of study)
- Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

As an additional exploratory variable, the Sponsor estimated the percentage of patients with sensitivity to nonallergic triggers.

Reviewer's Comment: Regarding onset of action, DPAP considers onset of action as the first timepoint after initiation of treatment when active drug demonstrated a statistically significant change greater than placebo treatment from baseline and the statistically significant difference between drug and placebo should be maintained for some period from this point forward (Draft Guidance for Industry- Allergic Rhinitis: Clinical Development Programs for Drug Products).

10.1.1.6.4 Safety parameters

10.1.1.6.4.1.1 Adverse experiences

Adverse events were recorded in patient diaries and assessed at each study visit during the randomized treatment period.

10.1.1.6.4.1.2 Laboratory assessments

Prick-puncture allergen skin testing was performed at Screening. No blood laboratory tests were routinely assessed during the study.

10.1.1.6.4.1.3 Physical exams

Complete physical exams were performed at Screening. Focused nasal exams were performed at subsequent study visits.

10.1.1.6.4.1.4 Vital signs

Vital sign measurements included the following: Body weight, temperature, blood pressure, heart rate, and respiratory rate. These assessments were performed at each study visit.

10.1.1.7 Statistical plan

Efficacy analyses were based on an ITT population consisting of all randomized patients with at least one post-baseline observation. A separate analysis was based on the evaluable patient population, consisting of all patients who completed the 2-week, double-blind treatment period as per protocol. Demographic and background information were summarized by means of frequency distributions for categorical variables and by the descriptive statistics for continuous variables. The primary efficacy endpoint was assessed using an ANOVA model to compare treatment groups with baseline as a covariate. Missing TNSS values were imputed using the last observation carried forward (LOCF). Individual nasal symptoms were not carried forward for calculating the total score. If any of the 4 nasal symptoms were missing, the TNSS was designated as missing. Sample size was calculated so that the study would have 80% power to detect a change of 1.76 units in the AM and PM combined TNSS from baseline compared to placebo. Descriptive statistics were used to report the frequency of adverse events and the distribution of vital sign measurements.

10.1.2 Results

10.1.2.1 Study patients

A total of 835 patients met inclusion criteria and were randomized to double-blind treatment at 31 sites. A total of 815 patients completed the study and 20 patients discontinued early.

Table 16 Study MP430: Patient disposition							
Disposition	1 spray BID			2 sprays BID			Total
	Astelir N(%)	MP03-33 N(%)	Placebo N(%)	Astelir N(%)	MP03-33 N(%)	Placebo N(%)	
Randomized	137	139	137	138	146	138	835
Completed	136 (99.3)	138 (99.3)	133 (97.1)	135 (97.8)	140 (95.9)	133 (96.4)	815 (97.6)
Discontinued	1 (0.7)	1 (0.7)	4 (2.9)	3 (2.2)	6 (4.1)	5 (3.6)	20 (2.4)
Adverse event	1 (0.7)	0	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	6 (0.7)
Treatment failure	0	0	1 (0.7)	0	0	2 (1.4)	3 (0.4)
Non-compliance	0	0	0	0	1 (0.7)	0	1 (0.1)
Withdrew consent	0	0	0	1 (0.7)	1 (0.7)	1 (0.7)	3 (0.4)
Lost to follow-up	0	1 (0.7)	0	0	1 (0.7)	1 (0.7)	3 (0.4)
Other	0	0	2 (1.5)	1 (0.7)	1 (0.7)	0	4 (0.5)
ITT ^a	137 (100.0)	139 (100.0)	137 (100.0)	137 (99.3)	146 (100.0)	138 (100.0)	834 (99.9)
Evaluable population ^b	129 (94.2)	129 (92.8)	125 (91.2)	132 (95.7)	137 (93.8)	132 (95.7)	784 (93.9)
Safety population ^c	137 (100.0)	139 (100.0)	137 (100.0)	138 (100.0)	146 (100.0)	138 (100.0)	835 (100.0)

^a All patients who were randomized and had at least one post-baseline observation.

^b All patients who completed the 2-week treatment period per protocol.

^c All randomized patients who received at least one dose of study medication.

Source: Vol 21, Section 10.1, Text Table 1

10.1.2.2 Protocol deviations

No amendments were made to the study protocol. The Sponsor listed the following protocol deviations (some patients had more than 1 deviation):

- 1 patient did not have 10 lead-in doses
- 1 patient was found to have a prohibited medical condition
- 1 patient was randomized to the 1 spray BID regimen but actually took 2 sprays BID placebo
- 1 patient was randomized to the 2 sprays BID regimen but actually took 1 spray BID placebo
- 3 patients had a Final Visit outside of the 14 days +/- 2 day window
- 21 patients had <80% or >120% dosing compliance based on diary records
- 15 patients were non-compliant with the TNSS diary and/or study medication

Reviewer's comment: The protocol deviations noted are unlikely to have impacted the overall results and conclusions of Study MP430.

10.1.2.3 Treatment compliance

The duration of exposure and compliance are summarized in Table 9 as assessed by patient diary daily recorded doses and confirmed by bottle weights measured on Days 1, 7, and 14.

Table 17 Study MP430: Duration of exposure and compliance							
	1 spray BID			2 sprays BID			Total (N=834)
	Astelin (N=137)	MP03-33 (N=139)	Placebo (N=137)	Astelin (N=137)	MP03-33 (N=146)	Placebo (N=138)	
Duration (days)							
N	137	138	136	137	146	137	831
Mean	14.5	14.6	14.4	14.6	14.4	14.3	14.5
SD	1.17	1.04	1.48	1.78	1.43	1.61	1.44
Median	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Range	10-18	11-18	7-17	1-19	7-17	6-18	1-19
Total number of sprays							
N	137	138	137	137	146	138	
Mean	57.1	57.6	56.4	110.2	108.5	108.0	
SD	11.49	11.68	11.79	16.35	12.88	15.00	
Median	56.0	56.0	56.0	112.0	112.0	112.0	
Range	22-112	28-128	26-124	4-152	52-132	48-136	
# Patients ≥80% compliance [N(%)]	135 (98.5)	137 (98.6)	135 (98.5)	132 (96.4)	143 (97.9)	133 (96.4)	815 (97.7)

Source: Vol 21, Section 14.1, Table 14.1.4

Reviewer's comment: The 6 treatment arms appear comparable in terms of compliance.

10.1.2.4 Data sets analyzed

Efficacy analyses were performed on the intent-to-treat (ITT) population, including all patients who were randomized and had at least one post-baseline observation. An additional analysis on the evaluable patient population included patients who completed the 2-week double-blind treatment period as per protocol. The safety population included all randomized patients who received at least one dose of study medication and had at least one safety assessment following drug administration.

10.1.2.5 Demographics and baseline characteristics

Patient demographics and baseline characteristics for the ITT population are summarized in the table below.

Table 18 Study MP430: Patient demographics and baseline symptom score						
Variables	1 spray BID			2 sprays BID		
	Astelin N=137	MP03-33 N=139	Placebo N=137	Astelin N=137	MP03-33 N=146	Placebo N=138
Age (Mean, Range)	36.5 (12-73)	34.9 (12-83)	34.5 (12-77)	36.1 (12-71)	33.9 (12-76)	36.6 (12-72)
Gender (male, %)	58 (42.3)	62 (44.6)	56 (40.9)	56 (40.9)	53 (36.3)	54 (39.1)
Race						
Caucasian	95 (69.3)	95 (68.3)	96 (70.1)	93 (67.9)	91 (62.3)	105 (76.1)
Black	18 (13.1)	23 (16.5)	16 (11.7)	25 (18.2)	35 (24.0)	13 (9.4)
Hispanic	18 (13.1)	18 (12.9)	18 (13.1)	10 (7.3)	18 (12.3)	15 (10.9)
Asian	5 (3.6)	2 (1.4)	5 (3.6)	8 (5.8)	1 (0.7)	3 (2.2)
Native American	1 (0.7)	1 (0.7)	2 (1.5)	2 (1.5)	0	1 (0.7)
Other	0	0	0	1 (0.7)	1 (0.7)	1 (0.7)
Total score						
Mean, SD	18.2 (3.36)	18.2 (3.12)	18.0 (2.85)	18.2 (3.19)	18.0 (3.0)	18.1 (2.80)
Range	9-24	8-24	12-24	9-24	11-24	11-24
Duration of SAR (yrs)						
Mean, SD	20.6 (13.41)	19.0 (14.10)	18.1 (12.66)	20.0 (14.24)	18.1 (12.05)	21.1 (13.54)
Range	2-54	2-61	2-66	2-57	2-58	2-59

Source: Vol 21, Section 11.2, Text Table 2

The patients ranged in age from 12 to 83 years with a mean age of 35 years; 41% were male. The average duration of SAR in the study was 19.5 years.

Reviewer's comment: In terms of demographics, the treatment groups appear comparable in terms of age, gender, and racial make-up. Baseline symptom scores and history of SAR appear comparable as well.

10.1.2.6 Efficacy endpoint outcomes

All efficacy analyses are presented using the ITT population unless otherwise stated.

10.1.2.6.1 Primary efficacy endpoint: Change from Baseline to Day 14 in combined (AM plus PM) 12-hour reflective TNSS (rTNSS)

10.1.2.6.1.1 Primary endpoint analysis for ITT

Table 19 Study MP430: Change from baseline combined (AM plus PM) 12-hour rTNSS ^a					
Treatment	Baseline (SD) ^b	Change from baseline	P-value (vs placebo)	% Change from baseline	P-value
1 spray BID					
Astelin	18.14 (3.358)	-4.00 (4.560)	0.400	-21.13 (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)	

^a Based on ITT population

^b Least-square mean; standard deviation

Source: Vol 21, Section 11.4.1.1, Text Table 3

Results of the primary efficacy variable are presented in Table 5. Neither MP03-33 nor the active comparator, Astelin, showed any statistically significant benefit over placebo at the lower 1 spray BID dose. At 2 sprays BID, both MP03-33 and Astelin demonstrated efficacy over placebo.

Reviewer's comment: A statistically significant benefit over placebo was seen only with the higher dose of MP03-33. A treatment difference from placebo of -2.21 points on the combined rTNSS was observed (highest possible combined score = 32), comparable to the treatment difference (-1.40 points) observed for the approved active comparator, Astelin. The study was not designed to make statistical comparisons between MP03-33 and Astelin; however, numerically, MP03-33 appeared to be more efficacious than Astelin at both the lower and higher doses. The Applicant states that the placebo response rate was much higher than the placebo rate observed in previous clinical trials with Astelin and the prespecified sample size did not take such a large placebo effect into account.

10.1.2.6.1.2 Primary endpoint analysis by subgroups

The Applicant also performed subgroup analyses on the bases of age, ethnicity, and gender.

Age

Patients ages 12 to 17 years comprised 16% (N=133) of the ITT population (N=834). In this younger age group, only the 1 spray MP03-33 dose showed a statistically significant improvement over placebo (-4.38 vs. -1.43; p=0.006) [Source: Vol 21, Section 14.1, Table 14.2.1.3.2]. The 2 spray dose of MP03-33 numerically favored MP03-33 over placebo but was not statistically significant (-2.43 vs. -1.41; p=0.363), nor was either dose of Astelin. The Applicant attributes this discrepancy to the small number of young patients. For patients ≥ 65 years of age (n=22), no statistically significant differences from placebo were noted for any of the treatment groups (p=0.478 to 0.894). Of note, the older age group in general had marked placebo responses for both the 1-spray and 2-spray groups (-8.43 and -5.53, respectively).

Ethnicity

Subgroup analyses by ethnicity demonstrated a lack of statistically significant effect among Black/African American patients (n=130), Asians (n=24), and Other races (n=105) in all treatment groups, but numerically favored MP03-33 over placebo for both the 1- and 2-spray doses. Results were comparable to Astelin. Efficacy consistent with the ITT population was observed for White/Caucasian patients (n=575; 69%), who formed the majority of the ITT population.

Gender

The ITT group was 59% female (n=495). Subgroup analyses by gender showed statistically significant differences from placebo only for females receiving the 2 spray MP03-33 dose (-5.60 vs. -2.94; p<0.001). No statistically significant improvements over placebo were noted for female patients receiving the Astelin or the 1 spray dose MP03-33 dose or for male patients in all treatment groups

Reviewer's comment: In general, the subgroup analyses does not show statistically robust support for efficacy, although the results numerically all favor MP03-33 over placebo at both the 1- and 2-spray dose. In addition, MP03-33 performed comparably to the active comparator, Astelin. While small numbers likely had a major impact on the analyses for certain subgroups, such as elderly patients or Asian patients, other factors may have distinguished one subgroup from another. For example, the baseline rTNSS for the younger age group (ages 12 to 17 years) was consistently lower in all treatment arms than for the overall ITT population, while in patients older than 65 years, the baseline rTNSS was higher. The placebo response appears to have been less prominent for the younger age group than for the ITT population, whereas in the older patients, the placebo response seemed very prominent. In the younger age group, however, this discrepancy still does not explain why the 1-spray MP03-33 dose outperformed the 2-spray MP03-33 dose. The 1-spray and 2-spray placebo groups had comparable changes from baseline (-1.41 and -1.43, respectively).

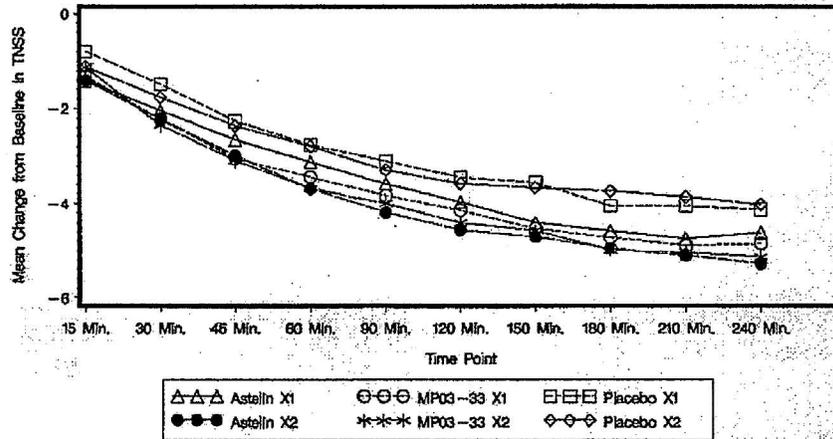
10.1.2.6.2 Secondary efficacy endpoints

10.1.2.6.2.1 Onset of action

Onset of action was defined as the first timepoint after initiation of treatment when active drug demonstrated a statistically significant change from baseline iTNSS compared to placebo over

the 4-hour post-dose period following initial administration of study drug. Results are displayed in Figure 2.

Figure 2 Study MP430: Onset of action (Source: Vol 21, Figure 14.2.3.1, P 44)



A statistically significant and consistent improvement over placebo was seen at 30 minutes for MP03-33 2 sprays BID that lasted for the duration of the 4-hour observation period. Similar effect was seen starting at 45 minutes for Astelin 2 sprays BID. A statistically significant improvement over placebo was first seen at 15 minutes for MP03-33 1 spray BID but the effect was not consistently maintained over the duration of 4 hours. Likewise, a durable effect was not observed for Astelin 1 spray BID.

Reviewer's comment: _____

h(5)

10.1.2.6.2.2 Change from baseline iTNSS for the 14-day treatment period

Results for the change from baseline in combined (AM plus PM) iTNSS over the 14-day treatment period are presented in Table 20. Both the 1- and 2-spray doses of MP03-33 demonstrated statistically significant improvement over placebo.