

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Study	Subjects	Design	Dose	Duration	Relevance
MP429*	54 healthy adult males	R, open-label, parallel group, single-dose	1 or 2 sprays per nostril <ul style="list-style-type: none"> • MP03-33 • Astelin • MP03-36 (0.15% azelastine, 0.15% sucralose) 	Single dose	PK comparison
MP430*	1109	MC, R, DB, PC, 6-arm study	1 or 2 sprays per nostril: <ul style="list-style-type: none"> • MP03-33 • Astelin • Placebo 	2 weeks	Pivotal SAR efficacy/comparability study
MP432*	559	MC, open-label, active control	2 sprays per nostril: <ul style="list-style-type: none"> • MP03-33 • Placebo 	6 months	Long-term safety study

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* Primary studies to establish comparability between Astelin and MP03-33

5.2 Review Strategy

The clinical review focused on the Phase 3 efficacy and safety study (MP430), the 6-month safety study (MP432), and the _____). Detailed review of the individual studies can be found in Section 10 Individual Study Reviews.

_____. The pharmacokinetic study, MP429, was also briefly reviewed and is summarized in the preceding section. A more detailed review can be found in the Clinical Pharmacology reviewer's review.

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Reviews of the studies were based primarily on the study reports prepared by the Applicant. The Applicant's summary data tables were reviewed in detail. Tables and data listings were also reviewed in varying amounts of detail, depending upon the endpoint and review issue. Case report forms (CRF) of patients with Serious Adverse Events (SAE) were reviewed as well. The Applicant provided bibliographies within the study reports. These were reviewed to the extent of

their relevance to the review. Postmarketing safety data from unsweetened azelastine was provided by the Applicant and was reviewed. A literature review was also performed by the reviewer to identify any new safety signals with azelastine.

5.3 Discussion of Individual Studies

This section of the review provides an overview of the three clinical studies, Studies MP430, ~~MP431~~, and MP432. The design and conduct of the pivotal study MP430 and the 6-month safety study are presented here; results of these studies are presented in Sections 6 and Section 7, respectively. ~~MP431 and MP432~~ is presented in addition to a summary of the results. More detailed discussion of ~~MP431 and MP432~~ is located in Section 10 Individual Study Reviews.

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5.3.1 Study MP430

Study MP430 was a multicenter, randomized, double-blind, placebo-controlled, 6-arm parallel group 2-week trial of the safety and efficacy of MP03-33 in patients 12 years of age and older with seasonal allergic rhinitis. After a 1-week placebo lead in period, 835 patients with moderate to severe seasonal allergic rhinitis who met minimum symptom criteria were randomized to one of 6 treatment groups as shown in Table 4:

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)

The **primary efficacy endpoint** was the change from baseline to Day 14 in the combined (AM + PM) 12-h reflective Total Nasal Symptom Score (rTNSS) for MP03-33 compared to placebo. The TNSS included the following component symptoms rated on a 0-4 scale (none to severe): runny nose, sneezing, itchy nose, and nasal congestion. Patients recorded symptoms in diaries twice daily, AM and PM. Astelin was included as a benchmark comparator, but the statistical analysis plan did not specify a formal statistical comparison between MP03-33 and Astelin.

Secondary efficacy variables included onset of action data obtained during the 4-hour period following the initial dose of study medication, instantaneous TNSS (iTNSS), individual symptom rTNSS scores, rTNSS over different time intervals, and the Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Onset of action was defined as the timepoint at which a statistically significant and durable separation from placebo in iTNSS was observed after administration of the first dose of study drug.

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NDA 22-203, N000
TRADENAME (Azelastine hydrochloride intranasal inhalation solution, 137 mcg)

Efficacy analysis was 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.

Reviewer's comment: The study design and endpoints selected are appropriate and consistent with the study design recommended in the Draft Guidance for Industry- Allergic Rhinitis: Clinical Development Programs for Drug Products. Patient inclusion/exclusion criteria, described in the Section 10 Individual Study Reviews, were appropriate for defining a population of patients with moderate to severe SAR.

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5.3.3 Study MP432

Study MP432 is an ongoing, 1-year randomized, open-label, active-controlled, parallel-group study in patients 12 years of age and older with chronic allergic or non-allergic rhinitis. A total of 800 patients are expected to enroll. The submitted study report is based on the first 200 patients who have completed 6 months of the study. Patients were randomized to MP03-33 2 sprays to each nostril BID or Astelin 2 sprays to each nostril BID. The primary objective of the study was to evaluate the safety and tolerability of MP03-33 compared to the commercially available unsweetened formulation. Limited efficacy assessments were performed in patients 18 years of age and older using a truncated version of the RQLQ (Mini-RQLQ). No efficacy assessments were performed in patients 12 to 17 years of age. TNSS data was not collected in this study.

6 Review of Efficacy

Efficacy Summary

The NDA submission contains adequate data to support the proposed indication for MP03-33, the treatment of the symptoms of SAR in patients 12 years of age and older. Evidence of efficacy comes primarily from Study MP430 and pre-existing efficacy information on unsweetened azelastine. _____

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_____. Study MP432 was intended primarily as a safety study and included only limited efficacy assessments (Mini-RQLQ instead of TNSS) in patients 18 years of age and older. As a result, this portion of the efficacy review focuses on the results of Study MP430.

SAR indication

The study design and endpoints selected for Study MP430 were appropriate and consistent with recommendations made in the *Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products*. Patient inclusion/exclusion criteria, described in the Section 10 Individual Study Reviews, were appropriate for defining a population of patients with moderate to severe SAR. The doses selected for study, 1 and 2 sprays per nostril twice daily, correspond to the range of dosing approved for Astelin.

In Study MP430, the 2-spray dose of MP03-33 demonstrated a statistically significant difference from placebo for the primary efficacy endpoint, the change from baseline combined 12-h rTNSS. The 1-spray dose of MP03-33 did not show a statistically significant difference from placebo,

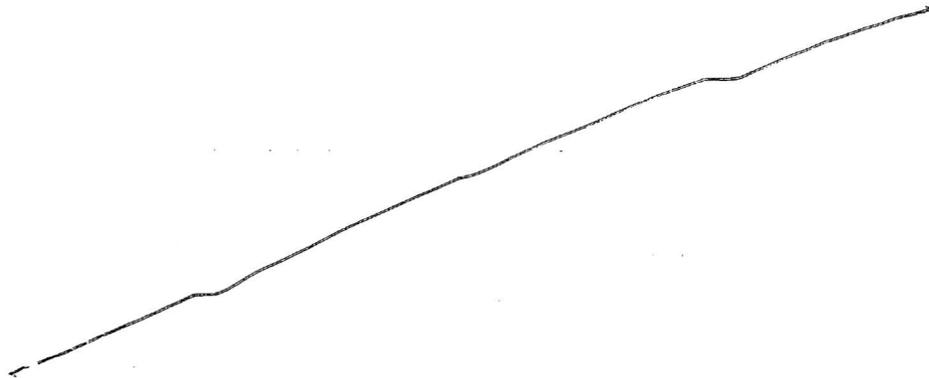
but the results numerically favored MP03-33 and were comparable to results for the commercially marketed product, Astelin. The primary efficacy findings of Study MP430 are summarized in **Table 5**.

Table 5 Study MP430: Change from baseline combined (AM plus PM) 12-hour rTNSS*						
Treatment	N	Baseline LS Mean	Change from baseline	Difference from placebo		
				LS Mean	95% CI	P-value
<i>1 spray BID</i>						
MP03-33	139	18.14	-4.21	-0.70	-1.72, 0.31	0.18
Placebo	137	17.93	-3.51	--	--	--
Astelin	137	18.10	-3.95	-0.44	-1.46, 0.58	0.40
<i>2 sprays BID</i>						
MP03-33	145	17.95	-4.95	-2.11	-3.12, -1.11	<0.001
Placebo	138	18.12	-2.84	--	--	--
Astelin	136	18.13	-4.24	-1.40	-2.42, -0.38	0.007

* The table reflects data values generated by the Statistical Review team's analysis and differ slightly from values generated by the Applicant. The numerical differences do not affect the efficacy conclusions.

Secondary efficacy variables, presented in detail in the Section 10 Individual Study Reviews, were also generally supportive of the 2-spray dose of MP03-33 over placebo; results for the lower 1-spray dose of MP03-33 were not statistically significant but were numerically favorable and comparable to results in the corresponding Astelin treatment arm. The reflective combined symptom scores for the individual symptom components of the TNSS supported the use of the composite TNSS as a primary endpoint. In addition, the iTNSS scores supported the twice-daily dosing interval.

Astelin was included in the study to evaluate the comparability of the sweetened and unsweetened formulations. Although the 1-spray dose of MP03-33 did not beat placebo, MP03-33 performed comparably to the 1-spray Astelin arm. The evidence of efficacy for the 1-spray dose of MP03-33 is based on the demonstrated comparability to Astelin, which has been previously shown to be efficacious at 1 or 2 sprays twice daily for SAR.



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6.1 Indication – Seasonal allergic rhinitis

6.1.1 Methods

See Section 5.3.1 Study MP430 for a description of the study design and conduct.

6.1.2 Demographics

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. The treatment groups appeared comparable in terms of age, gender, and racial make-up. Baseline symptom scores and history of SAR appeared comparable as well. Demographic and baseline rhinitis history are presented in Table 6.

Table 6 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	2-56	2-59

Source: Vol 21, Section 11.2, Text Table 2

Reviewer's comment: Study MP430 included patients down to the age of 12 years.

The implication of this omission is discussed further in Section 7.6.3.

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6.1.3 Patient Disposition

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. Patient disposition is summarized in Table 7.

Disposition	1 spray BID			2 sprays BID			Total
	Astelin N(%)	MP03-33 N(%)	Placebo N(%)	Astelin 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

6.1.4 Analysis of Primary Endpoint

The overall study design of Study MP430 and the primary endpoint, the change from baseline combined 12-h rTNSS, were appropriate for assessment of efficacy and are consistent with recommendations made in the *Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products*. The use of Astelin as an active comparator confirmed the comparability of the two formulations for the SAR indication.

The results for the primary efficacy endpoint are presented in Table 5. The 2-spray dose of MP03-33 demonstrated a statistically significant difference from placebo for the primary efficacy endpoint, the change from baseline combined 12-h rTNSS. 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 1-spray dose of MP03-33 did not show a statistically significant difference from placebo, but the results numerically favored MP03-33. 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. While cross-study comparisons of the placebo effect are difficult to evaluate, the efficacy for the 1-spray MP03-33 dose was comparable to results for the corresponding 1-spray Astelin treatment arm.

6.1.5 Analysis of Secondary Endpoints

The secondary endpoints support the primary efficacy endpoint, providing additional information on the onset of action, duration of effect, and quality of life measurements. The secondary endpoints assessed for Study MP430 were consistent with recommendations made in the *Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products*. Secondary endpoints were pre-specified but without any adjustments for multiplicity. Secondary

efficacy findings are summarized briefly here and reviewed in greater detail in the Section 10 Individual Study Reviews.

The change from baseline for individual TNSS symptom components supported the use of a composite TNSS score as a primary endpoint, demonstrating numerical, if not statistically significant superiority over placebo for itchy nose, runny nose, sneezing, and congestion (Table 21). In general, the 2-spray dose performed better than the 1-spray dose. Overall, MP03-33 performed comparably to Astelin. The change from baseline instantaneous TNSS scores over the 14-day treatment period supported the BID dosing interval.

In terms of onset of action, 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.

The Applicant also evaluated the RQLQ in the study, reporting that the overall mean RQLQ was 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; $p = 0.042$), although the treatment difference was less than 0.5, the difference previously accepted by the Agency as the minimally important difference in the RQLQ. No statistically significant improvements were noted for the lower dose MP03-33 ($p = 0.093$) or Astelin ($p = 0.648$) groups. While these results are generally supportive of MP03-33's efficacy, particularly at the 2-spray dose level, these results have not been replicated in another placebo-controlled study.

6.1.6 Other Endpoints

No other endpoints were assessed.

6.1.7 Subpopulations

The Applicant included subgroup analyses by age, gender, and ethnicity. The individual analyses are described in detail in the Section 10 Individual Study Reviews. In general, the subgroup analyses did not show statistically significant support for efficacy, although the results numerically all favored MP03-33 over placebo at both the 1- and 2-spray dose. In addition, MP03-33 performed comparably to the active comparator, Astelin.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The doses evaluated in the clinical development program are based on the current approved dosing for Astelin. Astelin was initially approved for 2 sprays twice daily, then later approved for 1 spray twice daily dosing. No formal efficacy comparisons between the 1- and 2-spray Astelin doses has been made, and the current product label recommends either 1 or 2 sprays without making a distinction in efficacy. In study MP430, both 1- and 2-spray doses of MP03-

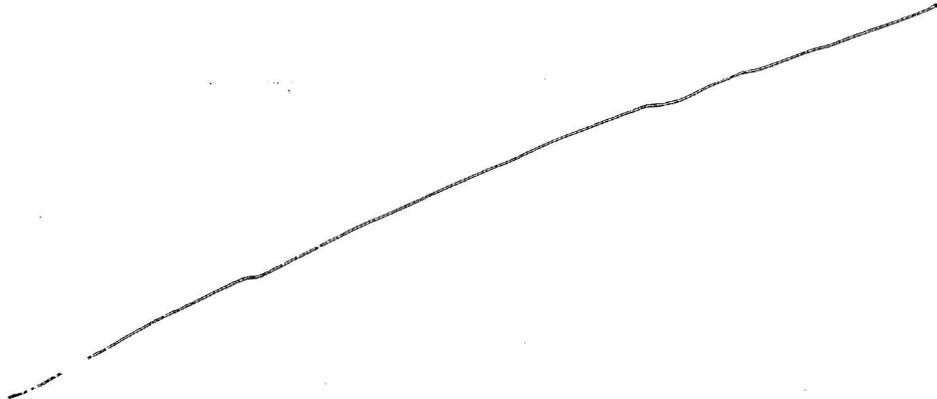
33 and Astelin were evaluated, but the study was not designed to compare the dosing regimens. Therefore, based on the comparability of MP03-33 to Astelin demonstrated in Study MP430 and the pre-existing efficacy data available for Astelin, the clinical recommendation is for both 1 or 2 sprays twice daily of MP03-33 as an appropriate dosing regimen for the proposed SAR indication in patients 12 years of age and older.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No tolerance effects were noted in Study MP430 and have not been previously shown for Astelin.

6.1.10 Additional Efficacy Issues/Analyses

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7 Review of Safety

Safety Summary

The NDA submission contains adequate data to support the safety of MP03-33 in patients 12 years of age and older. The safety of intranasal azelastine has been previously demonstrated in the clinical development program for the unsweetened formulation and is summarized in the current product label. Additional evidence of safety for MP03-33 is based primarily on the assessments performed in the Phase 3 efficacy study, MP430, and the dedicated 6-month safety study, MP432, supplemented by postmarketing data for Astelin and published literature reports up to June 1, 2007 and the subsequent 4-month safety update covering the time period from June 1, 2007 to November 30, 2007.

The data included in this submission shows that the addition of sucralose and sorbitol do not alter the known safety profile of intranasal azelastine in patients 12 years of age and older. The most common adverse events observed were dysgeusia, headache, epistaxis, fatigue, and somnolence. These adverse events are all described in the current product label for Astelin and are consistent with the postmarketing safety profile for Astelin. In the long-term safety study, no cases of nasal ulceration or septal perforation were reported. b(4)

Whether the addition of sucralose and sorbitol alters the safety profile of intranasal azelastine in this age group remains unknown. Therefore, the recommended age range for MP03-33 is patients 12 years and older.

Off-label use of MP03-33 for the treatment of VMR is likely, given that the reference product Astelin is currently approved for both the treatment of SAR and VMR. While the added excipients in MP03-33 may compromise the efficacy of azelastine in VMR, the risk of other adverse events not already associated with Astelin is low. Other significant adverse events are not anticipated with the use of MP03-33 in VMR. Off-label use of MP03-33 in patients 5 to 11 years of age remains a possibility as well, since Astelin is currently approved in this age group. Again, the occurrence of other adverse events not already associated with Astelin is not anticipated but remains a possibility in the absence of safety data in this age group.

As no new safety signals have been identified for MP03-33 compared to Astelin, no risk management plan or post-marketing safety studies are recommended from the clinical review standpoint.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The support for safety of intranasal azelastine has been previously reviewed under NDA 20-114. Evidence of safety for MP03-33 is based primarily on the assessments performed in the Phase 3 efficacy study (MP430) and the dedicated 6-month safety study (MP432) supplemented by postmarketing data for the unsweetened formulation and published literature reports. The design of Studies MP430 and MP432 is presented in Section 5.3.

7.1.2 Adequacy of Data

The data submitted to support the safety of MP03-33 in patients 12 years of age and older for the proposed indication was adequate. The doses and durations of exposure were appropriate, as were the safety evaluations performed during the development program. No safety data was provided for patients 5 to 11 years of age.

The Applicant provided patient data listings that were appropriately indexed for review, as well as CRFs for all SAEs.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

As previously agreed upon with the Division during the pre-NDA meeting held on June 29, 2006, the Applicant submitted the individual study reports for Studies MP430 and MP432 in lieu of a formal Integrated Summary of Safety with pooled data across studies. Therefore, the results of these two studies are discussed in parallel but have not been combined for the purposes of this review.

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