CLINICAL REVIEW

Application Type	NDA
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Reviewer Name	Susan Limb, MD
Review Completion Date	March 31, 2009
Established Name	Azelastine hydrochloride
(Proposed) Trade Name	Astepro® 0.15%
Therapeutic Class	Intranasal antihistamine
Applicant	MEDA
Priority Designation	S
Formulation	Intranasal solution
Dosing Regimen	1 or 2 sprays each nostril BID
Indications	Seasonal allergic rhinitis Perennial allergic rhinitis
Intended Population	Patients 12 years of age and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is Approval. The application contains adequate evidence to support the proposed indication for Astepro 0.15% Nasal Spray: "the treatment of the symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older." The application contains adequate evidence to support a dosing regimen of 1 or 2 sprays BID for the SAR indication and a regimen of 2 sprays BID for the PAR indication.

This is a 505(b)(1) application for a 0.15% concentration, sweetened formulation of azelastine hydrochloride (MP03-36). A sweetened formulation of 0.1% azelastine hydrochloride (Astepro® Nasal Spray; NDA 22-203) was approved on October 15, 2008, for the SAR indication in adults and adolescents 12 years of age and older. Astepro and MP03-36 differ only in terms of the azelastine concentration. An unsweetened formulation of 0.1% azelastine hydrochloride (Astelin® Nasal Spray, NDA 20-114) was originally approved for the SAR indication in adults and adolescents 12 years of age and older at 2 sprays twice daily on November 1, 1996; a 1-spray twice daily dose for patients 5 years of age and older was subsequently approved in a supplement to the original NDA (Supplement 014, approved February 17, 2006). Astelin, is also approved for the treatment of the symptoms of vasomotor rhinitis (VMR) in adults and children 12 years of age and older at a dose of two sprays per nostril twice daily. Neither Astepro nor Astelin carries a PAR indication, and the Applicant is not seeking a VMR indication for MP03-36. In addition to preclinical and clinical data previously reviewed in NDA 20-114 and NDA 22-203, the Applicant provided the results of animal toxicology studies using the 0.15% formulation, supporting CMC information, and new clinical data. The clinical development program included 4 clinical trials in SAR (Studies MP433, MP438, MP439, and MP440) and 3 PAR studies (Studies MP434, MP435, and MP436).

The clinical recommendation for an Approval action is based on the submitted clinical data, as well as the established efficacy and safety of the Astepro and Astelin formulations. The primary support for the SAR indication comes from Studies MP433 and MP438, two 2-week, randomized, placebo-controlled, double-blind studies. Each study demonstrated a statistically significant benefit for MP03-36 over placebo for the treatment of SAR symptoms at a dose of 2 sprays twice daily for the primary endpoint, the mean change from baseline combined AM and PM Reflective Total Nasal Symptom Score (rTNSS). Secondary endpoints were also supportive of efficacy. Each study also included an active comparator: Astelin in MP433 and Astepro in MP438. In each study MP03-36 showed a numerically greater treatment effect over the active comparators. These data indicate that some patients may benefit from use of a higher dose of azelastine in the treatment of SAR, providing justification for the approval of a higher concentration azelastine nasal spray.

Studies MP439 and MP440 were SAR studies intended to demonstrate the efficacy of a 2 sprays once daily dose, but these studies did not show convincing evidence to support a QD dosing regimen. The primary endpoint used in these two studies was the same endpoint used in the other SAR trials, the change from baseline in combined AM and PM rTNSS. However, a key secondary endpoint was the mean change from baseline in AM instantaneous TNSS (iTNSS), which was intended to assess the efficacy of MP03-36 at the dose trough and demonstrate the adequacy of the proposed dosing interval. Of the two studies, MP439 failed to demonstrate a statistically significant treatment difference for this key secondary endpoint. Study MP440 did show a statistically significant difference for AM iTNSS scores; however, it is worth noting that this study was conducted in patients allergic to Texas mountain cedar. Texas mountain cedar is known to provoke intense rhinitis symptoms in allergic patients. Clinical trials conducted in this specific SAR population are often noted to demonstrate particularly robust treatment differences which may not be fully generalizable to a more general SAR patient population. Overall, the results from the MP03-36 clinical program suggest that once-daily dosing is better than placebo, but the treatment benefit is mostly observed in the first half of the 24-hour dosing interval. Since the efficacy of MP03-36 appears to wane substantially towards the end of the 24-hour dosing interval, twice-daily dosing appears to be the optimal, appropriate regimen for efficacy. As a result, only the twice daily dosing regimen for the SAR indication is recommended for Approval.

The primary support for the PAR indication comes from Study MP434, a 4-week, randomized, placebo-controlled, double-blind study that showed a statistically significant benefit for MP03-36 over placebo for the treatment of PAR symptoms at a dose of 2 sprays twice daily. Secondary endpoints were also supportive of efficacy. According to the *Draft Guidance for Industry Allergic Rhinitis: Clinical Development Programs for Drug Products*, one PAR and one SAR trial can support both indications; therefore, replication of the PAR findings is not required. Study MP435 was a PAR study intended to support a once daily dose, but this study did not show statistically significant results to support a QD dosing regimen. Therefore, only the BID dosing regimen for the PAR indication is recommended for Approval. Study MP436 was an open-label, active-controlled, long-term safety study and contained minimal efficacy data.

The application did not contain efficacy data on a 1 spray twice daily regimen for either the SAR or PAR indications. However, based on the Agency's previous findings of efficacy for Astelin and the favorable comparison between MP03-36 and Astelin, the clinical review concludes that the application provides sufficient evidence to support both a 1 or 2 spray twice daily dose for the SAR indication. Since neither Astelin nor Astepro has a PAR indication, there is no pre-existing data to support a 1 spray twice daily dose for the PAR indication. Therefore, only the 2 spray twice daily dose of MP03-36 is recommended for approval for the treatment of PAR symptoms.

The safety of MP03-36 in SAR and PAR patients 12 years of age and older is supported by the submitted clinical study data for MP03-36 as well as the safety database to support approval of Astepro and Astelin. The safety database for MP03-36 included placebo-controlled data from the SAR and PAR efficacy studies, as well as long-term safety data from an open-label, active-controlled study of MP03-36 in PAR (Study MP436). Review of the safety data showed that MP03-36 is most commonly associated with dysgeusia, epistaxis, headache, nasal discomfort,

fatigue, and somnolence, similar to the safety profile for Astepro and Astelin. These adverse events are described in the current Astepro and Astelin product labels. No new safety signals were identified for the higher-strength azelastine formulation, MP03-36. Furthermore, there was no clear dose-response for the most commonly reported adverse events for MP03-36 compared to the lower concentration azelastine formulations.

The application did not include any pediatric efficacy or safety data in patients under the age of 12 years. (b) (4)

However, Astelin does not carry a PAR indication for any age group, and PAR is thought to occur in children as young as 6 months of age; therefore, formal study of MP03-36 in younger patients is recommended.

In summary, the application provides adequate support for the SAR indication (1 or 2 sprays twice daily) and the PAR indication (2 sprays twice daily) in patients 12 years of age and older for MP03-36. There is insufficient data to support the proposed once daily regimen for both the SAR and PAR indications. Therefore, the clinical recommended action for this application is as follows: 1) Approval of MP03-36 for the treatment of the symptoms of SAR in patients 12 years of age and older at a dose of 1 or 2 sprays twice daily; and 2) Approval of MP03-36 for the treatment of the symptoms of PAR in patients 12 years of age and older at a dose of 2 sprays twice daily.

1.2 Risk Benefit Assessment

A risk-benefit assessment for intranasal azelastine at a lower concentration (0.1%) in the treatment of SAR symptoms was previously performed in the review of the original Astelin NDA (NDA 20-114 and the subsequent supplement for the 1-spray dose) and the Astepro NDA (NDA 22-203). As efficacy may be improved in some patients with use of a higher concentration of azelastine and the safety profile for MP03-36 appears similar to the lower-strength formulations already approved on the market, the risk-benefit assessment remains unchanged or potentially improved. For the PAR indication, a similar risk-benefit assessment applies. The adverse event profile in PAR patients appears to be similar to the profile observed in SAR patients, and there is no apparent dose-dependence for adverse events between the 0.15% and 0.1% concentrations. The efficacy data provide sufficient support for the benefit of MP03-36 use in PAR patients. Furthermore, there are no intranasal antihistamine drug products approved for PAR in the US, so the approval of MP03-36 for this indication fills a niche in the PAR armamentarium. The application contains adequate evidence of efficacy for the proposed SAR and PAR indications with an acceptable safety profile in patients 12 years of age and older.

1.3 Recommendations for Postmarketing Risk Management Activities

No recommendations for postmarketing risk management activities are made.

1.4 Recommendations for other Post Marketing Study Commitments

PREA is triggered by this application as there is a new indication, PAR, for azelastine. The Applicant has requested a waiver for all pediatric studies, stating that the lower strength formulation, Astelin, is already approved for patients 5 to 11 years of age for the treatment of SAR. (b) (4) 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) because the diagnosis of SAR in children less than 2 years of age is questionable.

However, neither Astelin nor Astepro 0.1% carries a PAR indication for any age group, so the proposed PAR indication for MP03-36 is a new indication and triggers PREA for this application. PAR is thought to occur in children as young as 6 months of age. Formal study of intranasal azelastine for the treatment of PAR in patients 2 to 11 years of age is recommended. A lower strength of intranasal azelastine may be more appropriate for the treatment of children; therefore study of both MP03-36 and the 0.1% formulations is recommended. Since Astepro 0.1% is not approved for use in patients under the age of 12 years, the clinical review suggests studying both PAR and SAR in patients 2 to 11 years of age. Studies in children younger than 2 years of age is not recommended as the intranasal route of administration in this age group is unlikely to be reliable, and oral antihistamine formulations for the treatment of PAR symptoms are available in this age group.

2 Introduction and Regulatory Background

2.1 Product Information

Azelastine is a selective, H1 antihistamine administered as an intranasal spray. It is currently marketed under two tradenames, Astelin (azelastine hydrochloride 0.1% nasal spray) and Astepro (azelastine hydrochloride 0.1% with taste-masking excipients). Due to a distinctive bitter taste that limited marketing of Astelin, MEDA developed Astepro, which contained the same active ingredient as Astelin but with the addition of sweetening excipients, sucralose and sorbitol.

Astelin is approved for the following indications:

- Seasonal allergic rhinitis (SAR)
  - Children 5 to 11 years, 1 spray per nostril twice daily
  - Adults and children 12 years of age and older, 1 or 2 sprays per nostril twice daily
- Vasomotor rhinitis (VMR) in adults and children 12 years of age and older, 2 sprays per nostril twice daily

Astepro approved for the following indications:

- Seasonal allergic rhinitis (SAR)
    - Adults and children 12 years of age and older, 1 or 2 sprays per nostril twice daily

MP03-36 is a higher concentration (0.15%) azelastine solution that contains the same taste-masking excipients as Astepro, sucralose and sorbitol. The initial proposed tradename for MP03-36 was "(b) (4)." The Division and the Office of Surveillance and Epidemiology opposed the use of different tradenames for MP03-36 and Astepro, expressing concerns that the overlapping indications under different tradenames would result in consumer and health care provider confusion and potentially lead to unintentional overdosing. The Division has proposed the combination of MP03-36 and Astepro under the same tradename and product label, distinguished by their concentrations, 0.15% and 0.1%, respectively. This proposal remains under review at the time of this clinical review. For the purposes of this review, Astepro is referred to as Astepro 0.1% to distinguish it from MP03-36, the proposed drug product which is the subject of this NDA.

The following table compares the components of MP03-36, Astepro 0.1%, and Astelin.

Table 1 Components of MP03-36, Astepro, and Astelin

Component	MP03-36 (% w/v)	Astepro (% w/v)	Astelin (% w/v)	Function
Azelastine hydrochloride	0.15	0.100	0.100	Active ingredient
(b) (4)				

Source: Module 2, Volume 1.1, Table 2.3.P.1-1

The proposed drug product contains 0.15% w/v azelastine hydrochloride and is packaged as a 30mL fill volume in (b) (4) mL high density polyethylene bottles (HDPE) fitted with a metered spray pump for trade and a (b) (4) The Applicant has also proposed a 17ml fill volume in (b) (4) ml HDPE bottles, presumably for the proposed once-daily regimen.

Reviewer's comment: As the clinical review does not recommend approval of the once-daily dosing regimen, the proposed 17ml fill volume product may be superfluous.

2.2 Tables of Currently Available Treatments for Proposed Indications

Aside from Astepro and Astelin, there is currently one other intranasal antihistamine product available for treatment of allergic rhinitis. Intranasal olopatadine (Patanase® Nasal Spray; NDA

21-861) was approved on April 15, 2008, for the treatment of SAR in patients 12 years of age and older. In addition, six long-acting oral antihistamines are currently available for the SAR indication; two of these six also have a PAR indication. A summary of these antihistamines is provided in Table 2.

Table 2 Available antihistamine treatments for allergic rhinitis

Drug	Indications*	Dose	Age range
Olopatadine nasal spray (Patanase®)	SAR	2 sprays twice daily	12 years and older
Desloratadine (Clarinex®)	SAR, PAR, CIU	1 to 5 mg once daily	6 months and older
Fexofenadine (Allegra®)	SAR, CIU	30 mg to 60 mg twice daily or 180 mg once daily	6 years and older
Levocetirizine (Xyzal®)	SAR, PAR, CIU	2.5 to 5 mg once daily	6 years and older
Cetirizine (Zyrtec®)†	Allergic rhinitis, chronic hives	2.5 to 10 mg once daily	2 years of age and older (OTC); 6 months and older (Rx only)
Loratadine (Claritin®)‡	Allergic rhinitis, chronic hives	5 to 10 mg once daily	2 years of age and older (OTC)

* SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis; CIU = chronic idiopathic urticaria
† Available OTC for nasal allergy symptoms and hives indication; remains prescription-only for PAR in children under the age of 2 years and CIU in children under the age of 6 years
‡ Available OTC for nasal allergy symptoms and hives

2.3 Availability of Proposed Active Ingredient in the United States

Azelastine is currently marketed as a 0.1% intranasal spray for the treatment of the symptoms of SAR and VMR (Astelin, NDA 20-114, approved November 1, 2006) and as a sweetened 0.1% intranasal spray (Astepro, NDA 22-203, approved October 15, 2008) for the treatment of the symptoms of SAR. Azelastine is also marketed as 0.05% ophthalmic drops (Optivar®, NDA 21-127, approved May 20, 2000) for the treatment of itching of the eye associated with allergic conjunctivitis. No major safety concerns have been identified post-approval for any of the azelastine products.

2.4 Important Safety Issues With Consideration to Related Drugs

Somnolence and fatigue are the most common adverse events associated with antihistamines in general, and product labels typically recommend caution when performing activities requiring mental alertness, such as driving and operating heavy machinery. Somnolence has been noted in the clinical program for both the unsweetened and sweetened azelastine nasal sprays. The current Astelin and Astepro labels contain precaution language regarding activities requiring mental alertness. Similar language is recommended for the MP03-36 product label.

Terfenadine, one of the first second-generation antihistamines approved for the treatment of allergic rhinitis, was subsequently associated with QT interval prolongation and cardiac arrhythmias, leading to its removal from the market. A study evaluating the effect of intranasal azelastine was performed and is described in the current Astelin and Astepro labels. According to the labels, the study did not show an effect on cardiac repolarization.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following timeline summarizes the presubmission regulation activity related to the clinical development program for MP03-36 and this NDA submission.

- November 1, 1996 - Astelin Nasal Spray approved (NDA 20-114)
- May 4, 2004 – IND 69,785 opened to develop a sweetened formulation with varying concentrations of azelastine
- May 3, 2005, meeting
  - 0.1% sweetened formulation (MP03-33) proposed
  - 6 month IN toxicology study with sweetened formulation required
  - Pediatric discussion deferred
- June 8, 2005, meeting
  - Clarification of toxicology requirements for sweetened formulation
- February 17, 2006 - Approval of Astelin one spray per nostril
- August 29, 2006, meeting to discuss higher-strength sweetened formulation (MP03-36)
  - Addition of excipients which may trigger VMR symptoms
    - To support VMR indication, MEDA will need a study in SAR, PAR, and VMR each, or two dedicated VMR studies
  - Issue of parallel development of two different strength formulations (MP03-33 and MP03-36 with similar indications and dosing regimens)
    - Without demonstration of advantage of higher strength over lower strength, higher strength will be difficult to justify
  - Appropriate study design
    - Need direct head-to-head comparison of MP03-33 and MP03-36 to justify higher dose
    - 1 SAR and 1 PAR trial adequate for both indications if both trials well-controlled and supportive
    - Use of an afternoon placebo to support once-daily dosing regimen may confound efficacy findings and does not reflect intended use of the drug
    - Need for multiplicity adjustment with comparison of multiple dosing regimens (once vs. twice daily) to placebo
- October 15, 2008 – NDA 22-203 for MP03-33 (Astepro) approved

2.6 Other Relevant Background Information

Azelastine hydrochloride nasal spray (137 mcg) is approved and marketed for the treatment of symptoms of allergic rhinitis in more than 80 countries worldwide. The Applicant reports no marketing authorization withdrawals, suspensions, failures to obtain marketing authorization renewal, restrictions on distribution or clinical trial suspensions (Volume 1).

In addition, the Applicant in conjunction with (b) (4) previously submitted (b) (4) The Applicant

intended to (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission included complete study reports of the seven major clinical studies, proposed labeling, and appropriate case report forms. The study reports were appropriately indexed and organized to allow review. The submission included raw datasets for the major clinical studies.

Review of the application did not raise any data integrity concerns. There was 1 investigator with financial interests/arrangements (b) (6) upon preliminary review, there do not appear to be any study site effects. 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.

3.2 Compliance with Good Clinical Practices

The Applicant has certified that the studies were conducted in accordance with acceptable ethical standards. Study reports indicated that informed consent was obtained from all study participants. Analysis by treatment site did not indicate any systematic site-based bias.

3.3 Financial Disclosures

The Applicant provided financial disclosure information for one investigator, (b) (6), who participated as a clinical investigator in Studies (b) (6). The Applicant has certified that no other disclosable financial arrangements occurred for Studies MP433, MP434, MP435, MP436, MP438, MP439, and MP440.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Table 1 displays the ingredients in MP03-36 in comparison to approved Astepro and Astelin; the increased concentration of azelastine, the active ingredient, is the notable difference. The proposed drug product contains 0.15% w/v azelastine hydrochloride and is packaged as a 30 mg fill volume in (b) high density polyethylene bottles (HDPE) fitted with a metered spray pump for trade and a (b) (4). The Applicant has also proposed a 17ml fill volume in (b) (4) ml HDPE bottles, presumably for the proposed once-

daily regimen. The CMC review has been completed and no major issues have been identified. The recommended action from the CMC perspective is Approval.

Reviewer's comment: The clinical review does not find adequate efficacy support for the once-daily dose, so the proposed 17ml fill volume may be superfluous if only the twice-daily regimen is approved.

4.2 Clinical Microbiology

MP03-36 contains benzalkonium chloride as an (b) (4). The Applicant submitted data showing that at a concentration of (b) (4) % the formulation amount, the effectiveness of benzalkonium chloride met the requirements of USP 29 <51>.

4.3 Preclinical Pharmacology/Toxicology

The Preclinical Pharmacology/Toxicology review recommends Approval of the application.

Preclinical data to support the safety of 0.15% azelastine for intranasal administration was submitted in the application. Four toxicology studies were conducted: two 14-day repeat-dose studies in rats, one 6-month repeat dose study in rats, and one 14-day repeat dose study in beagle dogs. According to the Applicant's report, MP03-36 appeared to have similar local toxicities as those observed with a 0.1% azelastine formulation. The principal animal findings included subacute inflammation of the nasal turbinates and nasolacrimal duct, as well as evidence of goblet cell hyperplasia in the nasal turbinates and alveolar inflammation. The Applicant states that these findings are typical for repeat-dose intranasal studies and are predominantly attributed to the mode of dose administration rather than a direct-treatment related effect. No new data on genetic toxicity, carcinogenicity, reproductive and developmental toxicity were submitted with this application.

Reviewer's comment: Further details of the preclinical data can be found in Dr. Luqi Pei's review.

4.4 Clinical Pharmacology

The Clinical Pharmacology review remains pending at this time. No new clinical pharmacology studies were submitted in this application. Upon preliminary review, no major issues have been identified.

4.4.1 Mechanism of Action

Azelastine is a selective H1-receptor blocker. The nasal spray is a racemic mixture. No differences in pharmacological activity have been reported between the enantiomers in in vitro studies.

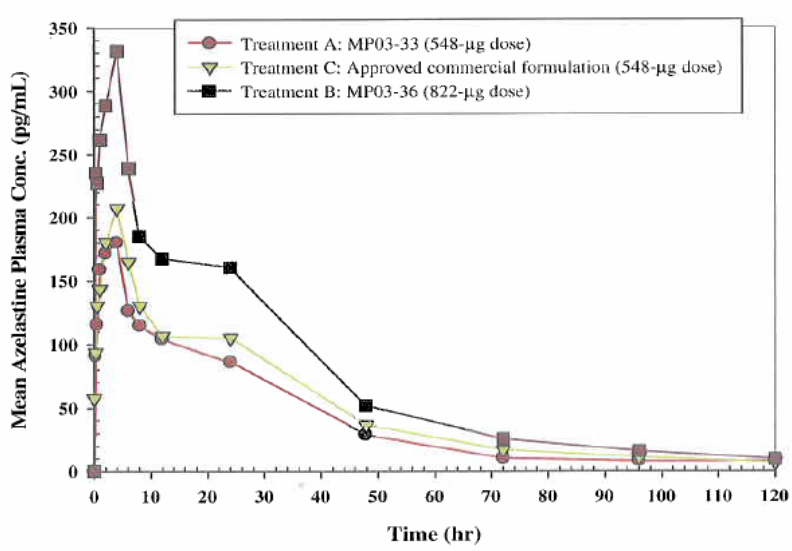
4.4.2 Pharmacodynamics

No new pharmacodynamic data is included in this submission.

4.4.3 Pharmacokinetics

The Applicant conducted Study MP429, a randomized open-label, parallel group, single-dose study in 54 healthy adult male volunteers to establish the comparability between MP03-33 (0.1% sweetened azelastine) and unsweetened azelastine. This study was previously reviewed under NDA 22-203, so only a brief overview will be presented here. Subjects received 1 or 2 sprays per nostril of MP03-36, Astepro 0.1%, and Astelin. Overall, higher systemic exposures and peak concentrations were observed for MP03-36 compared to Astepro and Astelin (Figure 1) and the major active metabolite, desmethylazelastine. Dose-proportional pharmacokinetics were observed for MP03-36 per the Applicant's report.

Figure 1 Study MP429: Pharmacokinetics of MP03-36 versus Astepro 0.1% and Astelin



The current product labels for Astepro and Astelin state that there was no evidence of a QTc interval prolongation effect in a placebo-controlled study of azelastine 2 sprays twice daily for 56 days in patients with SAR. No formal thorough QT study has been performed for azelastine. Previous drug-drug interaction studies did not show any interactions between oral azelastine and erythromycin. Ketoconazole interfered with measurement of azelastine plasma levels but no effects on QTc intervals were observed.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Table 3 Clinical development program for MP03-36

Study	Subjects	Design	Dose	Duration	Relevance
Phase 2 PK study					
MP429	54 ≥18 yrs	R, OL	Single dose • MP03-36 • MP03-33 • Astelin	Single dose	• Comparative PK study
Phase 3 SAR trials					
MP433	617 ≥12 yrs	R, DB, PC	2 sprays per nostril • MP03-36 once daily (AM) + placebo once daily (PM) • MP03-36 twice daily • Astelin twice daily • Placebo twice daily	2 weeks	• Pivotal SAR trial • Onset of action
MP438	526 ≥12 yrs	R, DB, PC	2 sprays per nostril twice daily: • MP03-36 • MP03-33 (0.1% azelastine, 0.15% sucralose) • Placebo	2 weeks	• Pivotal SAR trial • Onset of action
MP439	481 ≥12 yrs	R, DB, PC	2 sprays per nostril once daily: • MP03-36 • Placebo	2 weeks	• SAR trial for once-daily dose
MP440	536 ≥12 yrs (mountain cedar-allergic)	R, DB, PC	2 sprays per nostril once daily: • MP03-36 • Placebo	2 weeks	• SAR trial for once-daily dose
Phase 3 PAR trials					
MP434	526 ≥12 yrs	R, DB, PC	2 sprays per nostril twice daily: • MP03-36 • MP03-33 • Placebo	4 weeks	• Pivotal PAR trial for twice-daily dose
MP435	156 ≥12 yrs	R, DB, PC	2 sprays per nostril once daily: • MP03-36 (AM) • MP03-36 (PM) • Placebo (AM) • Placebo (PM)	4 weeks	• Pivotal PAR trial for once-daily dose
MP436	547 ≥12 yrs	R, OL, AC	2 sprays per nostril twice daily • MP03-36 • Nasonex	6 months	• Long-term safety study

MP03-36 = to-be-marketed 0.15% formulation
MP03-33 = Astepro 0.1% formulation

5.2 Review Strategy

The clinical review focused on the Phase 3 efficacy and safety studies for SAR (MP433, MP438, MP439, and MP440), PAR (MP434 and MP435), and the 6-month long-term safety study (MP436). Detailed review of the individual studies can be found in Section 10 in the individual study summaries. The pharmacokinetic study, MP429, was previously reviewed as part of NDA 22-203 and is briefly summarized in the preceding section. A more detailed review can be found in the Clinical Pharmacology reviewer's review.

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 based on annual reports submitted for Astelin (NDA 20-114) was briefly 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 study design, conduct, and major efficacy results of the four SAR and two PAR Phase 3 efficacy studies. The major findings in regards to efficacy are summarized in this section and discussed further in Section 6. Pooled safety information from these placebo-controlled studies is presented and discussed in Section 7. More detailed discussion of the efficacy and safety results from the individual studies can be found in Section 10. An overview of the long-term safety study, Study MP436, is also presented here. Detailed discussions of the safety results are located in Section 7 and in the individual study summary.

5.3.1 MP433

Study design and conduct

MP433 was a US multi-center, randomized, double-blind, placebo-controlled trial of the efficacy and safety of MP03-36 in patients 12 years of age and older with SAR. In total, 617 patients were enrolled with a minimum 2-year history of SAR with a positive skin test to a relevant fall allergen. After an initial 1-week, single-blind, placebo run-in period, patients who met a minimum threshold symptom score were randomized to 1 of 4 possible **treatment groups**:

- MP03-36 2 sprays per nostril once daily (AM) + placebo 2 sprays per nostril once daily (PM)
- MP03-36 2 sprays per nostril twice daily
- Astelin 2 sprays per nostril twice daily
- Placebo 2 sprays per nostril twice daily

The **primary efficacy variable** was the change from baseline in 12-hour combined (AM plus PM) reflective Total Nasal Symptom Score (rTNSS) over the 2-week, double-blind treatment period compared to placebo. The 4 nasal symptoms scored on a 0-3 scale (none to severe) that comprise the TNSS are as follows: runny nose, sneezing, itchy nose, and nasal congestion. 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. The highest possible combined score on this scale was 24 (maximum AM rTNSS of 12 + maximum PM rTNSS of 12).

Secondary efficacy variables that were assessed 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 instantaneous TNSS (iTNSS) for the 14-day treatment period
- Change from baseline rTNSS for individual symptom scores for the 14-day treatment period
- Daily change from baseline in TNSS
- Change from baseline 12-hour iTNSS to Day 2 (AM)
- Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

Safety assessments included screening for adverse events, focused nasal exams, and vital signs at each study visit.

Reviewer's comment: The first arm of the study was intended to evaluate a QD regimen of MP03-36. However, the use of a placebo spray in the PM confounds this assessment, since a vehicle spray may impact rhinitis symptoms. As a result, there is no true QD dosing arm in this study. Therefore, the clinical review considers Study MP433 to be a valid study of the BID regimen only and focuses mainly on the results of the BID MP03-36 versus placebo comparison.

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).

Results

Patient disposition is summarized in Table 4. A total of 617 patients met inclusion criteria and were randomized to double-blind treatment at 31 sites. A total of 593 patients completed the study and 20 patients discontinued early.

Table 4 Study MP433: Patient disposition

Disposition	MP03-36 QAM + Placebo QPM N(%)	MP03-36 BID N(%)	Astelin BID N(%)	Placebo BID N(%)	Total
Randomized	158	153	153	153	617
Completed	154 (97.5)	144 (94.1)	148 (96.7)	147 (96.1)	593 (96.1)
Discontinued	4 (2.5)	9 (5.9)	5 (3.3)	6 (3.9)	24 (3.9)
Adverse event	2 (1.3)	5 (3.3)	0	4 (2.6)	11 (1.8)
Treatment failure	1 (0.6)	0	0	2 (1.3)	3 (0.5)
Non-compliance	0	1 (0.7)	4 (2.6)	0	5 (0.8)
Withdrew consent	0	0	0	0	0
Lost to follow-up	0	2 (1.3)	0	0	2 (0.3)
Other	1 (0.6)	1 (0.7)	1 (0.7)	0	3 (0.5)
ITT[a]	158 (100.0)	153 (100.0)	153 (100.0)	153 (100.0)	617 (100.0)
Evaluable population[b]	147 (93.0)	150 (91.5)	142 (92.8)	142 (92.8)	571 (92.5)
Safety population[c]	158 (100.0)	153 (100.0)	153 (100.0)	153 (100.0)	617 (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: Module 5, Vol 7, Section 9.7.1, Text Table 1

Demographics and baseline characteristics of the patients enrolled in MP433 are shown below.

Table 5 Study MP433: Patient demographics and baseline characteristics

Variables	MP03-36 QAM + Placebo QPM (n=158)	MP03-36 BID (n=153)	Astelin BID (n=153)	Placebo BID (n=153)	Total (n=617)
Age (Mean, Range)	36.2 (13-78)	38.5 (13-75)	37.5 (13-83)	37.0 (13-74)	37.3 (13-83)
Gender (male, %)	61 (38.6%)	60 (39.2)	57 (37.3)	58 (37.9)	236 (38.2)
Race					
Caucasian	120 (75.9)	104 (68.0)	105 (68.6)	104 (68.0)	433 (702.)
Black	18 (11.4)	20 (13.1)	23 (15.0)	28 (18.3)	89 (14.4)
Hispanic	12 (7.6)	25 (16.3)	21 (13.7)	14 (9.2)	72 (11.7)
Asian	6 (3.8)	4 (2.6)	5 (2.6)	5 (3.3)	19 (3.1)
Native American	1 (0.6)	0	0	0	1 (0.2)
Other	1 (0.6)	0	0	2 (1.3)	3 (0.5)
Total score					
Mean, SD	18.7 (2.99)	18.3 (2.82)	18.0 (2.81)	18.2 (3.01)	18.3 (2.91)
Range	9-24	10-24	8-24	8-24	8-24
Duration of SAR (yrs)					
Mean, SD	19.4 (13.0)	21.7 (14.69)	19.6 (13.80)	17.7 (11.52)	19.6 (13.34)
Range	2-73	2-67	2-69	3-49	2-73

Source: Volume 7, Section 11.2, Text table 2

Primary efficacy results are shown in **Table 6**, along with the primary efficacy results for the other pivotal SAR studies; secondary efficacy results are discussed in Section 6 and in the individual study summaries located in Section 10. MP03-36 BID compared favorably to placebo in terms of the primary efficacy endpoint: -4.25 vs. -3.04, p=0.01.

Table 6 Primary efficacy results for SAR studies: Change from baseline in combined AM and PM 12-hours rTNSS averaged over 14-day treatment period*

Study Treatment groups	N	LE mean baseline	Mean change from baseline	Treatment difference from placebo	P-value vs placebo	95% CI†
MP433						
MP03-36 QAM + placebo QPM	158	18.61	-3.85	-0.81	0.08	(-1.72, 0.10)
MP03-36 BID	153	18.19	-4.25	-1.21	0.01	(-2.12, -0.29)
Astelin BID	153	17.94	-3.89	-0.85	0.07	(-1.77, 0.06)
Placebo BID	153	18.08	-3.04			
MP03-36 vs. Astelin‡					0.45‡	(-1.27, 0.57) ‡
MP438						
MP03-36 BID	177	17.72	-5.09	-2.97	<0.001	(-3.87, -2.06)
Astepro 0.1% BID	169	18.18	-4.19	-2.07	<0.001	(-2.99, -1.15)
Placebo BID	177	17.73	-2.12			
MP03-36 vs. MP03-33‡					0.06‡	(-1.82, 0.02) ‡
MP439						
MP03-36 QAM	238	17.40	-3.38	-0.98	0.008	(-1.71, -0.26)
Placebo QAM	242	17.38	-2.40			
MP440						
MP03-36 QPM	266	18.48	-3.29	-1.41	<0.001	(-2.06, -0.76)
Placebo QPM	266	17.98	-1.88			

* The values displayed in this table are based on the Agency's statistical re-analysis and vary slightly from the values provided by the Applicant in the NDA submission and represented in the individual study summaries in Section 10. These small differences do not alter the conclusions of the clinical review.
† 95% confidence interval for active minus placebo treatment difference
‡ MP03-36 vs. active comparator post-hoc analysis performed by Agency

Conclusions

The results of Study MP433 provide support for the efficacy of twice-daily dosing of MP03-36 for SAR. The proposed twice-daily regimen for MP03-36 is supported by the primary efficacy endpoint; the once-daily MP03-36 regimen is not supported both by a flawed study design as well as the actual results which fell short of statistical significance. Secondary efficacy variables were also generally supportive of twice daily MP03-36 over placebo if not statistically significant. Although not statistically significant, the treatment difference between MP03-36 and Astelin shows a numerical dose-related trend that suggests that some patients with SAR may experience greater efficacy with use of a higher concentration of azelastine.

5.3.2 MP438

Study design and conduct

Study MP438 was a US multi-center, randomized, double-blind, placebo-controlled trial of the efficacy and safety of MP03-36 compared to Astepro 0.1% and placebo in the treatment of patients 12 years and older with SAR. The study had a similar design as Study MP433, with a 1-week placebo run-in period followed by a 2-week treatment period. In total, 526 patients 12 years of age and older with a minimum 2-year history of SAR with a positive skin test to a local fall pollen allergen were randomized 1:1:1 to 3 possible **treatment groups**:

- MP03-36 (0.15% azelastine) 2 sprays per nostril twice daily (1644 mcg total daily dose)
- Astepro 0.1% 2 sprays per nostril twice daily (1096 mcg total daily dose)

- Vehicle placebo 2 sprays per nostril twice daily

The **primary efficacy endpoint** was the same as that described for Study MP433: the change from baseline in 12-hour combined (AM plus PM) reflective Total Nasal Symptom Score (rTNSS) over the 2-week, double-blind treatment period compared to placebo. Astepro 0.1% was included as a direct comparison between the two dose levels of azelastine; a formal statistical comparison between the two active treatments was not prespecified in the statistical analysis plan. **Secondary efficacy** variables and **safety assessments** were similar to those described for Study MP433.

Results

Patient disposition for Study MP438 is summarized in Table 7. A total of 526 subjects were randomized to double-blind treatment. A total of 509 subjects completed the study and 17 subjects discontinued early.

Table 7 Study MP438: Patient disposition

Disposition	Astepro 0.1%	MP03-36	Placebo	Total
Randomized	170	178	178	526
Completed	166 (97.6)	172 (96.6)	171 (96.1)	509 (96.8)
Discontinued	4 (2.4)	6 (3.4)	7 (3.9)	17 (3.2)
Adverse event	3 (1.8)	4 (2.2)	5 (2.8)	12 (2.3)
Abnormal test result	0	0	0	0
Treatment failure	0	0	0	0
Non-compliance	0	0	1 (0.6)	1 (0.2)
Withdrew consent	1 (0.6)	0	0	1 (0.2)
Lost to follow-up	0	1 (0.6)	0	1 (0.2)
Administrative	0	0	0	0
problems	0	1 (0.6)	1 (0.6)	2 (0.4)
Other				
ITT[a]	169 (99.4)	177 (99.4)	178 (100.0)	523 (99.4)
Per protocol population[b]	161 (94.7)	170 (95.5)	162 (91.0)	493 (93.7)
Safety population[c]	170 (100.0)	178 (100.0)	178 (100.0)	526 (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: Module 5, Vol 22, Section 10.1, Table 3

Demographics and baseline characteristics for Study MP438 are summarized below.

Table 8 Study MP438: Patient demographics and baseline characteristics			
Variables	**Astepro 0.1% (N=169)**	**MP03-36 (N=177)**	**Placebo (N=177)**
Age (Mean, Range)	35.4 (12-790	38.0 (12-76)	36.9 (12-69)
Gender (male, %)	58 (34.3)	70 (39.5)	61 (34.5)
Race			
Caucasian	134 (79.3)	143 (80.8)	140 (79.1)
Black	30 (17.8)	23 (13.0)	26 (14.7)
Hispanic	27 (16.0)	21 (11.9)	20 (11.3)
Asian	1 (0.6)	3 (1.7)	5 (2.8)
Native American	1 (0.6)	1 (0.6)	0
Native Hawaiian or Pacific Islander	1 (0.6)	0	1 (0.6)
Other	2 (1.2)	7 (4.0)	5 (2.8)
Total score			
Mean, SD	18.3 (3.23)	18.3 (3.28)	17.9 (3.30)
Range	5-24	9-24	8-24
Duration of SAR (yrs)			
Mean, SD	19.0 (10.77)	20.4 (13.52)	19.5 (11.76)
Range	2-51	3-54	3-57

Source: Module 5, Volume 22, Section 11.2.1, Table 5

Primary efficacy results for MP438 are displayed in Table 6. MP03-36 compared favorably to Astepro 0.1% in terms of the primary endpoint: -5.09 vs. -2.12, $p<0.001$.

Conclusions

The efficacy and safety results of Study MP438 support the twice daily dosing of MP03-36 for the treatment of SAR symptoms. The study also demonstrates the efficacy of twice-daily Astepro 0.1% for the same indication compared to placebo. Although the results of the post-hoc comparison are not statistically significant, MP03-36 appears to have a numerically greater, dose-related efficacy when compared to MP03-33. The safety profiles of the two dosage strengths appear comparable and are discussed in further detail in Section 7. As a result, Study MP438 suggests that some patients may benefit from the use a of a higher strength azelastine formulation without a compromise in safety.

5.3.3 MP439

Study design and conduct

Study MP439 was a US multi-center, randomized, double-blind, placebo-controlled trial of the efficacy and safety of MP03-36 compared to placebo in the treatment of patients 12 years and older with SAR. The study was intended to evaluate the efficacy of a 2 sprays once daily dosing regimen, in contrast to the BID regimen approved currently for Astepro 0.1% and Astelin. The study had a similar design as Study MP433, with a 1-week placebo run-in period followed by a 2-week treatment period. In total, 481 patients 12 years of age and older with a minimum 2-year history of SAR with a positive skin test to a local fall pollen allergen were randomized 1:1 to 2 possible **treatment groups**:

- MP03-36 two sprays per nostril once daily (AM) (822 mcg total daily dose)
- Vehicle placebo two sprays per nostril once daily (AM)

The **primary efficacy endpoint** was the same as that described for Study MP433: the change from baseline in 12-hour combined (AM plus PM) reflective Total Nasal Symptom Score (rTNSS) over the 2-week, double-blind treatment period compared to placebo.

Secondary efficacy variables included the following:

- End of 24-hr dosing interval – mean change from baseline in iTNSS for the entire 14-day study period compared to placebo to determine if the duration of efficacy lasted 24 hours
- Change from baseline in 12-hr rTNSS individual symptom component scores
- Change from baseline in for daily 12-hr iTNSS and rTNSS
- Change from baseline for daily SSCS (postnasal drip, itchy eyes, cough, headache)
- Change from baseline to Day 14 in RQLQ for subjects 18 years of age and older

The iTNSS scores were key endpoints for evaluating the efficacy the proposed 24-hr dosing interval. No onset of action variables were assessed in Study MP439. **Safety assessments** were similar to those described for Study MP433.

Results

Patient disposition for Study MP439 is summarized in Table 9. A total of 481 patients were randomized to double-blind treatment. A total of 467 completed the study and 14 patients discontinued early.

Table 9 Study MP439: Patient disposition

Disposition	MP03-36	Placebo	Total
Randomized	239	242	481
Completed	233 (97.5)	234 (96.7)	467 (97.1)
Discontinued	6 (2.5)	8 (3.3)	14 (2.9)
Adverse event	2 (0.8)	1 (0.4)	3 (0.6)
Abnormal test result	0	0	0
Treatment failure	0	3 (1.2)	3 (0.6)
Non-compliance	0	1 (0.4)	1 (0.2)
Withdrew consent	0	1 (0.4)	1 (0.2)
Lost to follow-up	1 (0.4)	0	1 (0.2)
Administrative problems	0	0	0
Other	3 (1.3)	2 (0.8)	5 (1.0)
ITT[a]	238 (99.6)	242 (100)	480 (99.8)
Per protocol population[b]	219 (91.6)	213 (88.0)	432 (89.8)
Safety population[c]	239 (100.0)	242 (100.0)	481 (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: Module 5, Vol 40, Section 10.1, Table 3

Demographics and baseline characteristics for Study MP439 are summarized in the table below.

Table 10 Study MP439: Patient demographics and baseline characteristics

Variables	MP03-36 (N=238)	Placebo (N=242)	Total (N=480)
Age (Mean, Range)	35.5 (12-78)	35.3 (12-75)	35.4 (12-78)
Gender (male, %)	84 (35.3)	80 (33.1)	164 (34.2)
Race			
Caucasian	186 (78.2)	179 (74.0)	365 (76.0)
Black	38 (16.0)	49 (20.2)	87 (18.1)
Hispanic	25 (10.5)	27 (11.2)	52 (10.8)
Asian	3 (1.3)	3 (1.2)	6 (1.3)
Native American	1 (0.4)	0	1 (0.2)
Native Hawaiian or Pacific Islander	2 (0.8)	3 (1.2)	5 (1.0)
Other	8 (3.4)	8 (3.3)	16 (3.3)
Total score			
Mean, SD	17.1 (3.54)	17.7 (3.31)	17.7 (3.42)
Range	9-24	6-24	6-24
Duration of SAR (yrs)			
Mean, SD	19.2 (12.57)	18.6 (12.82)	18.9 (12.68)
Range	2-56	2-62	2-62

Source: Module 5, Volume 40, Section 11.2.1, Table 5

Primary efficacy results for MP439 are displayed in Table 6. The comparison between MP03-36 and placebo was statistically significant for the primary endpoint (-3.38 vs. -2.40; p=0.008). However, the **key secondary efficacy variables**, namely iTNSS scores, were not supportive of the QD dosing interval. The end of 24-h dosing interval as assessed by the overall AM iTNSS did not show a statistically significant difference between MP03-36 and placebo, as shown in Table 11. Furthermore, the treatment difference observed for the AM iTNSS over the 14-day treatment period was rather small (-0.3). The combined AM and PM iTNSS over the 14-day period did show a difference between MP03-36 and placebo (-3.0 vs. -2.2; p=0.023) as did overall PM iTNSS scores (-1.7 vs. -1.1; p=0.011), suggesting that once-daily dosing is better than placebo but that efficacy wanes substantially over the 24-hour dosing interval.

Table 11 Study MP439: Change from baseline in AM iTNSS[a]

Treatment	Baseline (SD)[b]	Change from baseline	Treatment difference	P-value vs placebo, 95% CI
MP03-36	8.2 (2.5)	-1.4 (2.3)	-0.3	0.112 (-0.67, 0.07)
Placebo	8.4 (1.9)	-1.1 (2.1)		

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 40, Table 14.2.7.1

Reviewer's comment: The end of 24-h dosing assessment was intended to demonstrate the efficacy of a once-daily MP03-36 regimen. Although the combined iTNSS and PM iTNSS show a statistically significant benefit over placebo, the AM iTNSS which is measuring symptoms at drug trough do not show a statistically significant difference. These results indicate that once-daily dosing of MP03-36 is better than placebo for more than half of the 24 hour dosing interval, but this benefit diminishes significantly toward the end of the dosing interval. Also, the treatment difference is markedly smaller than that observed in Studies MP433 and MP438 looking at the BID regimen. Based on these results, the once-daily dose does not appear to

provide consistent efficacy through the duration of the dosing interval and appears inferior to BID dosing.

Conclusions
The results of MP0439 are generally supportive of MP03-36's efficacy and safety in SAR; however, the study does not provide conclusive support for the once-daily dosing regimen. Although the once-daily dosing regimen did win over placebo in terms of the primary efficacy variable, it did not win over placebo for the secondary variable intended to assess the adequacy of the dosing interval, the end-of-24hr iTNSS. Based on these results, the once-daily dose does not appear to provide consistent efficacy through the duration of the dosing interval and appears inferior to BID dosing.

5.3.4 MP440

Study design and conduct
Like Study MP439, Study MP440 was intended to evaluate the efficacy and safety of a QD dosing regimen for MP03-36. The study had a similar randomized, placebo-controlled, 2-2-week treatment study design as Study MP439, but enrolled patients with sensitivity to Texas mountain cedar in particular, confirmed by history and skin testing. A total of 536 patients were randomized 1:1 to receive one of the following two treatments:

- MP03-36 (0.15% azelastine) 2 sprays per nostril once daily in AM (822 mcg total daily dose)
- Vehicle placebo 2 sprays per nostril once daily in AM

Primary and **secondary endpoints** were the same as those described for Study MP439 above, with emphasis on iTNSS scores to assess the appropriateness of the proposed 24-hr dosing interval. **Safety assessments** were also the same as those described for Study MP433.

Reviewer's comment: Texas mountain cedar is a highly allergenic pollen, and patients sensitive to this pollen typically report intense rhinitis symptoms. It is expected that an efficacious rhinitis medication would demonstrate a larger treatment difference in mountain cedar-allergic patients compared to a more heterogeneous population of pollen-sensitive individuals.

Results
Patient disposition for Study MP440 is summarized in Table 12.

Table 12 Study MP440: Patient disposition			
Disposition	**MP03-36**	**Placebo**	**Total**
Randomized	268	268	536
Completed	249 (92.9)	250 (93.3)	499 (93.1)
Discontinued	19 (7.1)	18 (6.7)	37 (6.9)
Adverse event	4 (1.5)	3 (1.1)	7 (1.3)
Abnormal test result	0	0	0
Treatment failure	3 (1.1)	2 (0.7)	5 (0.9)
Non-compliance	4 (1.5)	0	4 (0.7)
Withdrew consent	2 (0.7)	1 (0.4)	3 (0.6)
Lost to follow-up	2 (0.7)	3 (1.1)	5 (0.9)
Administrative	0	0	0
problems	4 (1.5)	9 (3.4)	13 (2.4)
Other			
ITT[a]	266 (99.3)	22 (00.3)	532 (99.3)
Per protocol population[b]	242 (90.3)	245 (91.4)	487 (90.9)
Safety population[c]	268 (100.0)	268 (100.0)	536 (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: Module 5, Vol 55, Section 10.1, Table 3

Demographics and baseline characteristics for Study MP440 are summarized in the table below.

Table 13 Study MP440: Patient demographics and baseline characteristics		
Variables	**MP03-36 N=266**	**Placebo N=266**
Age (Mean, Range)	40.9 (12-80)	40.0 (12-81)
Gender (male, %)	91 (34.2)	95 (35.7)
Race		
Caucasian	231 (86.8)	241 (90.6)
Black	26 (9.8)	13 (4.9)
Hispanic	84 (31.6)	80 (30.1)
Asian	1 (0.4)	4 (1.5)
Native American	1 (0.4)	0
Native Hawaiian or Pacific	0	1 (0.4)
Islander	7 (2.6)	7 (2.6)
Other		
Total score		
Mean, SD	18.5 (3.28)	18.0 (3.33)
Range	7-24	6-24
Duration of SAR (yrs)		
Mean, SD	18.3 (12.6)	18.3 (13.1)
Range	2-60	2-70

Source: Vol 55, Section 11.2.1, Table 5

Primary efficacy results are shown in Table 6. MP03-36 compared favorably to placebo in terms of the primary efficacy endpoint: -3.29 vs. -1.88 ($p<0.001$). **Secondary efficacy** endpoints were also numerically supportive, if not statistically significant, including iTNSS assessments made to support a once-daily dosing regimen. The dosing interval as assessed by change from baseline in AM iTNSS at the end of the 24-hour dosing interval demonstrated a statistically significant benefit for MP03-36 over placebo (Table 14).

Table 14 Study MP440: Change from baseline in AM iTNSS over the 14-day treatment period[a]

Treatment	Baseline (SD)[b]	Change from baseline	Treatment difference	P-value vs placebo, 95% CI
MP03-36	8.7 (2.0)	-1.4 (2.1)	-0.8	<0.001 (-1.1, -0.4)
Placebo	8.3 (2.0)	-0.6 (1.9)		

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 55, Table 14.2.7.1

Conclusions

The results of MP440 support the efficacy and safety of once-daily MP03-36 for the treatment of SAR. In contrast to Study MP439, the iTNSS scores support the 24-hr dosing interval. However, it is worth noting that this study was conducted in patients with allergy to Texas mountain cedar allergen, a potent allergen that appears to cause particularly intense rhinitis symptoms in sensitized patients. Accordingly, it is expected that a treatment difference would be more exaggerated in this particular SAR population and results from a study conducted in mountain cedar allergic patients may not necessarily be generalizable to a wider SAR patient population. The overall safety profile for the once-daily dosing regimen was similar the profile observed in other studies in the clinical development program.

5.3.5 MP434

Study design and conduct

Study MP434 was a US multi-center, randomized, double-blind, placebo-controlled trial of the efficacy and safety of MP03-36 in the treatment of patients 12 years of age with PAR. The study compared MP03-36 administered 2 sprays twice daily to Astepro 0.1% and placebo. The study was conducted in the winter to minimize confounding due to seasonal pollen allergens. The study consisted of a 1-week placebo lead-in period followed by a 4-week double-blind treatment period for those patients qualifying with a minimum symptom score. A total of 581 patients were randomized 1:1:1 to one of the following three **treatment groups**:

- MP03-36 2 sprays twice daily (1644 mcg total daily dose)
- Astepro 0.1% 2 sprays twice daily (1096 mcg total daily dose)
- Vehicle placebo 2 sprays twice daily

The **primary efficacy endpoint** was similar to the endpoint used in the SAR studies but adapted to cover the 28-day treatment period: the change from baseline in 12-hour combined (AM plus PM) reflective TNSS (rTNSS) to Day 28 compared to placebo. **Secondary efficacy endpoints** included the following:

- Change from baseline in iTNSS for the entire 28-day study period
- Change from baseline in 12-hr rTNSS individual symptom scores
- Daily scores – both 12hr rTNSS and iTNSS compared to placebo

- Change from baseline in 12-hr rSSCS for the entire 28-day period. The SSCS was scored on a 0-3 scale (none to severe) for the following symptoms: postnasal drip, itchy eye, cough, and headache.
- Change from baseline in individual 12-hr SSCS symptoms over the entire 28-day period compared to placebo
- Change from baseline to Day 28 in the RQLQ in subjects 18 years of age and older

Safety assessments were the same as those used in the SAR studies: adverse event screening, local nasal exams, and vital signs.

Reviewer's comment: As in Study MP438, Astepro 0.1% was included as an active comparator to justify the approval of two different dose levels of azelastine nasal spray.

Results

Patient disposition for Study MP434 is summarized in Table 15.

Table 15 Study MP434: Patient disposition

Disposition	Astepro 0.1%	MP03-36	Placebo	Total
Randomized	197	192	192	581
Completed	180 (91.4)	180 (93.8)	175 (91.1)	535 (92.1)
Discontinued	17 (8.6)	12 (6.3)	17 (8.9)	46 (7.9)
Adverse event	4 (2.0)	7 (3.6)	3 (1.6)	14 (2.4)
Abnormal test result	0	0	0	0
Treatment failure	0	1 (0.5)	1 (0.5)	2 (0.3)
Non-compliance	0	0	3 (1.6)	3 (0.5)
Withdrew consent	2 (1.0)	1 (0.5)	4 (2.1)	7 (1.2)
Lost to follow-up	4 (2.0)	0	1 (0.5)	5 (0.9)
Administrative problems	0	0	0	0
Other	7 (3.6)	3 (1.6)	5 (2.6)	15 (2.6)
ITT[a]	194 (98.5)	192 (100.0)	192 (100.0)	578 (99.5)
Per protocol population[b]	173 (87.8)	172 (89.6)	166 (86.5)	511 (88.0)
Safety population[c]	197 (100.0)	192 (100.0)	192 (100.0)	581 (100.0)

[a] All patients who were randomized and had at least one post-baseline observation.
[b] All patients who completed the 4-week treatment period per protocol.
[c] All randomized patients who received at least one dose of study medication.
Source: Module 5, Vol 70, Section 10.1, Table 3

Demographics and baseline characteristics for patients in Study MP434 are summarized below. In general, the treatment groups appeared comparable and reflective of a general PAR population.

Table 16 Study MP434: Patient demographics and baseline characteristics			
Variables	**Astepro 0.1% (N=194)**	**MP03-36 (N=192)**	**Placebo (N=192)**
Age (Mean, Range)	36.9 (12-64)	35.6 (12-71)	38.1 (12-84))
Gender (male, %)	58 (29.9)	65 (33.9)	62 (32.3)
Race			
Caucasian	160 (82.5)	159 (82.8)	172 (89.6)
Black	28 (14.4)	26 (13.5)	11 (5.7)
Hispanic	32 (16.5)	36 (18.8)	29 (15.1)
Asian	2 (1.0)	3 (1.6)	2 (1.0)
Native American	1 (0.5)	1 (0.5)	0
Native Hawaiian or Pacific Islander	2 (1.0)	1 (0.5)	2 (1.0)
Other	1 (0.5)	2 (1.0)	5 (2.6)
Total score			
Mean, SD	15.6 (3.80)	15.9 (3.89)	17.9 (3.30)
Range	5-24	6-24	8-24
Duration of SAR (yrs)			
Mean, SD	19.0 (12.69)	19.6 (12.82)	20.2 (13.45)
Range	2-52	2-59	2-64

Source: Module 5, Volume 70, Section 11.2.1, Table 5

Primary efficacy results are displayed in Table 17. According to the Applicant's analysis, MP03-36 did not show a statistically significant difference from placebo for the primary efficacy endpoint, change from baseline to Day 14 in combined 12-h rTNSS. In keeping with the gatekeeping protocol, the comparison for MP03-33 versus placebo was not calculated. Numerically, both performed better than placebo and MP03-36 appeared to have an advantage over MP03-33. The Applicant did not perform subgroup analyses of the primary endpoint, but did provide a per-protocol analysis. When looking at the PP analysis, the results were statistically significant for MP03-36 versus placebo (p=0.018).

However, in the Agency's reanalysis of the primary endpoint, which was consistent with the methods used in the other PAR and SAR studies, MP03-36 compared favorably to placebo in terms of the primary efficacy endpoint: -4.01 vs. -3.13 (p=0.033). The reanalysis used a statistical model based on ANCOVA with treatment and center as fixed effect and the TNSS at baseline as a covariate. This is the same approach that was used by the Applicant for the pivotal SAR studies, MP433 and MP438. In comparison, the Applicant used a repeated measure model that included effects of treatment, center, days (2-28), and treatment-by-days interaction with baseline as covariate in the analysis of MP434's results. Therefore, the clinical review has relied on the Agency's reanalysis values in determining the efficacy of MP03-36 in PAR.

Secondary efficacy endpoints were numerically supportive, if not statistically significant. Numerically, MP03-36 also compared favorably to Astepro 0.1% in terms of the primary endpoint but did not distinguish itself from Astepro 0.1% in the secondary endpoints.

Table 17 Primary efficacy results for PAR indication: Change from baseline in combined AM and PM 12-hour rTNSS averaged over 28-day treatment period*

Study *Treatment groups*	N	LS mean baseline	LE mean change from baseline	Treatment difference from placebo	P-value vs. placebo	95% CI†
MP434						
MP03-36 BID	192	15.75	-4.01	-0.88	0.03	(-1.69, -0.07)
Astepro 0.1% BID	194	15.48	-3.84	-0.71	0.08	(-1.52, 0.09)
Placebo BID	192	14.71	-3.13			
MP435						
MP03-36 QAM	53	15.17	-4.89	-1.19	0.30	(-3.48, 1.09)
MP03-36 QPM	50	15.13	-3.90	-0.88	0.42	(-3.04, 1.28)
Placebo QAM	23	15.17	-3.70			
Placebo QPM	27	14.34	-3.02			

* The values displayed in this table are based on the Agency's statistical re-analysis and vary somewhat from the values provided by the Applicant in the NDA submission.

Reviewer's comment: Astepro 0.1% was included to benchmark MP03-36's performance, even though neither Astepro 0.1% nor Astelin currently has a PAR indication. Therefore, it is not necessary to justify the approval of multiple dosage strengths of azelastine for PAR.

Conclusions

Based on the Agency's primary endpoint analysis, Study MP434 showed support for the efficacy of MP03-36 twice daily for the treatment of PAR. Secondary efficacy endpoints were supportive of efficacy. This reanalysis is consistent with the methods of analysis performed in the other PAR and SAR studies. Therefore, the clinical review has relied on the Agency's reanalysis values in determining the efficacy of MP03-36 in PAR.

5.3.6 MP435

Study design and conduct

Study MP434 was a US multi-center, randomized, double-blind, placebo-controlled trial of the efficacy and safety of MP03-36 in the treatment of patients 12 years of age with PAR intended to assess the efficacy of a QD dosing regimen in the treatment of PAR. The study compared MP03-36 administered 2 sprays twice daily to placebo. The study was conducted in the winter to minimize confounding due to seasonal pollen allergens. Like Study MP434, the study consisted of a 1-week placebo lead-in period followed by a 4-week double-blind treatment period for those patients qualifying with a minimum symptom score. A total of 156 patients were randomized 1:1:1:1 to one of the following three **treatment groups**:

- MP03-36 2 sprays per nostril once daily AM (MAM)
- MP03-36 2 sprays per nostril once daily PM (MPM)
- Placebo 2 sprays per nostril once daily AM (PAM)
- Placebo 2 sprays per nostril once daily PM (PPM)

The **primary efficacy endpoint** was the same as that described for Study MP434: the change from baseline in 12-hour combined (AM plus PM) reflective TNSS (rTNSS) to Day 28 compared to placebo.

Secondary efficacy endpoints included the following:

- End of 24-hours dosing interval: Mean change from baseline in iTNSS for the 28-day study period compared to placebo (key secondary endpoint)
- Change from baseline in iTNSS for the entire 28-day study period
- Change from baseline in 12-hr rTNSS individual symptom scores
- Daily scores – both 12hr rTNSS and iTNSS compared to placebo
- Change from baseline in 12-hr rSSCS for the entire 28-day period. The SSCS was scored on a 0-3 scale (none to severe) for the following symptoms: postnasal drip, itchy eye, cough, and headache.
- Change from baseline in individual 12-hr SSCS symptoms over the entire 28-day period compared to placebo
- Change from baseline to Day 28 in the RQLQ in subjects 18 years of age and older

Safety assessments were the same as those described for Study MP434.

Reviewer's comment: As in the SAR studies intended to support a QD dosing regimen (Studies MP439 and MP440), iTNSS was a key efficacy variable for assessing the efficacy of the proposed 24-hour dosing interval.

Results

Patient disposition for Study MP435 is summarized in Table 18.

Table 18 Study MP435: Patient disposition

Disposition	MP03-36 QAM	Placebo QPM	MP03-36 QPM	Placebo QPM
Randomized	53	24	52	27
Completed	53 (100.0)	22 (91.7)	48 (92.3)	26 (96.3)
Discontinued	0	2 (8.3)	4 (7.7)	1 (3.7)
Adverse event	0	0	1 (1.9)	0
Treatment failure	0	1 (4.2)	0	1 (3.7)
Non-compliance	0	0	0	0
Withdrew consent	0	0	0	0
Lost to follow-up	0	1 (4.2)	2 (3.8)	0
Other	0	0	1 (1.9)	0
ITT[a]	53 (100.0)	23 (95.8)	50 (96.2)	27 (100.0)
Per protocol population[b]	49 (92.5)	16 (66.7)	45 (86.5)	23 (95.2)
Safety population[c]	53 (100.0)	24 (100.0)	52 (100.0)	27 (100.0)

[a] All patients who were randomized and had at least one post-baseline observation.
[b] All patients who completed the 4-week treatment period per protocol.
[c] All randomized patients who received at least one dose of study medication.
Source: Module 5, Vol 93, Section 10.1, Table 1

Demographics and baseline characteristics of patients enrolled in Study MP435 are summarized below. The treatment groups appeared comparable.

Table 19 Study MP435: Patient demographics and baseline characteristics					
Variables	**MP03-36 QAM N=53**	**Placebo QPM N=23**	**MP03-36 QPM N=50**	**Placebo QPM N=27**	**Total N=153**
Age (Mean, Range)	38.5 (12-76)	37.0 (14-62)	40.1 (12-70)	42.0 (13-67)	39.5 (12-76)
Gender (male, %)	14 (26.4)	5 (21.7)	17 (34.0)	10 (37.0)	46 (30.1)
Race/Ethnicity					
Caucasian	44 (83.0)	19 (82.6)	45 (90.0)	22 (81.5)	130 (85.0)
Black	5 (9.4)	3 (13.0)	3 (6.0)	2 (7.4)	13 (8.5)
Hispanic	10 (18.9)	5 (21.7)	13 (26.0)	4 (14.8)	32 (20.9)
Asian	0	0	0	1 (3.7)	1 (0.7)
Native American	0	0	0	1 (3.7)	1 (0.7)
Native Hawaiian or Pacific Islander	1 (1.9)	0	0	0	1 (0.7)
Other	3 (5.7)	1 (4.3)	2 (4.0)	1 (3.7)	7 (4.6)
Total score					
Mean, SD	15.3 (4.6)	16.2 (3.3)	15.3 (4.3)	14.5 (3.4)	15.3 (4.1)
Range	6-24	9-21	6-24	9-22	6-24
Duration of SAR (yrs)					
Mean, SD	19.5 (13.4)	15.4 (8.6)	23.7 (15.2)	20.7 (12.2)	20.5 (13.4)
Range	3-57	4-38	3-62	3-48	3-62

Source: Module 5, Volume 93, Section 11.2.1, Table 2

Primary efficacy results for MP435 are shown in Table 17. MP03-36 failed to demonstrate a statistically significant advantage over placebo in terms of the primary endpoint: -4.89 vs. -3.70 (p=0.30).

Conclusions
Study MP435 does not support the efficacy of MP03-36 dosed at 2 sprays once daily for the treatment of PAR.

5.3.7 MP436

Study design and conduct
MP436 was a US multi-center, randomized, open-label, active-controlled, 6-month safety study of the safety and tolerability of MP03-36 in PAR patients 12 years of age and older. The study included patients from MP434 (N=145) and MP435 (N=82), as well as new enrollees (N=476). MP03-36 was compared to a commonly used intranasal corticosteroid, mometasone furoate, Nasonex® (200 mcg). A total of 703 PAR were enrolled and randomized 2:1 to treatment with MP03-36 2 sprays twice daily or Nasonex 2 sprays twice daily. The RQLQ was the main efficacy assessment performed in this study, assessed in patients 18 years of age and older. Safety assessments included adverse event screening, focused nasal exams, and vital signs.

Results
Patient disposition for Study MP436 is summarized

Table 20 Study MP436: Patient disposition		
Disposition	**MP03-36**	**Nasonex**
Randomized	466	237
Completed (%)	329 (71)	194 (82)
Discontinued	176 (38)	59 (25)
Adverse event	54 (11)	17 (7)
Abnormal test result	-	-
Treatment failure	18 (4)	7 (3)
Non-compliance	15 (3)	5 (2)
Withdrew consent	47 (10)	11 (5)
Lost to follow-up	28 (6)	14 (6)
Administrative problems	-	-
Other	14 (3)	5 (2)
ITT[a]	455 (98)	232 (98)
Safety population[b]	466 (100)	237 (100)

[a] All patients who were randomized and had at least one post-baseline observation.
[b] All randomized patients who received at least one dose of study medication.
Source: Module 5, Vol 102, Section 10.1, Table 4 and 4-month safety update (dated December 22, 2008)

Demographics and baseline characteristics of patients enrolled in Study MP436 based on the 6-month interim report are shown below (updated demographic information was not included in the 4-month safety update).

Table 21 Study MP436: Patient demographics and baseline characteristics			
Variables	**MP03-36 N=465**	**Nasonex N=238**	**Total N=703**
Age (Mean, Range)	39 (12-84)	39 (12-72)	39 (12-84)
Gender (male, %)	158 (34)	62 (26)	220 (31)
Race			
Caucasian	359 (77)	192 (81)	552 (78)
Black	66 (14)	29 (12)	95 (14)
Asian	15 (3)	6 (3)	21 (3)
Native American	0	0	0
Native Hawaiian or Pacific Islander	4 (1)	1 (0.4)	5 (1)
Other	21 (5)	9 (4)	30 (4)
Total score			
Mean, SD	12.5 (5.6)	12.1 (5.6)	12.4 (5.6)
Range	0.4-24.0	1.8-24.0	0.4-24.0
Duration of PAR (yrs)			
Mean, SD	20 (15)	19 (14)	20 (14)
Range	0-70	0-59	0-70

Source: Module 5, Volume 102, Section 11.2.1, Table 5

Based on completion of patient diaries, 42% of the MP03-36 arm and 35% of the Nasonex arm were >75% compliant with study medication. Sixty-eight percent and 63%, respectively, were >50% compliant during the 6-month treatment period. Compliance was also assessed using the RQLQ data, which indicated improvement from baseline for both treatment arms (Table 22). In terms of the overall RQLQ, both MP03-36 and Nasonex demonstrated improvement from baseline. In all of RQLQ components, (activity, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional), Nasonex was numerically superior to MP03-36 (p=0.06 to 0.18).

Table 22 Study MP436: Overall RQLQ						
Overall RQLQ	N	Baseline (SD)	N	Change from baseline (SD)	P-value vs baseline	P-value vs Nasonex
MP03-36	333	3.0 (1.2)	230	-1.3 (1.2)	<0.001	0.06
Nasonex	174	3.0 (1.2)	143	-1.5 (1.3)	<0.001	

Source: Module 5, Volume 102, Section 11.4.1, Table 6

Reviewer's comment: RQLQ was the primary efficacy assessment performed in the safety study. Groups treated with MP03-36 and Nasonex both showed a statistically significant difference from baseline at Month 6 in the overall RQLQ score as well as the individual domains. The improvement in RQLQ is supportive of compliance with the study drug regimen. Further conclusion about efficacy is limited by the lack of placebo for comparison. Also, the RQLQ was assessed only in patients 18 years of age and older; the instrument is not validated for use in pediatric patients, so no efficacy data for patients 12 to 17 years of age was obtained.

Conclusions
Study MP436 had minimal efficacy measurements and was intended primarily as a long-term safety study. The lack of a placebo arm limits any conclusions about efficacy, although the RQLQ data is supportive of compliance with the study drug regimen and efficacy with chronic use. Safety results from MP436 are discussed in further detail in Section 7.

6 Review of Efficacy

Efficacy Summary

The NDA submission contains adequate data to support the proposed indication for MP03-36, the treatment of the symptoms or SAR and PAR in patients 12 years of age and older. Evidence of efficacy in SAR comes primarily from Studies MP433 and MP438 and pre-existing efficacy information on Astepro 0.1% and Astelin. For PAR, evidence comes primarily from Study MP434. The other efficacy studies were intended to support a once-daily dosing regimen for MP03-36, but failed to demonstrate convincing evidence to support a 24-hour dosing interval. Study MP436 was intended primarily as a safety study and included limited efficacy assessments (RQLQ instead of TNSS). As a result, this portion of the efficacy review focuses on the Studies MP433, MP438, MP439, MP440, MP434, and MP435. The results of Study MP436 are discussed in detail in Section 7.

In terms of the SAR indication, Studies MP433 and MP438 had study design and endpoints that 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. Both studies showed replicate, statistically significant evidence of efficacy for MP03-36 2 sprays BID compared to placebo. In MP433, the MP03-36 arm had a mean change from baseline combined AM and PM rTNSS of -4.25 compared to -3.04 for placebo (treatment difference -1.21; p=0.01).

In MP438, the mean change from baseline was more pronounced: -5.09 compared to -2.12, respectively (treatment difference -2.97; p<0.001).

Each study also included an active comparator as a benchmark as well as to provide justification for the approval of a higher dose level of azelastine. In MP433, the mean change from baseline combined rTNSS for the Astelin arm was -4.19, showing a numerically smaller treatment difference from placebo than MP03-36 (p=0.07). In post-hoc analysis performed by the Agency's statistical reviewer, MP03-36 did not show a statistically significant difference from Astelin (p=0.45) but was superior numerically. In MP438, the active comparator Astepro 0.1% arm was superior to placebo (P<0.001). In post-hoc analysis, MP03-36 arm was numerically superior to Astepro 0.1% and approached statistical significance (p=0.06). These results indicate that some patients may benefit from a higher dosage strength of azelastine in the treatment of their SAR symptoms.

Studies MP439 and MP440 were intended to support a QD dosing regimen in SAR for MP03-36. Neither Astepro 0.1% nor Astelin is approved for QD dosing. Both studies demonstrated statistically significant results for the primary efficacy endpoint, the change from baseline in combined AM and PM 12-hour rTNSS. Study MP439 showed a treatment difference of 0.98 between MP03-36 and placebo (p=0.008), and Study MP440 showed a treatment difference of -1.41 (p<0.001). However, review of the iTNSS scores suggested that QD dosing is inadequate and the treatment benefit wanes substantially towards the end of the 24-hr dosing interval. MP439 failed to demonstrate a statistically significant treatment difference for this key secondary endpoint (-1.4 vs. -1.1; p=0.11). Study MP440 did show a statistically significant difference for AM iTNSS scores (-1.4 vs -0.6; p<0.001), but this study was conducted in patients allergic to Texas mountain cedar. Texas mountain cedar is known to provoke particularly intense rhinitis symptoms in allergic patients. Clinical trials conducted in this patient population often have notably robust treatment differences. While a Texas mountain cedar-allergic population is acceptable for a SAR efficacy trial, results from this patient population may not be fully generalizable to a less specific SAR population and replication of these results in a general SAR population would be important for confirmation of efficacy. Study MP433 also had a MP03-36 QD dosing arm, but included the use of a placebo spray in the PM. Since a vehicle spray may impact rhinitis symptoms and confound results, there was no true QD dosing arm in this study to support a QD regimen for MP03-36. Even if this arm were considered a valid QD dosing arm, the results for the primary endpoint are not supportive (-1.2 vs. -1.0; p-0.408). Therefore, there is insufficient data to support the QD dosing regimen. Studies MP439 and MP440 suggest that once-daily dosing is better than placebo, but the treatment benefit is seen mainly in the first half of the 24-hr dosing interval. Efficacy is not consistently maintained over this extended dosing interval. The totality of the information in the NDA indicates that twice-daily dosing is the more appropriate, optimal regimen for MP03-36.

Although none of the SAR studies for MP03-36 evaluated a 1 spray BID regimen, 1 spray dosing is already approved for Astepro 0.1% and Astelin. Clinical studies to support the 1-spray dose were reviewed as part of a supplement to NDA 20-114 and approved in February 2000. No formal efficacy comparisons between the 1- and 2-spray Astelin doses has been made, and the current product labels for both Astelin and Astepro 0.1% recommend either 1 or 2 sprays

without making a distinction in efficacy. Since MP03-36 contains a higher concentration of azelastine, the active ingredient in Astelin, it is reasonable to extrapolate the efficacy data for 1-spray Astelin to MP03-36 and conclude that MP03-36 1 spray BID would also be efficacious in the treatment of SAR. On this basis, the clinical review recommends the approval of MP03-36 1 or 2 sprays BID for the treatment of SAR in patients 12 years of age and older.

Study MP434 provides the primary efficacy support for the PAR indication. The study design and endpoints of MP434 were appropriate and consistent with recommendations made in the *Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products*. The guidance also states that a single PAR study in conjunction with a winning SAR study may be used to support a PAR indication, so the results of MP434 are sufficient to support the PAR indication. In this study, MP03-36 compared favorably to placebo (-4.01 vs. -3.13; p=0.0.03 per the Agency's statistical review). The results for the MP03-36 arm were numerically favorable compared to the Astepro 0.1% arm. As in the case of SAR, it appears that some PAR patients may benefit from the use of a higher strength formulation of azelastine. Based on Study MP434's results, the clinical review recommends approval of MP03-36 2 sprays BID for the treatment of PAR in patients 12 years of age and older. The Applicant also submitted the results of Study MP435, a study of MP03-36 dosed once daily. However, the results for the primary efficacy analysis were not statistically significant, and the Applicant is not seeking a QD dosing regimen for the PAR indication.

6.1 Indication – Seasonal allergic rhinitis (SAR)

6.1.1 Proposed Indication

MP03-36 is proposed for the treatment of the symptoms of SAR in patients 12 years of age and older. The proposed dose is 2 sprays in each nostril once or twice daily.

6.1.2 Methods

See Section 5.3 for a description of the study design and conduct of Studies MP433, MP438, MP439, and MP440. The design and conduct of the respective studies were appropriate and consistent with recommendations made in the *Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products.*

6.1.3 Demographics

Detailed demographic data from the SAR efficacy and safety studies are shown in Section 5.3 and in the individual study summaries located in Section 10. 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. In general, patient recruitment was performed appropriately, and the patients enrolled in the MP03-36 SAR clinical development program appear to be representative of SAR patients in the general population.

6.1.4 Patient Disposition

Patient disposition in the individual studies is presented in Section 5.3 and in the individual study summaries located in Section 10. In general, the studies had a relatively high rate of completion (93-97%) and few cases of early discontinuation due to treatment failure in the active treatment arms.

6.1.5 Analysis of Primary Endpoint(s)

In terms of the SAR indication, Studies MP433 and MP438 had a primary endpoint that was appropriate and consistent with recommendations made in the *Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products* for evaluating efficacy in SAR. The studies showed replicate, statistically significant evidence of efficacy for MP03-36 2 sprays BID compared to placebo (**Table 6**). In MP433, the MP03-36 arm had a mean change from baseline combined AM and PM rTNSS of -4.47 compared to -3.27 for placebo (treatment difference -1.2; p=0.01). In MP438, the treatment difference was more pronounced: -5.36 compared to -2.36, respectively (treatment difference -3.0; p<0.001). In comparison to other development programs for antihistamines proposed for the treatment of SAR, these treatment differences as measured by the rTNSS are relatively robust.

Each study also included an active comparator as a benchmark as well as to provide justification for the approval of a higher dose level of azelastine. In MP434, the mean change from baseline combined rTNSS for the Astelin arm was -4.19, showing a numerically smaller treatment difference from placebo than MP03-36 (p=0.07). In post-hoc analysis performed by the Agency's statistical reviewer, MP03-36 did not show a statistically significant difference from Astelin (p=0.45) but was superior numerically. In MP438, the active comparator Astepro 0.1% arm was superior to placebo (P<0.001). In post-hoc analysis, MP03-36 arm was numerically superior to Astepro 0.1% and approached statistical significance (p=0.06). These results indicate that some patients may benefit from a higher dosage strength of azelastine in the treatment of their SAR symptoms.

6.1.6 Analysis of Secondary Endpoints(s)

The secondary endpoints were generally supportive of the primary efficacy endpoint, providing additional information on the adequacy of the dosing interval, quality of life measurements, and onset of action. The secondary endpoints assessed in Studies MP433, MP438, MP439 and MP440 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.

Change from baseline for individual rTNSS symptom components

The change from baseline for individual TNSS symptom components in Studies MP433 and MP438 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. For Study MP433, results were statistically significant for itchy nose, runny nose, and sneezing (p=0.001 to 0.033) but not for congestion (p=0.620). In Study MP438, comparison for all the individual rTNSS components were statistically significant (p<0.001). MP03-36 was numerically superior to Astelin and Astepro 0.1% in terms of the individual rTNSS symptom components as well, consistently demonstrating a larger treatment benefit for MP03-36.

Change from baseline iTNSS

Twice daily regimen

The iTNSS scores were generally supportive of the BID dosing regimen. The change from baseline combined AM and PM instantaneous TNSS scores over the 14-day treatment period in Study MP438 showed a statistically significant benefit for MP03-36 versus placebo (-4.6 vs. -2.0; p<0.001). The results were numerically supportive in Study MP433, but not statistically significant (-3.96 vs. -3.26; p=0.088). Support for the BID dosing interval also comes from pre-existing data for the lower-strength azelastine formulations, Astelin and Astepro 0.1%.

Once daily regimen

Studies MP439 and MP440 were intended to support a QD dosing regimen in SAR for MP03-36. Neither Astepro 0.1% nor Astelin is approved for QD dosing. Both studies demonstrated statistically significant results for the primary efficacy endpoint, the change from baseline in combined AM and PM 12-hour rTNSS. Study MP439 showed a treatment difference of 0.98 between MP03-36 and placebo (p=0.008), and Study MP440 showed a treatment difference of -1.41 (p<0.001). However, review of the iTNSS scores suggested that QD dosing is inadequate and the treatment benefit wanes substantially towards the end of the 24-hr dosing interval. MP439 failed to demonstrate a statistically significant treatment difference for this key secondary endpoint (-1.4 vs. -1.1; p=0.11). Study MP440 did show a statistically significant difference for AM iTNSS scores (-1.4 vs -0.6; p<0.001), but this study was conducted in patients allergic to Texas mountain cedar. Texas mountain cedar is known to provoke particularly intense rhinitis symptoms in allergic patients, which can result in exaggerated treatment differences between active drug and placebo. While a Texas mountain cedar-allergic population is acceptable for a SAR efficacy trial, results from this patient population may not be fully generalizable to a less specific SAR population and replication of these results in a general SAR population is recommended. Study MP433 also had a MP03-36 QD dosing arm, but included the use of a placebo spray in the PM. Since a vehicle spray may impact rhinitis symptoms and confound results, there was no true QD dosing arm in this study to support a QD regimen for MP03-36. Even if this arm were considered a valid QD dosing arm, the results for the primary endpoint are not supportive (-1.2 vs. -1.0; p-0.408).

Therefore, there is insufficient data to support the QD dosing regimen. Studies MP439 and MP440 suggest that once-daily dosing is better than placebo, but the treatment benefit is seen mainly in the first half of the 24-hr dosing interval. Efficacy is not consistently maintained over this extended dosing interval. The totality of the information indicates that twice-daily dosing is the more appropriate, optimal regimen for MP03-36, as is already approved for the lower strength azelastine formulations, Astelin and Astepro.

Onset of action

Onset of action was defines as the first timepoint after initiation of treatment when active drug demonstrated a statistically significant benefit from baseline iTNSS compared to placebo over the 4-hour post-dose period. In Study MP438, MP03-36 separated from placebo at 30 minutes and the effect was maintained through the duration of the 4-hour evaluation period. However, this onset of action was not replicated in another study. None of the treatment groups in MP433 demonstrated a durable, statistically significant onset of action in Study MP433.

Reviewer's comment: In the absence of replicate data, inclusion of onset of action information in the product label is not appropriate.

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.

In Study MP433, the overall mean RQLQ score was numerically improved at Day 14 compared to placebo with the twice-daily M2 dose (-1.44 vs. -1.13; p=0.073). The numerical trend in RQLQ results favored MP03-36 over placebo although the treatment difference is less than 0.5, which is generally regarded by the Division as the MCID. In Study MP438, the overall score for the RQLQ change from baseline compared to placebo was statistically significant for the MP03-36 group ($p<0.001$). These results further support the efficacy of MP03-36 at a dose of 2 sprays BID for the treatment of SAR.

6.1.7 Other Endpoints

No other endpoints were assessed,

6.1.8 Subpopulations

The Applicant included subgroup analyses by age, gender, and race. In general, there was no apparent association with efficacy by extremes of age, gender, or race, although the small sample sizes in some of these subgroups limits the conclusions.

Age

In patients <18 years of age (n=214 in the clinical development program), MP03-36 BID was numerically favored over placebo in Study MP433 (-2.32 vs. -1.81; p=0.69) but not in Study MP438 (-3.32 vs. -3.73; p=0.78). In patients ≥65 years of age (n=68), MP03-36 BID performed better than placebo in both Study MP433 (-6.05 vs. –1.95; p=0.37) and Study MP438 (-7.25 vs. -3.39; p-value not provided).

Gender
Subgroup analysis of the primary endpoint did not show any differences by gender. Both males (n=775) and females (n=1377) demonstrated statistically significant improvement when treated with MP03-36 BID compared to placebo.

Race
Analysis of the primary endpoint in Caucasians (n=1687), Asians (37), and Other (n=134) showed statistically significant treatment differences favoring MP03-36 over placebo similar to the differences observed for the study population as a whole. In Blacks (n=294), Study MP438 numerically favored MP03-36 over placebo (-4.38 vs. -2.36; p=0.21), but Study MP433 did not (-1.32 vs. -3.53; p=0.18). Paradoxically, the lower dose azelastine formulations (MP03-36 QAM and Astelin BID) did perform better than placebo in Blacks, suggesting that the non-supportive results may be a function of limited sample sizes for each dosing subgroup.

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Studies MP433 and MP438 each included an active comparator as a benchmark as well as to provide justification for the approval of a higher dose level of azelastine. Although a formal statistical comparison between the active treatments was not pre-specified in either study, the results suggest a relative dose response and support the approval of a higher dose of azelastine for the treatment of SAR. In MP434, the mean change from baseline combined rTNSS for the Astelin arm was -4.19, showing a numerically smaller treatment difference from placebo than MP03-36 (p=0.07). In post-hoc analysis performed by the Agency's statistical reviewer, MP03-36 did not show a statistically significant difference from Astelin (p=0.45) but was superior numerically. In MP438, the active comparator Astepro 0.1% arm was superior to placebo (P<0.001). In post-hoc analysis, MP03-36 arm was numerically superior to Astepro 0.1% and approached statistical significance (p=0.06). These results indicate that some patients may benefit from a higher dosage strength of azelastine in the treatment of their SAR symptoms.

Although none of the SAR studies for MP03-36 evaluated a 1 spray BID regimen, 1 spray dosing is already approved for Astepro 0.1% and Astelin. Clinical studies to support the 1-spray dose were reviewed as part of a supplement to NDA 20-114 and approved in February 2000. No formal efficacy comparisons between the 1- and 2-spray Astelin doses has been made, and the current product labels for both Astelin and Astepro 0.1% recommend either 1 or 2 sprays without making a distinction in efficacy. Since MP03-36 contains a higher concentration of azelastine, the active ingredient in Astelin, it is reasonable to extrapolate the efficacy data for 1-spray Astelin to MP03-36 and conclude that MP03-36 1 spray BID would also be efficacious in the treatment of SAR. On this basis, the clinical review recommends the approval of MP03-36 1 or 2 sprays BID for the treatment of SAR in patients 12 years of age and older.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

No tolerance effects were noted in the SAR studies for MP03-36 and have not been previously shown for Astelin or Astepro 0.1%.

6.1.11 Additional Efficacy Issues/Analyses

No other issues.

6.2 Indication – Perennial Allergic Rhinitis (PAR)

6.2.1 Proposed Indication

The proposed indication for MP03-36 is the treatment of the symptoms of PAR in patients 12 years of age and older. The proposed dosing is 2 sprays to each nostril twice daily.

6.2.2 Methods

See Section 5.3 for a description of the study design and conduct of Studies MP434 and MP435. The design and conduct of the respective studies were appropriate and consistent with recommendations made in the *Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products.*

6.2.3 Demographics

Detailed demographic data from the PAR efficacy and safety studies are shown in Section 5.3 and in the individual study summaries located in Section 10. Patient inclusion/exclusion criteria, described in the Section 10 Individual Study Reviews, were appropriate for defining a population of patients with moderate to severe PAR. The studies were conducted in the winter to minimize confounding from seasonal allergens, and patients with mountain cedar allergy, which is present in the winter months, were excluded. In general, patient recruitment was performed appropriately, and the patients enrolled in the MP03-36 PAR clinical development program appear to be representative of PAR patients in the general population.

6.2.4 Patient Disposition

Patient disposition in the individual studies is presented in Section 5.3 and in the individual study summaries located in Section 10. Study MP434, the main PAR study that supports efficacy for the PAR indication, had a study completion rate of 92%. One patient in the MP03-36 arm discontinued early due to treatment failure. Study MP435 had a 96% completion rate and no patients treated with MP03-36 discontinued early due to treatment failure.

6.2.5 Analysis of Primary Endpoint(s)

Study MP434 provides the primary efficacy support for the PAR indication. The study design and endpoints of MP434 were appropriate and consistent with recommendations made in the *Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products*. According to the Applicant's analysis, MP03-36 did not show a statistically significant difference from placebo for the primary efficacy endpoint, change from baseline to Day 14 in combined 12-h rTNSS. In keeping with the gatekeeping protocol, the comparison for MP03-33 versus placebo was not calculated. Numerically, both performed better than placebo and MP03-36 appeared to have an advantage over MP03-33. The Applicant did not perform subgroup analyses of the primary endpoint, but did provide a per-protocol analysis. When looking at the PP analysis, the results were statistically significant for MP03-36 versus placebo (p=0.018).

However, in the Agency's reanalysis of the primary endpoint, MP03-36 compared favorably to placebo in terms of the primary efficacy endpoint, and the results were statistically significant: -4.01 vs. -3.13 (p=0.033). However, in the Agency's reanalysis of the primary endpoint, which was consistent with the methods used in the other PAR and SAR studies, MP03-36 compared favorably to placebo in terms of the primary efficacy endpoint: -4.01 vs. -3.13 (p=0.033). The reanalysis used a statistical model based on ANCOVA with treatment and center as fixed effect and the TNSS at baseline as a covariate. This is the same approach that was used by the Applicant for the pivotal SAR studies, MP433 and MP438. In comparison, the Applicant used a repeated measure model that included effects of treatment, center, days (2-28), and treatment-by-days interaction with baseline as covariate in the analysis of MP434's results. Therefore, the clinical review has relied on the Agency's reanalysis values in determining the efficacy of MP03-36 in PAR. Numerically, MP03-36 also compared favorably to Astepro 0.1% in terms of the primary endpoint but did not distinguish itself from Astepro 0.1% in secondary endpoints. As in the case of SAR, it appears that some PAR patients may benefit from the use of a higher strength formulation of azelastine. Based on Study MP434's results, the clinical review recommends approval of MP03-36 2 sprays BID for the treatment of PAR in patients 12 years of age and older.

The Applicant also submitted the results of Study MP435, a study of MP03-36 dosed once daily. However, the results for the primary efficacy analysis were not statistically significant. The Applicant is not seeking a QD dosing regimen for the PAR indication.

Reviewer's comment: The Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products states that a single winning PAR study in conjunction with a winning SAR study may be used to support a PAR indication, so the results of MP434 are sufficient to support the PAR indication.

6.2.6 Analysis of Secondary Endpoints(s)

Secondary endpoints for Study MP434 were generally supportive of MP03-36 over placebo, if not statistically significant. The results for MP03-36 were similar to results for the benchmark

comparator, Astepro 0.1%, which currently does not have a PAR indication. No clear dose response in efficacy between the two dose levels was observed. This may be a reflection of the disease, PAR, which tends to be less responsive to medication therapy in clinical practice and in which it may be more difficult to demonstrate a dose-response curve. Secondary endpoint results from Study MP435, which failed to meet its pre-specified primary efficacy endpoint, are not discussed in this section but are described in the individual study summary located in Section 10.

Change from baseline iTNSS over the 28-day treatment period

In terms of change from baseline combined iTNSS scores averaged over the 28 day treatment period, MP03-36 compared favorably to placebo (-3.6 vs. -2.7; p=0.04), supporting the proposed BID dosing regimen. The results for the Astepro 0.1% arm were similar (mean change -3.4).

Change from baseline in individual rTNSS component nasal symptom scores

The change from baseline for individual TNSS symptom components in Study MP434 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 (p=0.39 to 0.299). MP03-36 was similar to the benchmark comparator, Astepro 0.1%, in terms of the individual rTNSS symptom components.

Daily symptom scores

The daily change from baseline in the 12h rTNSS generally favored MP03-36 over placebo but the results were not consistent over the 28-day treatment period. MP03-36 appeared more efficacious overall compared to Astepro 0.1%, but these were not statistically significant differences. Similar results were seen for the daily change from baseline in iTNSS as well.

Reflective SSCS

The MP03-36 group showed a statistically significant improvement in rSSCS compared to placebo over the 28-day treatment period (-2.92 vs. -1.79; p=0.002). For individual symptoms in the rSSCS, MP03-36 was superior to placebo in terms of itchy eyes, cough, and headache (p<0.001 to p=0.028) but not for post-nasal drip (p=0.29). The results for MP03-36 were numerically superior to the results for the comparator, Astepro 0.1%.

RQLQ

The RQLQ scores were statistically significantly different at baseline among the treatment groups, with the MP03-36 group having the highest mean score (3.29), followed by the Astepro 0.1% group (3.18) and the placebo group (2.98). The overall score for the RQLQ change from baseline compared to placebo was statistically improved for the Astepro 0.1% group (p=0.04) but not for the MP03-36 group compared to placebo (p=0.292).

6.2.7 Other Endpoints

No other endpoints, such as onset of action, were assessed.

6.2.8 Subpopulations

The Applicant included subgroup analyses by age, gender, and race. In general, there was no apparent association with efficacy by extremes of age, gender, or race, although small sample sizes limit the strength of any conclusions. The results presented below are based on Study MP434, the pivotal PAR study.

Age
In patients <18 years of age (n=50), MP03-36 BID was numerically favored over placebo in Study MP434 (-3.37 vs. =-0.67; p=0.41). In patients ≥65 years of age (n=14), similar results favoring MP03-36 were observed (-3.11 vs. -2.97; p=0.98).

Gender
Statistically significant differences between MP03-36 BID and placebo were observed in women (n=393; -4.58 vs. -3.22; p=0.008) but not in men (n=185; -3.28 vs. -3.50; p=0.74). Paradoxically, the lower dose azelastine formulations (Astepro 0.1%) did perform better than placebo in men, suggesting that the non-supportive results for MP03-36 may be a function of limited sample sizes for each dosing subgroup.

Race
In general, primary efficacy results in Caucasians (n=491), Blacks (n=65), Asians (n=7), and Other (n=15) were numerically favorable for MP03-36 over placebo if not statistically significant. P-values were not calculated for Asians and Other given the low numbers.

6.2.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Given the negative findings of MP435, only the 2 sprays twice daily regimen of MP03-36 for PAR is supported. One spray twice daily was not assessed in the MP03-36 clinical development program. Unlike the SAR indication, neither the related azelastine products, Astelin and Asterpro 0.1%, are approved for the PAR indication so there is no precedent for a 1-spray dosing regimen.

6.2.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

No tolerance effects were noted in the SAR studies for MP03-36 and have not been previously shown for Astelin or Astepro 0.1%.

6.2.11 Additional Efficacy Issues/Analyses

No other efficacy issues.

7 Review of Safety

Safety Summary

The NDA submission contains adequate data to support the safety of MP03-36 in patients 12 years of age and older for the treatment of SAR and PAR symptoms. The safety of 0.1% intranasal azelastine has been previously demonstrated in the clinical development programs for Astelin and, subsequently, Astepro 0.1% and is summarized in the current product labels, respectively. Evidence for safety for MP03-36 is based primarily on the assessments performed in the Phase 3 efficacy studies and the dedicated 6-month safety study, MP436. These data are supplemented by the NDA's 4-month safety update covering the time period from January 5, 2008, to June 20, 2008, post-marketing data for Astelin and Astepro 0.1%, and published literature reports up to March 15, 2009.

The data included in this submission shows that the higher concentration of azelastine does not alter the known safety profile of intranasal azelastine in patients 12 years of age older. The most common adverse events reported in both the SAR and PAR efficacy studies were dysgeusia, nasal discomfort, epistaxis, headache, and upper respiratory tract infection. For the MP03-36 BID regimen, somnolence was reported in 4 SAR patients (1.2%) and 2 (1.0%) PAR patients. The rate of somnolence in the open-label, long term safety study was slightly higher, reported in 3.6% of patients. These adverse events are all described in the current product labels for Astelin and Astepro 0.1% and are consistent with the postmarketing safety profiles for Astelin. In the development program, no new cases of nasal ulceration or septal perforation were reported.

Off-label use of MP03-36 for the treatment of VMR is likely, given that Astelin is currently approved for both the treatment of SAR and VMR. The added taste-masking excipients in MP03-36, sucralose and sorbitol, may compromise the efficacy of MP03-36 in VMR, which is a rhinitis condition characterized by sensitivity to certain sensorial triggers like smell and taste. However, the risk of other adverse events not already associated with Astelin is low. Other significant adverse events are not anticipated with the use of MP03-36 in VMR. Off-label use of MP03-36 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 MP03-36 compared to Astelin and Astepro 0.1%, 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

Evidence of safety for MP03-36 is based primarily on the assessments performed in the Phase 3 Studies, MP433 and MP438 for SAR and MP434 for PAR. The safety of chronic use is also supported by Study MP436, the long-term safety study in PAR. An interim 6-month study report

was submitted in the NDA for Study MP436. The 4-month safety update dated December 22, 2008, included updated patient disposition and adverse event data from the completed study. A full study report on the completed study was not submitted. In the discussion of adverse events in the clinical review, data from the 4-month safety update is incorporated into the clinical review.

Each of these studies assessed the safety of MP03-36 2 sprays BID, the highest dose evaluated in the Phase 3 program and the to-be-marketed dose. The study design and conduct of the studies are presented in Section 5.3 and in the individual study summaries in Section 10. These safety data are supplemented by postmarketing data for Astelin and Astepro 0.1% and published literature reports, as well as the original safety data from the clinical development programs for Astelin and Astepro 0.1% that were previously reviewed under NDA 20-114 and NDA 22-203.

7.1.2 Adequacy of Data

The data submitted to support the safety of MP03-36 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.

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

The Integrated Summary of Safety included pooled analysis of safety data from the Phase 3 program, organized by the SAR and PAR indications and by the dosing regimen of MP03-36 (QD vs. BID). This pooling strategy is appropriate for estimating and comparing the incidence of adverse events and other safety parameters. The clinical safety review utilized this organization by indication and dosing regimen and focused on the BID regimen, which was the highest dose of MP03-36 evaluated in the Phase 3 program and which represents the to-be-marketed dose and regimen. Long-term safety data from the active-controlled study, MP436, were evaluated separately and not included in the pooled placebo-controlled data.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The study design, patient population, doses and drug exposures in the Phase 3 program were appropriate for the safety assessment of MP03-36 in patients 12 years of age and older. Baseline characteristics and demographic information for patients in all the Phase 3 placebo-controlled SAR efficacy studies (Studies MP433, MP438, MP439, and MP440) and the placebo-controlled PAR efficacy studies (MP434 and MP435) are presented in **Table 23** and Table 24. Baseline demographics for patients in MP436, the active-controlled long-term safety study, are presented in Table 21. Overall, the study groups appeared comparable in terms of demographic distribution.

Table 23 SAR studies: Patient demographics and baseline characteristics

Demographics	MP03-36 N=996	Astepro 0.1% N=170	Astelin N=153	Placebo N=841	Total N=2007
Age (years)					
Mean	38	35	38	37	37
SD	14	14	14	14	14
Median	39	35	39	38	38
Range	12-80	12-79	13-83	12-81	12-81
12 to <18 [N(%)]	96 (10)	16 (9)	14 (9)	88 (10)	200 (10)
18 to <65 [N(%)]	869 (87)	152 (89)	134 (88)	732 (86)	1744 (87)
65 or older [N(%)]	31 (3)	2 (1)	5 (3)	30 (4)	63 (3)
Sex [N(%)]					
Male	369 (37)	59 (35)	57 (37)	297 (35)	725 (36)
Female	627 (63)	111 (65)	96 (63)	544 (65)	1282 (64)
Ethnicity [N(%)]					
Hispanic or Latino	167 (17)	27 (16)	21 (14)	143 (17)	337 (17)
Not Hispanic or Latino	829 (83)	143 (84)	132 (86)	698 (83)	1670 (83)
Race					
American Indian or Alaska Native	4 (0.4)	1 (1)	-	0	5 (0.2)
Asian	15 (2)	1 (1)	4 (3)	17 (2)	33 (2)
Black	125 (13)	30 (18)	23 (15)	116 (14)	271 (14)
Native Hawaiian or other Pacific Islander	4 (0.4)	1 (1)	-	5 (1)	10 (1)
White	788 (79)	135 (79)	105 (69)	667 (79)	1590 (79)
Other	60 (6)	2 (1)	-	36 (4)	98 (5)
TNSS*					
Mean	18.2	18.3	18.0	17.9	18.1
SD	3.3	3.2	2.8	3.3	3.3
Median	18.4	18.2	17.9	18.0	18.2
Range	7-24	5-24	8-24	6-24	5-24
Duration of rhinitis (years)					
Mean	20	19	20	19	19
SD	13	11	14	13	13
Median	16	17	16	16	16
Range	2-73	2-51	2-69	2-70	2-73

* Mean baseline reflective TNSS over 7-day lead-in period, including Day 1 AM.
Source: Module 2, Volume 2, Table 2.7.4.1.3-1

Table 24 PAR studies (Study MP434 and MP435): Patient demographics and baseline characteristics

Demographics	MP03-36 N=297	Astepro 0.1% N=197	Placebo N=243	Total N=737
Age (years)				
Mean	37	37	39	37
SD	14	13	15	14
Median	37	36	38	38
Range	12-76	12-64	12-84	12-84
12 to <18 [N(%)]	30 (10)	11 (6)	24 (10)	65 (9)
18 to <65 [N(%)]	258 (87)	186 (94)	208 (86)	652 (89)
65 or older [N(%)]	9 (3)	0	11 (5)	20 (3)
Sex [N(%)]				
Male	97 (33)	61 (31)	77 (32)	235 (32)
Female	200 (67)	136 (69)	166 (68)	502 (68)
Ethnicity [N(%)]				
Hispanic or Latino	59 (20)	32 (16)	39 (16)	130 (18)
Not Hispanic or Latino	238 (80)	165 (84)	204 (84)	607 (82)
Race				
American Indian or Alaska Native	1 (0.3)	1 (1)	1 (0.4)	3 (0.4)
Asian	3 (1)	3 (2)	3 (1)	9 (1)
Black	34 (11)	29 (15)	16 (7)	79 (11)
Native Hawaiian or other Pacific Islander	2 (1)	2 (1)	2 (1)	6 (1)
White	250 (84)	161 (82)	214 (88)	625 (85)
Other	7 (2)	1 (1)	7 (3)	15 (2)
TNSS*				
Mean	15.7	15.6	14.9	15.4
SD	4.1	3.8	3.9	4.0
Median	15.8	15.6	14.7	15.4
Range	6-24	5-24	5-24	4-24
Duration of rhinitis (years)				
Mean	20	19	20	20
SD	13	13	13	13
Median	17	16	17	17
Range	2-62	2-52	2-64	2-64

* Mean baseline reflective TNSS over 7-day lead-in period, including Day 1 AM.
Source: Module 2, Volume 2, Table 2.7.4.1.3-1

In general, the patients enrolled in the SAR and PAR efficacy studies as well as the long-term safety study were similar in terms of age and duration of rhinitis. Baseline rhinitis symptoms based on mean rTNSS tended to be the most severe in the SAR patients (mean score 18.1), which included patients with allergy to Texas mountain cedar, an allergen known to provoke particularly intense rhinitis symptoms. PAR efficacy patients had a slightly lower mean rTNSS score of 15.4 at baseline. The PAR patients enrolled in the safety study had the lowest mean rTNSS scores (mean 12.2). This difference is expected given the respective inclusion/exclusion criteria, which did not require a minimum baseline TNSS score for enrollment, in contrast to the efficacy studies.

The following tables detail the drug exposure and compliance in the MP03-36 development program. Table 25 shows exposure and compliance for the Phase 3 SAR and PAR efficacy studies. Exposure and compliance information for the Astelin arm in MP433 are displayed separated in Table 40. Information for Study MP436 is described separately in Section 5.3 and the individual study summary located in Section 10. For the Phase 3 efficacy studies, the estimated percentage of patients with >80% compliance was over 97%. The rate of compliance in the long-term safety study was lower, as might be expected. Based on completion of patient diaries, 42% of the MP03-36 arm and 35% of the Nasonex arm were >75% compliant with study medication. Sixty-eight percent and 63%, respectively, were >50% compliant during the 6-month treatment period. The overall duration of exposure and number of doses administered were adequate to assess the safety of MP03-36.

Table 25 Drug exposure and compliance in Phase 3 efficacy studies

	MP03-36 N=996	Astepro 0.1% N=170	Placebo N=841	Total N=2007
SAR				
Dosing [N (%)]				
BID	331 (33)	170 (100)	331 (39)	832 (42)
QD	665 (67)	-	510 (61)	1175 (59)
Duration (days)				
N	991	170	838	1999
Mean	14	15	14	14
SD	2	2	2	2
Median	15	15	15	15
Range	1-19	1-22	1-21	1-22
Total number of doses - BID				
N	328	169	330	827
Mean	27	28	27	27
SD	4	3	4	4
Median	28	28	28	28
Range	1-37	8-42	2-38	1-42
Total number of doses - QD				
N	663	-	510	1173
Mean	14		14	14
SD	2		2	2
Median	15		15	15
Range	1-18		1-19	1-19
# Patients ≥80% compliance [N(%)]	980 (98)	169 (99)	829 (99)	1978 (99)
PAR				
Dosing [N (%)]				
BID	192 (65)	197 (100)	192 (79)	581 (79)
QD	105 (35)	-	51 (21)	156 (21)
Duration (days)				
N	296	193	241	730
Mean	28	28	28	28
SD	4	4	4	4
Median	28	29	28	28
Range	2-38	1-38	2-35	1-38
Total number of doses - BID				
N	192	196	192	580
Mean	53	54	53	53
SD	10	10	10	10
Median	56	56	56	56
Range	3-71	1-76	3-70	1-76
Total number of doses - QD				
N	104	-	50	154
Mean	28		27	27
SD	2		3	3

Median Range	28 13-31		28 12-30	28 12-31
# Patients ≥80% compliance [N(%)]	288 (97)	189 (96)	234 (96)	711 (97)

Source: Module 2, Vol 2, Tables 2.7.4.1.2-1 and 2.7.4.1.2-2

Patient disposition in the SAR and PAR efficacy studies is shown in Table 26. Patient disposition for the long-term safety study, MP436, is shown separately in Table 20. In general, similar numbers of patients in all treatment arms completed the study, or discontinued secondary to adverse events and treatment failures. For a small number of patients, the reasons for discontinuation were not specified and reported as "other." Although the reasons for discontinuation were not evident from the individual line listings, the proportions of patients across treatment groups were similar, suggesting that the underlying reason is not due a specific untoward effect of MP03-36.

Table 26 Patient disposition in Phase 3 SAR and PAR efficacy studies

Disposition	MP03-36 N (%)	Astepro 0.1% N(%)	Placebo N (%)	Total N (%)
SAR				
Randomized	996	170	841	2007
Completed	952 (96)	166 (98)	802 (95)	1920 (96)
Discontinued	44 (4)	4 (2)	39 (5)	87 (4)
Adverse event	17 (2)	3 (2)	13 (2)	33 (2)
Abnormal test result	2 (0.2)	-	-	2 (0.1)
Treatment failure	4 (0.4)	-	7 (1)	11 (1)
Non-compliance	5 (1)	-	2 (0.2)	7 (0.3)
Withdrew consent	2 (0.2)	1 (1)	2 (0.2)	5 (0.2)
Lost to follow-up	6 (1)	-	3 (0.4)	9 (0.4)
Administrative problems	-	-	-	-
Other	8 (0.8)	-	12 (1)	20 (1)
Total safety population	996 (100)	170 (100)	841 (100)	2007 (100)
ITT population	992 (99.6)	169 (99.4)	838 (99.6)	1999 (99.6)
Per-protocol population	9218 (92)	161 (95)	762 (91)	1841 (92)
PAR				
Randomized*	297	197	243	737
Completed	281 (95)	180 (91)	223 (92)	684 (93)
Discontinued	16 (5)	17 (9)	20 (8)	53 (7)
Adverse event	8 (3)	4 (2)	3 (1)	15 (2)
Abnormal test result	-	-	-	-
Treatment failure	1 (0.3)	-	3 (1)	4 (1)
Non-compliance	-	-	3 (1)	3 (0.4)
Withdrew consent	1 (0.3)	2 (1)	4 (2)	7 (1)
Lost to follow-up	2 (0.7)	4 (2)	2 (1)	8 (1)
Administrative problems	-	-	-	-
Other	4 (1)	7 (4)	5 (2)	16 (2)
Total safety population	297 (100)	197 (100)	243 (100)	737 (100)
ITT population	295 (99)	194 (99)	242 (99.6)	731 (99)
Per-protocol population	266 (90)	173 (88)	205 (84)	644 (87)

Source: Module 2, Volume 2, Table 2.7.4.1.2-1

7.2.2 Explorations for Dose Response

Formal exploration for dose response and drug toxicity was not performed, but the lower strength azelastine products, Astelin and Astepro 0.1%, were included in the efficacy studies as benchmark comparators.

7.2.3 Special Animal and/or In Vitro Testing

No special animal testing and/or in vitro testing studies were included in this application.

7.2.4 Routine Clinical Testing

In the Phase 3 efficacy studies, routine clinical testing was limited to prick-puncture allergen skin testing at screening, urine pregnancy tests in female patients at screening, focused nasal exams, and vital sign measurements (weight, blood pressure, heart rate, and respiratory rate). Blood laboratory testing was performed at the discretion of the investigator for individual cases if deemed appropriate. Given the pre-existing safety database for Astelin and Astepro 0.1%, the duration of the study, and the target population, limited clinical testing was appropriate. A full schedule of safety assessments is presented in the respective individual study summaries located in Section 10.

In the long-term safety study, routine clinical testing included all of the above as well as a 12-lead ECG at Screening, Month 6, and Month 12 and standard clinical laboratory parameters at Screening, Month 6, and Month 12. These parameters included a complete blood count with white cell differential, quantitative urinanalysis, and chemistry panel (albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, CK, creatinine, glucose, AST, ALT, potassium, sodium, total protein, and uric acid). A full schedule of safety assessments is presented in the individual study summary located in Section 10.

7.2.5 Metabolic, Clearance, and Interaction Workup

Comparative pharmacokinetic evaluations between MP03-33 and Astelin are described in Section 4.4 Clinical Pharmacology, along with drug-drug interaction studies previously reviewed under NDA 20-114. No new in vitro or in vivo data on metabolism or clearance was submitted in this application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Azelastine is currently one of two approved antihistamines administered via intranasal inhalation for treatment of allergic rhinitis. In addition to somnolence, which is common to many antihistamines, the other major safety concern with this drug class and formulation is the risk of mucosal ulceration and perforation of the nasal septum. To address this issue, focused nasal exams were performed at regular intervals in the Phase 3 program. Nasal exam findings were scored and analyzed separately in the individual study reports.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the clinical development program.

7.3.2 Nonfatal Serious Adverse Events

Two SAEs were reported in the efficacy studies, both occurring in the placebo group in Study MP438. Patient 808-10 had exposure to placebo during pregnancy. The outcome is not reported. Patient 811-09 developed pneumonia requiring hospitalization and was reported as having complete recovery.

In Study MP436, 4 SAEs in 5 patients were reported in the MP03-36 group: acute appendicitis, acute exacerbation of chronic bronchitis secondary to toxic fume injury (gas leakage), angina pectoris, and dyspnea. Two SAEs in 2 patients were reported in the Nasonex group: cystocele surgery and abdominal wall cellulitis.

Reviewer's comment: The diffuse nature of the SAEs makes it difficult to draw conclusions about cause and effect, although given the known mechanism of action of MP03-36 and the pharmacokinetics, a causal relationship seems unlikely in the reported SAEs.

7.3.3 Dropouts and/or Discontinuations

In the placebo-controlled efficacy trials, the percentage of SAR patients that discontinued early due to an AE was 2.7% in the MP03-36 BID group, the same as in the placebo BID group. In the PAR studies, 3.6% of patients in MP03-36 BID arm compared to 1.6% in placebo discontinued early due to an AE. As shown in Table 27, the AEs cited were generally similar in nature to the AEs reported in patients who completed the study. Most of the AEs resulting in early discontinuation were reported by a single patient.

Table 27 Adverse events cited in patients discontinuing early from the Phase 3 efficacy studies (MedRA preferred terms)

	Adverse event	N
SAR		
MP03-36 BID (N=665)	Tachycardia	1
	Dysgeusia	1
	Dyspepsia	1
	Nausea	1
	Fatigue	1
	Rash	1
	Sinus headache	1
	Blood pressure increased	1
	Accidental overdose	1
	Gastroenteritis viral	1
MP03-36 QD (N=361)	Arthropod bite	1
	Pyrexia	2
	Pharyngolaryngeal pain	1
	Upper respiratory tract infection	1
	Nasal discomfort	1
	Pharyngeal hypoaesthesia	2
	Dysgeusia	1
	Sinusitis	2
	Bronchitis	1
	Cough	1
	Sinus congestion	1
PAR		
MP03-36 BID (N=192)	Nasal discomfort	2
	Sneezing	2
	Lacrimation increased	1
	Streptococcal pharyngitis	1
	Dermatitis contact	2
	Follicular conjunctivitis	1
	Upper respiratory tract infection	1
MP03-36 QD (N=104)	Epistaxis	1
	Sinusitis	1

Source: Module 2, Table 2.7.4.2.1.4-1

A wider range of AEs were cited among patients discontinuing prematurely from Study MP436. These included the following: vertigo, eye irritation, retinal vein occlusion, dry mouth, lip dry, nausea, oral discomfort, fatigue, acute sinusitis, bronchitis, pneumonia primary atypical, sinusitis, upper respiratory tract infection, urinary tract infection, weight increased, increased appetite, arthralgia, dizziness, dysgeusia, headache, migraine, sedation (n=1), sinus headache, somnolence, anger, breathing-related sleep disorder, depression, dysphonia, epistaxis, nasal discomfort, nasal mucosal disorder, pharyngolaryngeal pain, postnasal drip, sneezing, snoring, throat irritation, elevated ALT, and acne. Of note, were fatigue (n=4), somnolence (n=3), and sedation (n=1), compared to no cases in the Nasonex active control arm. Dysgeusia was also cited as a cause for early discontinuation by 12 patients in the MP03-36 arm, compared to 2 cases in the Nasonex arm. In most of the cases, the cited AEs were consistent with the safety profile described in the Astelin and Astepro 0.1% product labels. Other AEs, such as retinal vein occlusion, elevated ALT, and anger, occurred in single patients, making it difficult to draw conclusions about a causal effect. Overall, a review of the AEs related to early discontinuation did not indicate any new safety signals for intranasal azelastine.

7.3.4 Significant Adverse Events

No other significant adverse events were reported.

7.3.5 Submission Specific Primary Safety Concerns

Local nasal toxicity

Focused nasal exams were performed in the Phase 3 efficacy studies to assess local toxicity that may be associated with intranasal inhalation of MP03-36. The schedule of exams is detailed in the individual study summaries in Section 10. No significant changes in the focused nasal exam were recorded in any of the treatment groups for the 14-day and 28-day treatment periods. No new cases of mucosal ulceration or septal perforation were reported in the placebo-controlled efficacy studies. The most common observations were physical findings consistent with allergic rhinitis (e.g. boggy turbinates, pale mucosa, watery mucosa, etc.). The overall rate and severity of nasal irritation appeared comparable among MP03-36, Astelin, Astepro 0.1%, and placebo in the various studies. The rates of common adverse events related to local toxicity – such as nasal discomfort, epistaxis, pharyngolaryngeal pain, and nasapharyngitis – were similar among the treatment groups and there was no apparent dose-related effect. These and other common adverse events are presented in more detail in the following section, Section 7.4.

Reviewer's comment: In the PAR study MP434, one patient in the MP03-33 group was reported as having a nasal septum perforation, which the patient had been present since 1997, well before the study. The perforation was not reported on screening form; however, it seems unlikely that a septal perforation could have developed during the limited treatment period..

In the active-controlled long-term safety study, MP03-36 had a similar rate and severity of nasal irritation as Nasonex. No nasal septal perforations or mucosal ulcerations were reported in either group. Other signs and symptoms of nasal irritation were observed as follows: Grade 1A mucosal erosion (3% in MP03-36 vs. 3% Nasonex), epistaxis (9% vs. 10%), nasopharyngitis (9% vs. 8%), and pharyngolaryngeal pain (5% vs. 6%).

Somnolence, fatigue, and sedation

As an antihistamine, azelastine is associated with a sedating effect which is reported in the current products labels for Astelin (somnolence 11.5% and fatigue 2.3% for the 2-spray BID dose) and Astepro 0.1% (somnolence 1% for the 1-spray BID dose and 2% for the 2-spray BID dose). When examining the issue of somnolence for MP03-36 (MedDra preferred terms: somnolence, fatigue, and sedation), there did appear to be a slightly increased rate with MP03-36 compared to the 0.1% azelastine formulations, suggesting a possible dose-related effect (Table 28). However, the total numbers of patients with these adverse events were small and the MP03-36 treatment group was significantly larger than the other treatment groups, which may have affected the ascertainment of these infrequent events in the Astelin and Astepro 0.1% groups. In general, the rates reported in the MP03-36 development program were lower than the rates observed in the development programs for Astelin and Astepro 0.1%.

Table 28 Somnolence, fatigue and sedation in the MP03-36 Phase 3 efficacy studies

Preferred term	BID				QD	
	MP03-36 N, %	Astepro 0.1% N, %	Astelin N, %	Placebo N, %	MP03-36 N, %	Placebo N, %
SAR						
N	331	170	153	331	665	510
Somnolence	4 (1.2)	1 (0.6)	-	1 (0.3)	5 (0.8)	3 (0.6)
Fatigue	3 (0.9)	-	-	1 (0.3)	2 (0.3)	1 (0.6)
Sedation	-	-	-	-	2 (0.3)	-
PAR						
N	192	197	N/A	192	105	51
Somnolence	2 (1.0)	-		-	-	-
Fatigue	2 (1.0)	1 (0.5)		-	1 (1.0)	-
Sedation	-	-		-	2 (0.3)	-

In the long-term safety study, MP436, fatigue and somnolence occurred at a rate of 4.1% and 3.6%, respectively. These rates were higher than those observed for the Nasonex (0.8% and 0.4%), which is an intranasal corticosteroid and not expected to cause sedation like an antihistamine. The rates of somnolence and fatigue were slightly higher than those observed in the placebo-controlled efficacy studies, but lower than the rates reported in the original Astelin development program (NDA 20-114).

Reviewer's comment: The results from the pooled Phase 3 adverse event analysis suggest a possible dose-related effect in regards to somnolence. However, the total numbers reported were low, and the treatment group sizes were unequal. The clinical review cannot confirm a dose-response for these particular adverse events with any certainty. In general, the rate reported in the MP03-36 program was lower than the rates described for Astelin and Astepro 0.1% in the current product labels. The clinical review does not find it appropriate to state that the lower azelastine concentration formulations have a lower rate of somnolence than MP03-36, given the information provided in the current product labels and the proposal to merge MP03-36 and Astepro 0.1% under a single tradename with clinical trial data for both formulations in the same product label.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events associated with MP03-36 in both the SAR and PAR efficacy studies included the following: dysgeusia, nasal discomfort, epistaxis, headache, and upper respiratory tract infection. These AEs are consistent with the known safety profile of Astelin and Astepro 0.1%. In general, the frequency of AEs was lower than the rates observed in the controlled clinical trials supporting approval of Astelin 2 sprays BID for the 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%. The frequency of AEs was similar to the rates reported for Astepro 0.1% in the current product label.

There was no clear dose response in terms of overall common adverse events when comparing MP03-36 to the lower strength formulations of Astelin and Astepro 0.1% in Studies MP433, MP438, MP439, and MP434. There was no clear dose response when comparing the BID to the QD MP03-36 regimen as well. Common adverse events occurring in 1% or more of the safety population in placebo-controlled Phase 3 studies are shown in Table 29 and Table 30.

Table 29 MP03-36 SAR efficacy studies: Adverse events occurring in 1% or more of the safety population

Preferred term	BID				QD	
	MP03-36 N=331 N, %	**Astepro 0.1%** N=170 N, %	**Astelin** N=153 N, %	**Placebo** N=331 N, %	**MP03-36** N=665 N, %	**Placebo** N=510 N, %
Any AE	52 (15.7)	37 (21.8)	27 (17.6)	51 (15.4)	123 (18.5)	58 (11.4)
Dysgeusia	22 (6.6)	16 (9.4)	8 (5.2)	4 (1.2)	30 (4.5)	2 (0.4)
Nasal discomfort	5 (2.9)	5 (2.9)	3 (2.0)	5 (1.5)	22 (3.3)	4 (0.8)
Epistaxis	3 (0.9)	2 (1.2)	3 (2.0)	4 (1.2)	11 (1.7)	8 (1.6)
Headache	4 (1.2)	3 (1.8)	6 (3.9)	7 (2.1)	5 (0.8)	7 (1.4)
Upper respiratory tract infection	-	-	-	1 (0.3)	5 (0.8)	3 (0.6)
Sneezing	4 (1.2)	1 (0.6)	1 (0.7)	1 (0.3)	6 (0.9)	-
Pharyngolaryngeal pain	1 (0.3)	1 (0.6)	2 (1.3)	-	6 (0.9)	5 (1.0)
Nausea	1 (0.3)	3 (1.8)	1 (0.7)	3 (0.9)	4 (0.6)	2 (0.4)
Sinus headache	1 (0.3)	3 (1.8)	-	2 (0.6)	5 (0.8)	3 (0.6)
Nasal mucosal disorder	-	-	-	-	4 (0.6)	2 (0.4)
Somnolence	4 (1.2)	1 (0.6)	-	1 (0.3)	5 (0.8)	3 (0.6)
Nasopharyngitis	1 (0.3)	2 (1.2)	1 (0.7)	1 (0.3)	2 (0.3)	1 (0.2)

Source: Module 2, Volume 2, Table 2.7.4.2.1-1; Module 5, Volume 7, Section 12.2.2, Text Table 16

Table 30 MP03-36 PAR efficacy studies: Adverse events occurring in 1% or more of the safety population

Preferred term	BID			QD	
	MP03-36 N=192 N, %	**Astepro 0.1%** N=197 N, %	**Placebo** N=192 N, %	**MP03-36** N=105 N, %	**Placebo** N=51 N, %
Any AE	46 (24.0)	48 (24.4)	39 (20.3)	32 (30.5)	12 (23.5)
Dysgeusia	9 (4.7)	11 (5.6)	1 (0.5)	2 (1.9)	-
Nasal discomfort	13 (6.8)	7 (3.6)	7 (3.6)	2 (1.9)	-
Epistaxis	2 (1.0)	4 (2.0)	3 (1.6)	6 (5.7)	2 (3.9)
Headache	1 (0.5)	4 (2.0)	6 (3.1)	4 (3.8)	1 (2.0)
Upper respiratory tract infection	2 (1.0)	1 (0.5)	4 (2.1)	4 (3.8)	1 (2.0)
Sneezing	5 (2.6)	-	-	3 (2.9)	-
Nasal mucosal disorder	2 (1.0)	1 (0.5)	2 (1.0)	2 (1.9)	-

Source: Module 2, Volume 2, Table 2.7.4.2.1-2

A similar adverse event profile was observed in the long-term study, MP436. The most common adverse events were dysgeusia, sinusitis, epistaxis, upper respiratory tract infection, headache, and pharyngolaryngeal pain.

Table 31 Study MP436: Adverse events occurring in 2% or more of the MP03-36 safety population

Preferred term	MP03-36 N=466 N, %	Nasonex N=237 N, %
Any AE	349 (74.9)	163 (68.8)
Dysgeusia	62 (13.3)	3 (1.3)
Sinusitis	44 (9.4)	19 (8.0)
Epistaxis	43 (9.2)	24 (10.1)
Upper respiratory tract infection	43 (9.2)	20 (8.4)
Nasopharyngitis	43 (9.2)	20 (8.4)
Headache	41 (8.8)	30 (12.7)
Pharyngolaryngeal pain	22 (4.7)	14 (5.9)
Bronchitis	19 (4.1)	6 (2.5)
Fatigue	19 (4.1)	2 (0.8)
Somnolence	17 (3.6)	1 (0.4)
Back pain	16 (3.4)	5 (2.1)
Sinus headache	15 (3.2)	4 (1.7)
Cough	15 (3.2)	12 (5.1)
Influenza	15 (3.2)	9 (3.8)
Sneezing	14 (3.0)	-
Mucosal erosion	13 (2.8)	6 (2.5)
Rhinitis allergic	11 (2.4)	4 (1.7)

Source: 4-month safety update, submission dated December 22, 2008

Less common adverse events

A range of adverse events were reported occurring at a frequency of <1% in the efficacy studies. Those adverse events included several events that were reported in ≥2% of the MP436 population, such as fatigue, somnolence, cough, pharygnolaryngeal pain, and sneezing. These events are also listed on the current product label for Astelin. A wide range of other events were reported but the relationship to treatment is difficult to assess due to the low numbers and the nature of the specific events. Additional details of these events are provided in the Section 10 Individual Study Reviews in the individual study reviews. In general, review of the less common adverse events did not indicate a new safety signal for MP03-36.

7.4.2 Laboratory Findings

In the placebo-controlled, Phase 3 efficacy studies, limited laboratory testing was performed at the discretion of the investigator for individual cases if deemed appropriate. No routine follow-up assessments or formal analyses (e.g. measures of central tendency, outliers or shifts from normal to abnormal, or marker outliers and dropouts for laboratory abnormalities) were made.

Formal serial laboratory testing was performed in Study MP436, as described in Section 7.1. The following data refer to these assessments as presented in the interim 6-month study report. Updated laboratory testing was not provided in the 4-month safety update submission dated December 22, 2008.

Overview of laboratory testing

In MP436, routine clinical testing included all of the above as well as a 12-lead ECG at Screening, Month 6, and Month 12 and standard clinical laboratory parameters at Screening, Month 6, and Month 12. These parameters included a complete blood count with white cell differential, quantitative urinanalysis, and chemistry panel (albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, CK, creatinine, glucose, AST, ALT, potassium, sodium, total protein, and uric acid). A full schedule of safety assessments is presented in the individual study summary located in Section 10.

Hematology

Measures of central tendency

No clinically relevant changes in mean hematology parameters were reported at 6-month follow-up (Table 32). Patients who discontinued early from the study had negligible mean changes as well.

Table 32 Study MP436: Changes in mean hematology parameters at 6-month follow-up

Indices	MP03-36 N=465		Nasonex N=238	
	Baseline	6-month visit	Baseline	6-month visit
Hematocrit (%)				
N	321	321	166	191
Mean (SD)	41.6 (3.9)	41.3 (3.6)	41.5 (3.6)	41.3 (3.6)
Min-Max	26-55	32-51	32-52	34-54
Hemoglobin (g/dl)				
N	321	321	166	191
Mean (SD)	13.9 (1.4)	13.7 (1.2)	13.8 (1.3)	13.7 (1.3)
Min-Max	7-18	10-17	10-17	11-18
RBC (10^6/mcl)				
N	321	321	166	191
Mean (SD)	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)	4.5 (0.5)
Min-Max	3-6	3-6	4-6	4-6
WBC (10^3/mcl)				
N	321	321	166	191
Mean (SD)	6.7 (1.8)	6.5 (1.8)	6.5 (1.7)	6.6 (2.0)
Min-Max	3-15	3-13	2-12	2-13
Lymphocytes (%)				
N	321	321	166	191
Mean (SD)	31.0 (7.4=9)	31.3 (7.4)	31.1 (8.5)	30.1 (7.8)
Min-Max	12-67	313-57	11-61	14-57
Monocytes (%)				
N	321	321	166	191
Mean (SD)	6.2 (2.1)	6.1 (2.1)	6 (1.9)	6.1 (2.3)
Min-Max	2-17	1-20	2-13	0-15
Neutrophils (%)				
N	321	321	166	191
Mean (SD)	59.4 (9.0)	59.3 (8.4)	59.8 (9.3)	60.9 (8.9)
Min-Max	25-80	32-85	29-83	34-81
Basophils (%)				
N	321	321	166	191
Mean (SD)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)
Min-Max	0-1	0-2	0-1	0-1
Eosinophils (%)				
N	312	321	166	191
Mean (SD)	2.8 (2.6)	2.8 (2.4)	2.7 (2.2)	2.6 (2.7)
Min-Max	0-21	0-19	0-14	0-28
Platelets (10^3/mcl)				
N	318	315	166	187
Mean (SD)	274 (61)	275 (58)	274 (62)	274 (69)
Min-Max	131-450	125-453	121-524	113-581

Source: Module 5, Volume 102, Table 14.3.5.1.1

Outliers and shifts from normal to abnormal

The majority of hematology values stayed within the normal reference range for all hematology indices. No consistent patterns or clinically relevant shifts from normal to abnormal were observed for MP03-36 in comparison to the active comparator, Nasonex.

Table 33 Study MP436: Shifts from normal to abnormal hematology parameters

Indices	MP03-36 N=465 N, %		Nasonex N=238 N, %	
	Normal → Low	Normal → High	Normal → Low	Normal → High
Hematocrit	-	5 (2.3)	1 (0.7)	4 (3.0)
Hemoglobin	-	-	4 (3.0)	1 (0.7)
RBC	-	4 (1.9)	1 (0.7)	3 (2.2)
WBC	2 (0.9)	5 (2.3)	3 (2.2)	5 (3.7)
Lymphocytes	1 (0.5)	3 (1.4)	2 (1.5)	-
Neutrophils	3 (1.4)	10 (4.7)	1 (0.7)	9 (6.7)
Monocytes	16 (7.5)	2 (0.9)	15 (11.1)	4 (3.0)
Basophils	-	4 (1.9)	-	-
Eosinophils	-	7 (3.3)	-	3 (2.2)

Source: Module 5, Volume 102, Table 14.3.5.1.2

Marked outliers and dropouts for hematology abnormalities

No marked outliers or dropouts due to hematology abnormalities were reported in the clinical development program.

Clinical laboratory parameters

Measures of central tendency

No clinically relevant changes in mean laboratory parameters were reported at 6-month follow-up (Table 34). Patients who discontinued early from the study had negligible mean changes as well.

Table 34 Study MP436: Changes in mean laboratory parameters at 6-month follow-up

Indices	MP03-36 N=465		Nasonex N=238	
	Baseline	6-month visit	Baseline	6-month visit
Albumin (g/dl)				
N	321	323	166	194
Mean (SD)	4.4 (0.3)	4.3 (0.3)	4.4 (0.3)	4.4 (0.3)
Min-Max	4-5	4-5	4-5	4-5
Alk phosphatase (U/L)				
N	321	323	165	194
Mean (SD)	86.2 (51.2)	78.8 (41.3)	81.5 (37.0)	79.4 (34.5)
Min-Max	23-438	31-436	37-327	34-283
Total bilirubin (mg/dl)				
N	321	322	166	194
Mean (SD)	0.4 (0.2)	0.4 (0.2)	0.4 (0.3)	0.4 (0.3)
Min-Max	0-2	0-1	0-2	0-2
BUN (mg/dl)				
N	321	323	166	194
Mean (SD)	13.5 (4.0)	13.8 (3.9)	13.3 (3.9)	13.6 (3.8)
Min-Max	6-36	7-44	6-28	7-26

Calcium (mEq/L)				
N	321	323	165	194
Mean (SD)	4.8 (0.2)	4.7 (0.2)	4.8 (0.2)	4.7 (0.2)
Min-Max	4-5	4-5	4-6	4-5
Chloride (mEq/L)				
N	321	323	166	194
Mean (SD)	103 (3)	103 (2)	103 (2)	103 (3)
Min-Max	88-111	93-110	95-111	96-110
CK (U/L)				
N	321	323	166	194
Mean (SD)	138 (125)	156 (388)	130 (116)	142 (358)
Min-Max	19-1034	28-6757	32-963	25-4964
Creatinine (mg/dl)				
N	321	323	166	194
Mean (SD)	0.9 (0.2)	0.9 (0.2)	0.8 (0.2)	0.9 (0.2)
Min-Max	1-2	0-2	1-1	1-1
Glucose (mg/dl)				
N	319	316	166	192
Mean (SD)	90 (20)	91 (22)	87 (15)	93 (24)
Min-Max	52-216	53-231	49-157	43-246
AST (U/L)				
N	321	323	166	194
Mean (SD)	22 (8)	22 (10)	21 (8)	21 (8)
Min-Max	9-65	11-135	11-70	8-75
ALT (U/L)				
N	321	323	166	194
Mean (SD)	23 (15)	23 (14)	23 (17)	21 (12)
Min-Max	4-147	5-90	7-182	4-97
Potassium (mEq/L)				
N	321	323	165	194
Mean (SD)	4.3 (0.4)	4.2 (0.4)	4.3 (0.4)	4.2 (0.4)
Min-Max	3-6	3-6	3-6	3-6
Sodium (mEq/L)				
N	321	323	165	194
Mean (SD)	140 (2)	140 (2)	140 (2)	140 (2)
Min-Max	127-146	129-145	134-147	134-147
Total protein (g/dl)				
N	321	323	166	194
Mean (SD)	7.3 (0.5)	7.2 (0.4)	7.3 (0.5)	7.1 (0.4)
Min-Max	5-9	6-8	6-9	6-8
Uric acid (mg/100ml)				
N	321	323	166	194
Mean (SD)	5 (1.4)	4.9 (1.4)	4.9 (1.4)	4.7 (1.3)
Min-Max	2-10	1-11	2-9	1-9

Source: Module 5, Volume 102, Table 14.3.5.2.1

Outliers and shifts from normal to abnormal

The majority of laboratory values stayed within the normal reference range for all chemistry indices. Overall, no consistent patterns or clinically relevant shifts from normal to abnormal were observed for MP03-36. However, there were an increased number of patients with shifts from normal to high for both CK and AST levels. The majority of CK elevations were slight increases over the upper limit and not clinically relevant. A few patients had more marked elevations and these are discussed in the next section. Five patients had AST elevations that were between 1 and 1.5 x ULN; the remainder were < 1x ULN, and the majority with just out of range and not clinically relevant. Other hepatic indices, included ALT, alkaline phosphatase, total bilirubin, and total protein were not indicative of a consistent pattern of hepatic injury or decreased hepatic function.

Table 35 Study MP436: Shifts from normal to abnormal laboratory parameters				
Indices	**MP03-36 N=465 N, %**		**Nasonex N=238 N, %**	
	Normal → Low	**Normal → High**	**Normal → Low**	**Normal → High**
Albumin	-	-	-	-
Alkaline phosphatase	-	1 (0.5)	-	-
Total bilirubin	-	3 (1.4)	-	1 (0.7)
BUN	-	1 (0.5)	-	4 (2.9)
Calcium	-	-	-	-
Chloride	-	-	-	-
CK	-	15 (6.9)	1 (0.7)	5 (3.6)
Creatinine	-	11 (5.1)	-	6 (4.4)
Glucose	15 (7.2)	2 (1.0)	7 (5.1)	5 (3.7)
AST	-	15 (6.9)	-	3 (2.2)
ALT	-	12 (5.6)	-	7 (5.1)
Potassium	1 (0.5)	5 (2.3)	-	4 (2.9)
Sodium	-	-	-	1 (0.7)
Total protein	1 (0.5)	-	1 (0.7)	-
Uric acid	2 (0.9)	8 (3.7)	2 (1.5)	3 (2.2)

Source: Module 5, Volume 102, Table 14.3.5.2.2

Marked outliers and discontinuation due to abnormal laboratory parameters.
Two SAR patients discontinued from the Phase 3 efficacy studies to abnormal test results. These patients were not described in the original individual study reports, so an information request was sent to the Applicant on March 30, 2009, requesting the Applicant to identify the patients, provide the aberrant test results and any follow-up if available. A response to the request is pending at the time of this review.

In Study MP436, 1 patient (066-005) in the MP03-36 arm discontinued due to an elevated ALT. At screening, the patient had an ALT slightly out of range (42 U/L, normal range 1-39). At the 6-month lab screening, the ALT was elevated at 74 U/L. At follow-up 2 weeks later, the ALT had risen further to 118 U/L. Further follow-up on the patient is not available. This patient was reported in the December 22, 2008, safety update as a discontinuation due to an adverse event, not as an abnormal test result.

In addition to early discontinuations, the following individual marked outliers who received MP03-36 in Study MP436 were noted:

- Patient 021-004 had an elevated CK level of 1009 U/L at the 6-month visit. Follow-up is not available.
- Patient 063-004 had an elevated CK level of 6757 U/L at the 6-month visit. Follow-up is not available.

Reviewer's comment: Although a causal relationship cannot be ruled out, given the limited systemic exposure of MP03-36 and the known pharmacology of the drug, the cases of transaminitis and CK elevation appear unlikely to be related to MP03-36.

7.4.3 Vital Signs

Overview of vital signs testing
In the SAR efficacy studies, vital signs were assessed at Screening, Randomization, Day 7, Day 14 or the last day of the study. In the PAR efficacy studies, vital signs were assessed at Screening, Randomization, Day 14, and Day 29 or the last day of the study. In Study MP436, vital signs were assessed at Screening, Randomization, Months 1, 3, 6, 9, and 12 or the last day of the study. Vital sign assessments included body temperature, systolic and diastolic blood pressure, pulse rate, respiration rate.

Measures of central tendencies
No clinically significant changes in mean and median values for blood pressure, pulse, respiratory rate, or body temperature were observed during the 2-week and 4- week treatments in the SAR and PAR efficacy studies nor over the first 6-month interval for Study MP436.

Outliers or shifts from normal to abnormal
The Applicant did not provide a formal analysis of shifts from normal to abnormal. Review of individual patient data listings did not reveal any clinically significant outliers or persistent changes in vital signs, although several patients who discontinued early cited vital sign changes (described below).

Marked outliers and dropouts for vital sign abnormalities
The following patients who received MP03-36 reported a vital sign abnormality as the reason for discontinuation:

- Study MP433, Patient 18-005, reported tachycardia on Day 2.
- Study MP433, Patient 20-004, reported pyrexia on Day 12 and was reported to be fully recovered 4 days later.
- Study MP438, Patient 818-03, reported elevated blood pressure on Day 8.
- Study MP440, Patient 005-067 reported pyrexia on Day 2 and was reported to be fully recovered 7 days later. The AE of pyrexia was accompanied by reports of cough and bronchitis.

Reviewer comment: The vital sign outliers appear to have resolved spontaneously without any sequelae. A causal relationship between MP03-36 and the adverse events does not appear likely although it cannot be ruled out.

7.4.4 Electrocardiograms (ECGs)

No thorough QT study was performed during the clinical development program. Information on azelastine's effect on the QT interval is included in the current Astelin and Astepro 0.1% product labels and is described in Section 4.4 Clinical Pharmacology. The current product labels for Astepro 0.1% and Astelin state that there was no evidence of a QTc interval prolongation effect in a placebo-controlled study of azelastine 2 sprays twice daily for 56 days in patients with SAR.

Serial ECGs were performed in Study MP436 at Screening, Month 6, and Month 12. These ECGs were categorized as "abnormal/clinically significant" or "within normal limits or abnormal/not clinically significant" by the investigator. The ECGs were not centrally read and no formal measures of central tendency nor shifts from normal to abnormal were conducted. No ECG abnormalities were reported for the MP03-36 treatment group.

Reviewer's comment: Given the limited systemic availability and prior experience with intranasal azelastine, the limited ECG monitoring was acceptable for evaluating the safety of MP03-36.

7.4.5 Special Safety Studies

No special safety studies were included in this submission.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No formal dose exploration was performed in the clinical development program. Study MP433 examined MP03-36 with the lower concentration Astelin as an active comparator. Studies MP438, MP439, and MP434 included Astepro 0.1% as an active comparator. Review of the adverse event frequency between MP03-36 and lower-strength concentrations of azelastine does not suggest a dose-dependence for the common adverse events reported, including dysgeusia, epistaxis, headache, nasal discomfort, fatigue, or somnolence.

7.5.2 Time Dependency for Adverse Events

Comparison of the adverse event profiles for the 2-week studies, 4-week studies, and the long-term safety study do not suggest a time-dependency for the common adverse events reported for MP03-33. Nasal irritation is expected to be cumulative to some degree, although focused nasal exams over the 1-year study period in MP436 did not show any cases of significant mucosal erosion or septal perforation.

7.5.3 Drug-Demographic Interactions

There are no clear patient-predictive factors such as age, sex, gender, or race for the common adverse events reported. In general, elderly patients appear to be more likely to experience sedation secondary to antihistamines, and the proposed product label includes a recommendation for conservative dosing in elderly patients. However, the small number of patients over the age

of 65 in the development program limits this type of subgroup analysis for adverse events occurring at such low frequencies.

7.5.4 Drug-Disease Interactions

No apparent interactions between MP03-36 and allergic rhinitis and concomitant therapies were identified. Theoretically, nasal discomfort and epistaxis may be increased in patients also using intranasal corticosteroids for the treatment of SAR and/or PAR. However, intranasal corticosteroids were not permitted during the studies, so no formal assessment of this potential interaction was made.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were included in this submission. The current product label for Astelin states that concomitant use of azelastine with alcohol or other CNS depressants should be avoided due to additional reductions in alertness and additional impairment of CNS performance may occur. Cimetidine (400 mg twice daily) has been shown to increase the mean Cmax and AUC of orally administered azelastine by 65%. Ketoconazole interferes with the measurement of plasma concentrations of azelastine but does not appear to cause any clinically relevant effects. Concomitant administration of theophylline with oral azelastine does not cause any drug-drug interactions.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

No formal carcinogenicity studies with MP03-36 have been conducted. The adverse event profile for MP03-36 does not suggest a carcinogenic effect. Preclinical studies performed with oral azelastine did not demonstrate a tumorigenic effect. These studies were previously reviewed under NDA 20-114.

7.6.2 Human Reproduction and Pregnancy Data

No formal data on MP03-36 and human pregnancy is available. Information in the current product labels for Astelin and Astepro 0.1% note that azelastine is rated as Pregnancy Category C.

7.6.3 Pediatrics and Effect on Growth

No formal growth effect studies in children have been conducted with intranasal azelastine.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Accidental overdose in one patient was reported as a cause for early discontinuation. No further clinical sequelae were reported. Due to the route of administration, overdosage is unlikely to result in clinically significant adverse events, with the exception of potential increase in somnolence. Azelastine is not expected to have drug abuse potential, or cause withdrawal of rebound effects.

7.7 Additional Submissions

The Applicant submitted a 4-month safety update, dated December 22, 2008. The update included updated adverse event data for the long-term safety study, MP436, as well post-marketing spontaneous adverse events and literature reports covering the time period from January 5, 2008, to June 20, 2008. The information in the update has been incorporated in the discussion of safety in this review.

8 Postmarketing Experience

There are no post-marketing data for MP03-36. The Applicant previously submitted a summary of the postmarketing experience for Astelin covering the time period from December 13, 2005 to November 30, 2007, to NDA 22-203 for Astepro 0.1%, approved on October 15, 2008. Data on Astelin since initial approval up to December 13, 2005 was previously reviewed as part of Supplement 014 to NDA 20-114 for Astelin, approved on February 17, 2006. The data was presented as report frequencies using MedDRA preferred terms, along with case narratives for SAEs. Additional data covering the time period from November 1, 2007, to October 31, 2008, was submitted in an annual report to NDA 20-114 for Astelin. In general, the post-marketing safety profile is similar to the safety profile observed in clinical trials and no new safety issues have been identified during the post-marketing period for intranasal azelastine.

9 Appendices

9.1 Literature Review/References

The Applicant did not provide any references to MP03-36 in the scientific literature. A PubMed search performed by the reviewer [search term: azelastine; limits: human, clinical trial, randomized clinical trial, meta-analysis, review] yielded 198 references. There were no reports for a 0.15% azelastine formulation specifically. Brief review of the other references did not indicate any new safety signals.

9.2 Labeling Recommendations

At the time of this review, labeling discussions are ongoing. Major labeling recommendations include the following:

1. Change Astepro and (b) (4) to Astepro 0.1% and Astepro 0.15%. The tradename remains under review so these changes are tentative at this time. These changes have been done in the Highlights, Indications and Usage, and Dosage and Administration sections. Revise the remainder of the sections of the label accordingly.
2. Reorganize each section of the label so that information for the lower concentration, Astepro 0.1%, is provided before Astepro 0.15% unless otherwise indicated.
3. Indications and Usage and Dosage and Administration information should be organized by indication (SAR and PAR), not by drug concentration level. See highlighted changes.
4. Remove data on the once daily regimen from the Adverse Reactions Section 6 and the Clinical Trials Section 14.
5. Combine the adverse reactions listed in the Highlights section since the events for each dose are similar and there does not appear to be a clear dose-related frequency. The Adverse Events section should remain organized by dose level, excluding the once-daily dosing regimen for Astepro 0.15%.
6. Clinical Trials section

   Organize by indication not by formulation: SAR followed by PAR (see changes). Fill in blanks and tables where indicated.
   - SAR
     - Astepro 0.1% results as in current product label
     - Astepro 0.15%: results for Study MP433 (minus the once daily arm) and MP438
   - PAR
     - Astepro 0.15%: results for Study MP434
7. Combine the Patient Information section for the 2 dosage strengths into one Patient Information section.

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this application. Intranasal azelastine is already approved in two different formulations, Astelin and Astepro 0.1%. No new safety or efficacy concerns were identified with MP03-36. Given the pre-existing efficacy and safety data available for intranasal azelastine and the information on MP03-36 provided in the application, an AC discussion was not warranted.

10 Individual Study Summaries

10.1Individual Study Report: Study MP433

10.1.1 Study protocol: MP433

10.1.1.1 Study administrative information

- Title: Randomized, double-blind, placebo-controlled trial of the safety and efficacy of MP03-36 in patients with seasonal allergic rhinitis
- Study initiation date: August 14, 2006
- Study completion date: November 15, 2006
- Study report date: April 1, 2008
- Location: 30 study sites in the US

10.1.1.2 Objectives/Rationale

- Evaluate the safety and efficacy of MP03-36 at 2 sprays once daily and 2 sprays twice daily in patients with SAR

10.1.1.3 Study design overview

MP433 was a randomized, double-blind, placebo-controlled, parallel-group trial in patients with moderate-to-severe SAR. The study consisted of a 1-week placebo lead-in period followed by a 2-week double-blind treatment period for those patients qualifying with a minimum symptom score.

10.1.1.4 Study population

600 patients (150 patients per treatment group) 12 years of age and older with a minimum 2-year history of SAR with a positive skin test to a local fall pollen during the previous year.

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

- IgE-mediated hypersensitivity to local fall pollen confirmed by skin prick or intradermal teating within the last year.
    - ≥3mm wheal larger than control on SPT *OR*
    - ≥7mm 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

Table 36 Treatment groups for Study MP433

Group	Treatment	Total daily dose	Regimen
M1	MP03-36	822 mcg (205.5 mcg/spray)	2 sprays QAM + 2 sprays vehicle placebo QPM
M2	MP03-36	1644 mcg (205.5mcg/spray)	2 sprays BID
A2	Astelin*	1096 mcg (137 mcg/spray)	2 sprays BID
P2	Placebo	Vehicle only (sorbitol 0.7% with 0.1% sucralose)	2 sprays BID

* Commercially available, unsweetened azelastine nasal spray (Astelin)

Reviewer's comment: The M1 treatment group is not a true assessment of once-daily dosing, since the placebo dose administered in the evening is expected to confound efficacy results. The flawed study design was previously discussed with the Applicant during the August 27, 2006 meeting.

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 MP03-36 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:

Table 37 Study MP433: Concomitant medications washout periods	
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 38 shows the schedule of assessments and evaluations performed in Study MP433.

Table 38 Study MP433: Assessments and evaluations				
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 used study medication		X		X

[a] May be omitted if patient had positive skin test for fall 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
Source: Module 5, Vol 7

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 0-3 scale (none to severe): runny nose, sneezing, itchy nose, and nasal congestion. The highest possible combined score on this scale was 24 (maximum AM rTNSS of 12 + maximum PM rTNSS of 12).

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
- Daily change from baseline in TNSS
- Change from baseline 12-hour iTNSS to Day 2 (AM)
- Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

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. Safety analyses were performed on all randomized patients who received at least one dose of study medication.

A sample size of 128 patients 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 617 patients met inclusion criteria and were randomized to double-blind treatment at 31 sites. A total of 593 patients completed the study and 20 patients discontinued early.

Table 39 Study MP433: Patient disposition

Disposition	MP03-36 QAM + Placebo QPM N(%)	MP03-36 BID N(%)	Astelin BID N(%)	Placebo BID N(%)	Total
Randomized	158	153	153	153	617
Completed	154 (97.5)	144 (94.1)	148 (96.7)	147 (96.1)	593 (96.1)
Discontinued	4 (2.5)	9 (5.9)	5 (3.3)	6 (3.9)	24 (3.9)
Adverse event	2 (1.3)	5 (3.3)	0	4 (2.6)	11 (1.8)
Treatment failure	1 (0.6)	0	0	2 (1.3)	3 (0.5)
Non-compliance	0	1 (0.7)	4 (2.6)	0	5 (0.8)
Withdrew consent	0	0	0	0	0
Lost to follow-up	0	2 (1.3)	0	0	2 (0.3)
Other	1 (0.6)	1 (0.7)	1 (0.7)	0	3 (0.5)
ITT[a]	158 (100.0)	153 (100.0)	153 (100.0)	153 (100.0)	617 (100.0)
Evaluable population[b]	147 (93.0)	150 (91.5)	142 (92.8)	142 (92.8)	571 (92.5)
Safety population[c]	158 (100.0)	153 (100.0)	153 (100.0)	153 (100.0)	617 (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: Module 5, Vol 7, Section 9.7.1, Text Table 1

10.1.2.2 Protocol deviations

No amendments were made to the study protocol. Protocol deviations are summarized in the complete study report for Study MP433 in Volume 7, Section 10.2. The violations detail those patients who were excluded for a variety or reasons, including failure to meet compliance requirements, final visits that occurred outside the 2 day window of Day 14, failure to follow-up,

and the adverse events of URI and sinus infection. One patient took diphenhydramine prior to the Final Visit and one patient was dosed 3 times during the onset of action assessment.

Reviewer's comment: The protocol deviations noted are unlikely to have impacted the overall results and conclusions of Study MP433.

10.1.2.3 Treatment compliance

The duration of exposure and compliance are summarized in Table 40 as assessed by patient diary daily recorded doses and confirmed by bottle weights measured on Days 1, 7, and 14.

Table 40 Study MP433: Duration of exposure and compliance

	M1 (n=158)	M2 (n=153)	A2 (n=153)	P2 (n=153	Total (n=617)
Duration (days)					
N	158	152	153	153	616
Mean	14.6	14.2	14.7	14.5	14.5
SD	1.53	2.35	2.34	1.93	2.07
Median	15.0	15.0	15.0	15.0	15.0
Range	5-18	1-19	3-35	1-21	1-35
Total number of sprays					
N	158	151	152	153	614
Mean	110.9	108.4	111.4	109.1	109.9
SD	12.5	17.03	14.60	15.34	14.95
Median	112.0	112.0	112.0	112.0	112.0
Range	32-140	4-148	56-212	8-152	4-212
# Patients ≥80% compliance [N,%]	157 99.4	149 97.4	146 95.4	152 99.3	604 97.9

Source: Module 5, Vol 7, Section 14.1, Table 14.1.3

Reviewer's comment: The 4 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 41 Study MP433: Patient demographics and baseline characteristics

Variables	M1 (n=158)	M2 (n=153)	A2 (n=153)	P2 (n=153	Total (n=617)
Age (Mean, Range)	36.2 (13-78)	38.5 (13-75)	37.5 (13-83)	37.0 (13-74)	37.3 (13-83)
Gender (male, %)	61 (38.6%)	60 (39.2)	57 (37.3)	58 (37.9)	236 (38.2)
Race					
Caucasian	120 (75.9)	104 (68.0)	105 (68.6)	104 (68.0)	433 (702.)
Black	18 (11.4)	20 (13.1)	23 (15.0)	28 (18.3)	89 (14.4)
Hispanic	12 (7.6)	25 (16.3)	21 (13.7)	14 (9.2)	72 (11.7)
Asian	6 (3.8)	4 (2.6)	5 (2.6)	5 (3.3)	19 (3.1)
Native American	1 (0.6)	0	0	0	1 (0.2)
Other	1 (0.6)	0	0	2 (1.3)	3 (0.5)
Total score					
Mean, SD	18.7 (2.99)	18.3 (2.82)	18.0 (2.81)	18.2 (3.01)	18.3 (2.91)
Range	9-24	10-24	8-24	8-24	8-24
Duration of SAR (yrs)					
Mean, SD	19.4 (13.0)	21.7 (14.69)	19.6 (13.80)	17.7 (11.52)	19.6 (13.34)
Range	2-73	2-67	2-69	3-49	2-73

Source: Module 5, Volume 7, Section 11.2, Text table 2

The patients ranged in age from 13 to 83 years with a mean age of 37 years; 38.2% were male. The average duration of SAR in the study was 19.6 years.

Reviewer's comment: In terms of demographics, the treatment groups appear similar 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 42 Study MP433: Change from baseline combined (AM plus PM) 12-hour rTNSS[a]

Treatment	Baseline (SD)[b]	Change from baseline	P-value (vs placebo)	Treatment difference from placebo
M1	18.67 (2.992)	-4.03 (4.099)	0.106	-0.76
M2	18.25 (2.822)	-4.47 (4.059)	0.012	-1.20
A2	17.98 (2.813)	-4.11 (4.912)	0.086	-0.84
P2	18.12 (3.005)	-3.27 (4.406)	-	-

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 7, Section 11.4.1.1, Text Table 3

Results of the primary efficacy variable are presented in Table 42. Neither once daily MP03-36 nor the active comparator, Astelin, showed a statistically significant benefit over placebo at the lower 1 spray BID dose. At 2 sprays BID, MP03-36 demonstrated efficacy over placebo.

Reviewer's comment: The twice-daily dosing of MP03-36 was statistically better than placebo and numerically better than the lower concentration comparator, Astelin (0.1% azelastine).

10.1.2.6.1.2 Primary endpoint analysis by subgroups
The Applicant did not perform any subgroup analyses.

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. None of the treatment groups demonstrated a durable, statistically significant onset of action.

10.1.2.6.2.2 Combined AM and PM iTNSS
Although numerically favorable, the results for combined AM and PM iTNSS scores over the 14-day treatment period were not statistically significant (-3.96 vs. -3.26; p=0.088). Similar results for the daily change from baseline iTNSS for Days 2 through 14.

10.1.2.6.2.3 End of 24-hour dosing – iTNSS prior to AM dose on Day 2
Results for the end of 24-hour dosing interval iTNSS prior to AM dose on Day 2 are presented in Table 43. None of the treatment groups demonstrated a statistically significant improvement over placebo.

Table 43 Study MP433: End of 24-hour dosing – iTNSS prior to AM dose on Day 2

Treatment	Baseline (SD)[a]	Change from baseline	P-value (vs placebo)[b]
M1	9.2 (1.7)	-1.2 (2.5)	0.408
M2	8.8 (1.7)	-1.5 (2.2)	0.062
A2	8.7 (1.7)	-1.3 (2.5)	0.242
P2	8.8 (1.8)	-1.0 (2.5)	

[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: Module 5, Vol 7, Section 11.4.1.2, Text table 4

Reviewer's comment: Although numerically favorable compared to placebo, the iTNSS scores do not support a once-daily dosing interval. A statistically significant difference was not observed for BID dosing as well; however, pre-existing data for Astelin and MP03-33 support a BID regimen for the 0.1% formulation. Extrapolation from this data for the lower concentration supports the BID regimen for the 0.15% formulation.

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

Table 44 Study MP433: 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	M1	4.57 (1.038)	-0.95 (1.268)	0.106
	M2	4.48 (1.216)	-1.09 (1.142)	0.009
	A2	4.47 (1.037)	-1.05 (1.455)	0.019
	P2	4.50 (1.007)	-0.73 (1.231)	
Runny nose	M1	4.67 (1.042)	-0.96 (1.271)	0.322
	M2	4.64 (0.987)	-1.12 (1.216)	0.033
	A2	4.61 (1.036)	-0.94 (1.434)	0.409
	P2	4.57 (1.097)	-0.83 (1.319)	
Sneezing	M1	4.19 (1.198)	-1.31 (1.443)	0.005
	M2	4.04 (1.185)	-1.38 (1.330)	0.001
	A2	3.78 (1.261)	-1.28 (1.374)	0.010
	P2	3.94 (1.307)	-0.91 (1.336)	
Congestion	M1	5.23 (0.682)	-0.82 (1.061)	0.859
	M2	5.08 (0.775)	-0.86 (1.151)	0.620
	A2	5.13 (0.747)	-0.82 (1.294)	0.871
	P2	5.12 (0.729)	-0.80 (1.215)	

[a] Least-square mean and standard deviation
[b] P-value calculated from repeated measures ANCOVA model and baseline as a covariate.
Source: Module 5, Vol 7, Section 11.4.1.2, Text Tables 7-13

Reviewer's comment: The individual symptom scores generally support the efficacy of MP03-36 over placebo at the twice daily dose (M2) for the individual symptoms. A statistically significant difference from placebo for itchy nose, runny nose, and sneezing were observed; scores for congestion were not statistically significant but numerically favorable. This result is not unexpected as an antihistamine is expected to have a limited effect on congestion. Results for the once daily dose (M1) were numerically favorable for most of the symptoms and statistically significant for sneezing. The Astelin comparator arm performed similarly to the M1 arm.

10.1.2.6.2.5 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 numerically improved at Day 14 compared to placebo with the twice-daily M2 dose (-1.44 vs. -1.13; p=0.073). The twice daily Astelin dose was also statistically superior to placebo (-1.47 vs. -1.13; p=0.046). No statistically significant improvements were noted for the once daily MP03-36 dose (p=0.095).

Reviewer's comment: The numerical trend in RQLQ results favors MP03-36 over placebo although the treatment difference is less than 0.5.

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.

Table 45 Study MP433: Early discontinuation due to adverse event

Treatment group	N	Reason for discontinuation
M1 (n=158)	1	Insect bite
	1	Fever, sore throat
M2 (n=153)	1	Tachycardia
	1	Dysgeusia
	1	Heartburn, nausea
	1	Fatigue
	1	Rash
A2 (n=153)	1	Moderate headaches
	1	Pharyngitis, fever
P2 (n=153)	1	Viral illness
	1	Exacerbation of SAR

Source: Module 5, Vol 8,Section 14.0, Table 14.3.2.3

Reviewer's comment: No new safety signals are identified upon review of the listed events.

10.1.2.7.4 Common adverse events
The most common adverse event reported for all of the active treatment groups was dysgeusia, despite the addition of sucralose in MP03-36. Common adverse events are summarized in Table 46 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 MP03-36 that occurred at a rate greater than placebo included dysgeusia, headache, nasal discomfort (M1 only), epistaxis (M1 only), sneezing (M2 only), pharyngolaryngeal pain, fatigue (M2 only), and dizziness. The somnolence rate reported for both doses of MP03-36 was <1%.

Table 46 Study MP433: Adverse events occurring in 1% or more of the safety population

Preferred Term [N(%)]	M1 (n=158)	M2 (n=153)	A2 (n=153)	P2 (n=153	Total (n=617)
Any AE	33 (20.9)	23 (15.0)	27 (17.6)	26 (17)	109 (17.7)
Dysgeusia	10 (6.3)	7 (4.6)	8 (5.2)	2 (1.3)	27 (4.4)
Headache	1 (0.6)	4 (2.6)	6 (3.9)	4 (2.6)	15 (2.4)
Nasal discomfort	4 (2.5)	1 (0.7)	3 (2.0)	2 (1.3)	10 (1.6)
Epistaxis	3 (1.9)	1 (0.7)	3 (2.0)	2 (1.3)	9 (1.5)
Sneezing	1 (0.6)	3 (2.0)	1 (0.7)	1 (0.7)	6 (1.0)
Pharyngolaryngeal pain	2 (1.3)	1 (0.7)	2 (1.3)	0	5 (0.8)
Fatigue	0	3 (2.0)	0	1 (0.7)	4 (0.6)
Dizziness	1 (0.6)	2 (1.3)	1 (0.7)	0	4 (0.6)

Source: Module 5, Vol 7, Section 12.2.2, Text Table 16

Reviewer's comment: The types of adverse events reported for MP03-36 are consistent with the known safety profile of intranasal azelastine. MP03-36 appears similar to Astelin in terms of dysgeusia. There is no clear dose relationship for adverse events for once-daily versus twice-daily MP03-36 or MP03-36 versus Astelin. In general, the overall frequency of adverse events was lower than the rates observed in the controlled clinical trials supporting approval of Astelin 2 sprays 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 8, 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.). No ulcerations or septal perforations were noted.

10.1.2.8 Clinical laboratory evaluations
No laboratory evaluations were performed.

10.1.3 Study summary and conclusions
The results of Study MP433 provide support for the efficacy of twice-daily dosing of MP03-36 for SAR. When compared to the once-daily dose and lower strength Astelin, MP03-36 appears to have improved dose-related efficacy numerically, but the differences are not statistically significant. The proposed twice-daily regimen for MP03-36 is supported by the primary efficacy endpoint; the once-daily MP03-36 regimen is not supported both by a flawed study design as

well as the actual results. Secondary efficacy variables were also generally supportive of twice daily MP03-36 over placebo 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.

10.2 Individual Study Report: Study MP438

10.2.1 Study Protocol: MP438

10.2.1.1 Administrative information

- Title: Randomized, double-blind, placebo-controlled trial of the safety and efficacy of MP03-36 and MP03-33 compared to placebo in patients with seasonal allergic rhinitis
- Study initiation date: August 16, 2007
- Study completion date: November 19, 2007
- Study report date: June 2, 2008
- Location: 30 study sites in the US

10.2.1.2 Objectives/Rationale

- Evaluate the efficacy and safety of MP03-36 and MP03-33 compared to placebo
- Compare the efficacy and safety of MP03-36 versus MP03-33

10.2.1.3 Study design overview

MP438 was a randomized, double-blind, placebo-controlled, parallel-group trial in patients with moderate-to-severe SAR. The study consisted of a 1-week single-blind, placebo lead-in period followed by a 2-week double-blind treatment period for those patients qualifying with a minimum symptom score.

10.2.1.4 Study population

526 patients (172 in MP03-36 arm, 166 in MP03-33 arm, and 171 in placebo arm) 12 years of age and older with a minimum 2-year history of SAR with a positive skin test to a local fall pollen during the previous year.

<u>Inclusion criteria</u>

- 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
- IgE-mediated hypersensitivity to local fall pollen confirmed by skin prick or intradermal teating within the last year.
    - ≥3mm wheal larger than control on SPT *OR*

  - ≥7mm 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

10.2.1.5 Study treatments

Treatment groups

- MP03-36 (0.15% azelastine) 2 sprays per nostril twice daily (1644 mcg total daily dose)
- MP03-33 (0.1% azelastine) 2 sprays per nostril twice daily (1096 mcg total daily dose)
- Vehicle placebo 2 sprays per nostril twice daily

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.

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.

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.

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.

10.2.1.6 Study procedures

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:

Table 47 Study MP438: Concomitant medications washout periods

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

Assessments and evaluations

Table 48 shows the schedule of assessments and evaluations performed in Study MP433.

Table 48 Study MP438: Assessments and evaluations				
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
Dispense study medication		X		
Onset of action assessment		X		
AE assessment		X	X	X
Collect TNSS diary		X	X	X
Collect used study medication		X		X

[a] May be omitted if patient had positive skin test for fall 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

10.2.1.7 Efficacy parameters

Primary efficacy variable

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 0-3 scale (none to severe): runny nose, sneezing, itchy nose, and nasal congestion. The highest possible combined score on this scale was 24 (maximum AM rTNSS of 12 + maximum PM rTNSS of 12).

Secondary efficacy variables

- Change from baseline iTNSS for the 14-day treatment period
- Change from baseline rTNSS for individual symptom scores for the 14-day treatment period
- 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
- Daily change from baseline in TNSS
- Change from baseline 12-hour iTNSS to Day 2 (AM)
- Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

10.2.1.8 Safety parameters

Adverse experiences

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

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

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

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.

10.2.1.9 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 ANCOVA model. A gate-keeping strategy was employed to adjust for multiplicity, so that MP03-36 vs. placebo was tested first at the 0.05 significance level. If significant, the MP03-33 vs. placebo comparison was to be performed. 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. Safety analyses were performed on all randomized patients who received at least one dose of study medication.

A sample size of 180 patients was calculated so that the study would have 80% power to detect a change of 1.5 units in the AM and PM combined TNSS from baseline for MP03-36 compared to placebo. Descriptive statistics were used to report the frequency of adverse events and the distribution of vital sign measurements.

Reviewer's comment: The study report notes that this sample size should be adequate to show a dose-response difference between MP03-36 and MP03-33 but does not specify a statistical comparison of the two active treatments.

10.2.2 Results

10.2.2.1 Study patients
A total of 526 subjects were randomized to double-blind treatment. A total of 509 subjects completed the study and 17 subjects discontinued early.

Table 49Study MP438: Patient disposition

Disposition	MP03-33	MP03-36	Placebo	Total
Randomized	170	178	178	526
Completed	166 (97.6)	172 (96.6)	171 (96.1)	509 (96.8)
Discontinued	4 (2.4)	6 (3.4)	7 (3.9)	17 (3.2)
Adverse event	3 (1.8)	4 (2.2)	5 (2.8)	12 (2.3)
Abnormal test result	0	0	0	0
Treatment failure	0	0	0	0
Non-compliance	0	0	1 (0.6)	1 (0.2)
Withdrew consent	1 (0.6)	0	0	1 (0.2)
Lost to follow-up	0	1 (0.6)	0	1 (0.2)
Administrative problems	0	0	0	0
Other	0	1 (0.6)	1 (0.6)	2 (0.4)
ITT[a]	169 (99.4)	177 (99.4)	178 (100.0)	523 (99.4)
Per protocol population[b]	161 (94.7)	170 (95.5)	162 (91.0)	493 (93.7)
Safety population[c]	170 (100.0)	178 (100.0)	178 (100.0)	526 (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: Module 5, Vol 22, Section 10.1, Table 3

10.2.2.2 Protocol deviations

The most notable protocol violation was the administration of active study drug to 19 subjects during the placebo run-in period. These subjects were not included in the randomized population.

Additional protocol deviations included failure to meet minimum TNSS scores for inclusion, non-compliance with the TNSS diary and study medication, and failure to complete the study. Table 4 in Section 10.2 of the complete study report (Volume 22) lists the reason for exclusion for individual patients.

Reviewer's comment: The protocol deviations noted are unlikely to have impacted the overall results and conclusions of Study MP438.

10.2.2.3 Treatment compliance

The duration of exposure and compliance are summarized in Table 50 as assessed by patient diary daily recorded doses and confirmed by bottle weights measured on Days 1, 7, and 14.

Table 50 Study MP438: Duration of exposure and compliance			
	MP03-33 (N=170)	**MP03-36 (N=178)**	**Placebo (N=178)**
Duration (days)			
N	170	177	178
Mean	14.5	14.4	14.5
SD	1.92	1.93	1.83
Median	15.0	15.0	15.0
Range	1-22	1-18	1-18
Total number of doses			
N	169	177	177
Mean	27.6	27.5	27.6
SD	3.16	3.56	3.45
Median	28.0	28.0	28.0
Range	8-42	2-35	6-36
# Patients ≥80% compliance [N,%]	169 99.4	175 98.3	175 98.3

Source: Module 5, Vol 22, Section 11.3 and 12.1, Tables 6 and12

10.2.2.4 Datasets 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.

10.2.2.5 Demographics and baseline characteristics

Table 51 Study MP438: Patient demographics and baseline characteristics			
Variables	**MP03-33 (N=169)**	**MP03-36 (N=177)**	**Placebo (N=177)**
Age (Mean, Range)	35.4 (12-790	38.0 (12-76)	36.9 (12-69)
Gender (male, %)	58 (34.3)	70 (39.5)	61 (34.5)
Race			
Caucasian	134 (79.3)	143 (80.8)	140 (79.1)
Black	30 (17.8)	23 (13.0)	26 (14.7)
Hispanic	27 (16.0)	21 (11.9)	20 (11.3)
Asian	1 (0.6)	3 (1.7)	5 (2.8)
Native American	1 (0.6)	1 (0.6)	0
Native Hawaiian or Pacific Islander	1 (0.6)	0	1 (0.6)
Other	2 (1.2)	7 (4.0)	5 (2.8)
Total score			
Mean, SD	18.3 (3.23)	18.3 (3.28)	17.9 (3.30)
Range	5-24	9-24	8-24
Duration of SAR (yrs)			
Mean, SD	19.0 (10.77)	20.4 (13.52)	19.5 (11.76)
Range	2-51	3-54	3-57

Source: Module 5, Volume 22, Section 11.2.1, Table 5

The patients ranged in age from 12 to 79 years with a mean age of 37 years. The average duration of SAR in the study was 20years.

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

10.2.2.6 Efficacy endpoint outcomes

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

Table 52 Study MP438: Change from baseline combined (AM plus PM) 12-hour rTNSS[a]

Treatment	Baseline (SD)[b]	Change from baseline	P-value vs placebo, 95% CI	Treatment difference from placebo
MP03-33 N=169	18.3 (3.2)	-4.4 (4.7)	<0.001 (-3.0, -1.1)	-2.0
MP03-36 N=177	17.7 (3.3)	-5.4 (5.1)	<0.001 (-4.0, -2.1)	-3.0
Placebo N=177	17.9 (3.3)	-2.4 (4.2)	-	-

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 22, Section 11.4.1.1, Table 7

Results of the primary efficacy variable are shown in the table above. Both MP03-36 and MP03-33 demonstrated a statistically significant benefit over placebo. Numerically, MP03-36 appeared to have a greater effect than MP03-33, suggesting a dose-response. The Applicant did not perform any subgroup analyses of the primary endpoint.

Reviewer's comment: Although the results of the primary efficacy analysis suggest a dose-response numerically, the results of MP03-36 and MP03-33 are not statistically significantly different. Whether a numerical difference alone is sufficient to justify the approval of both concentrations is questionable, as the efficacy of MP03-36 is not clearly better to warrant higher exposure and the marketing of two dosage strengths under different tradenames for the same indication may lead to confusion.

Secondary efficacy endpoints

Instantaneous TNSS
Results for change from baseline iTNSS over the whole 14-day treatment period are shown in the table below.

Table 53 Study MP438: Change from baseline combined (AM plus PM) 12-hour iTNSS[a]

Treatment	Baseline (SD)[b]	Change from baseline	P-value vs placebo, 95% CI	% Change from baseline	P-value vs. placebo, 95% CI
MP03-33 N=169	17.2 (3.8)	-3.7 (4.8)	<0.001 (-2.7, -0.8)	-21.4 (28.0)	<0.001 (-17.2, -5.0)
MP03-36 N=177	16.4 (4.0)	-4.6 (5.3)	<0.001 (-3.6, -1.7)	-26.3 (32.7)	<0.001 (-22.1, -10.0)
Placebo N=177	16.6 (4.0)	-1.96 (4.3)	-	-10.3 (28.7)	-

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Vol 22, Section 11.4.1.1, Table 8

Individual nasal symptom scores

Table 54 Study MP438: 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], 95% CI
Itchy Nose	MP03-33 N=169	4.6 (1.1)	-1.1 (1.4)	<0.001 (-0.8, -0.3)
	MP03-36 N=177	4.5 (1.1)	-1.3 (1.4)	<0.001 (-1.1, -0.5)
	Placebo N=177	4.6 (1.2)	-0.53 (1.3)	-
Runny nose	MP03-33 N=169	4.6 (1.0)	-1.2 (1.4)	<0.001 (-0.8, -0.3)
	MP03-36 N=177	4.5 (1.0)	-1.4 (1.5)	<0.001 (-1.0, -0.5)
	Placebo N=177	4.4 (1.0)	-0.7 (1.2)	-
Sneezing	MP03-33 N=169	3.9 (1.3)	-1.3 (1.5)	<0.001 (-1.0, -0.4)
	MP03-36 N=177	3.9 (1.3)	-1.5 (1.5)	<0.001 (1.2, -0.6)
	Placebo N=177	3.9 (1.3)	-0.6 (1.3)	-
Congestion	MP03-33 N=169	5.1 (0.8)	-0.9 (1.3)	0.013 (-0.6, -0.1)
	MP03-36 N=177	4.9 (0.9)	-1.1 (1.3)	<0.001 (-0.8, -0.4)
	Placebo N=177	5.1 (0.8)	-0.6 (1.1)	-

[a] Least-square mean and standard deviation
[b] P-value calculated from repeated measures ANCOVA model and baseline as a covariate.
Source: Module 5, Vol 22, Section 11.4.1.1, Table 9

Reviewer's comment: The individual symptom scores support the efficacy of MP03-36 over placebo for all four of the symptom components. The score also support the efficacy of MP03-33 over placebo. MP03-36 performed better than MP03-33 numerically across each of the 4 symptoms.

Onset of action

MP03-36 separated from placebo at 30 minutes and the effect was maintained through the duration of the 4-hour evaluation period. The MP03-33 arm showed an onset of action of 180 minutes but the effect was not durable.

Daily symptom scores
Both MP03-36 and MP03-33 showed statistically significant improvements compared to placebo in the daily change from baseline in iTNSS and rTNSS.

RQLQ Change from baseline
The overall score for the RQLQ change from baseline compared to placebo was statistically significant for the MP03-36 group ($p<0.001$) but not for the MP03-33 group ($p=0.187$).

Reviewer's comment: The secondary efficacy outcomes support the efficacy of MP03-36 for the treatment of SAR. MP03-33 also appears efficacious. MP03-36 generally outperformed MP03-33 in terms of numerical trend, although the difference does not appear to be statistically significant.

10.2.2.7 Safety outcomes

Adverse events

Deaths and serious adverse events
No deaths were reported in the study. Two SAEs were reported, both occurring in the placebo group.

Discontinuations from the study due to adverse events
Twelve patients discontinued from the study due to adverse events: 4 in the MP03-36 group, 3 in the MP03-33 group, and 5 in the placebo group. In the MP03-36 group, AEs leading to discontinuation included sinus headache, increased blood pressure, accidental overdose, and viral gastroenteritis. The accidental overdose consisted of a patient taking an additional dose of study medication on one day without any sequelae. In the MP03-33 group, AEs included dysgeusia, sinus headache, and influenza. In the placebo group, discontinuations were attributed to somnolence, nasal discomfort, lymphangitis, pharyngitis, hypersensitivity, and asthma.

Common adverse events
The most common adverse event reported for both MP03-36 and MP03-33 was dysgeusia (16.9% and 12.8%, respectively). In general, common adverse events were consistent with adverse events noted in the clinical trials to support the approval for Astelin. These AEs are summarized in the table below.

Table 55 Study MP438: Adverse events occurring in 1% or more of the safety population

Preferred Term [N(%)]	MP03-36 (N=178)	MP03-33 (N=170)	Placebo (178)
Any AE	30 (16.9)	37 (21.8)	25 (14.0)
Dysgeusia	15 (8.4)	16 (9.4)	2 (1.1)
Nasal discomfort	4 (2.2)	5 (2.9)	3 (1.7)
Epistaxis	2 (1.1)	2 (1.2)	2 (1.1)
Headache	0	3 (1.8)	3 (1.7)
Somnolence	3 (1.7)	1 (0.6)	1 (0.6)
Sinus headache	1 (0.6)	3 (1.8)	0
Nausea	1 (0.6)	3 (1.8)	1 (0.6)
Nasopharyngitis	1 (0.6)	2 (1.2)	0
Upper abdominal pain	0	2 (1.2)	1 (0.6)
Dry mouth	1 (0.6)	0	2 (1.1)

Source: Module 5, Vol 22, Section 12.2.3.1, Table 14

Reviewer's comment: The types of adverse events reported for MP03-36 are consistent with the known safety profile of intranasal azelastine. MP03-36 appears similar to MP03-33 in terms of dysgeusia. There is no clear dose relationship for adverse events for MP03-36 versus MP03-33. Somnolence was reported in slightly more MP03-36 (n=3) patients than in MP03-33 patients (n=1), but it is hard to determine whether this is truly related to dose given the low numbers. In general, the overall 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%.

Vital signs

No notable derangements in vital signs were noted in any of the treatment groups during the 14-day treatment period (Source Volume 23, Section 14.3.5).

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.).

Clinical laboratory evaluations

No laboratory evaluations were performed.

10.2.3 Study summary and conclusions

The efficacy and safety results of Study MP438 support the twice daily dosing of MP03-36 for the treatment of SAR symptoms. The study also demonstrates the efficacy of twice-daily MP03-33 for the same indication compared to placebo. Although the results of the post-hoc comparison are not statistically significant, MP03-36 appears to have a numerically greater,

dose-related efficacy when compared to MP03-33. The safety profiles of the two dosage strengths appear comparable. As a result, Study MP438 suggests that some patients may benefit from the use a of a higher strength azelastine formulation without a compromise in safety.

10.3 Individual Study Report: Study MP439

10.3.1 Study Protocol: MP439

10.3.1.1 Administrative information

- Title: Randomized, double-blind, placebo-controlled trial of the safety and efficacy of MP03-36 in subjects with SAR
- Study initiation date: August 20, 2007
- Study completion date: November 14, 2007
- Study report date: June 13, 2008
- Location: 21 centers in the continental US

10.3.1.2 Objectives/Rationale

- To evaluation the safety and efficacy of MP03-36 2 sprays per nostril once daily (AM) compared to placebo once daily

10.3.1.3 Study design overview

Study MP439 was a randomized, double-blind, placebo-controlled, parallel-group trial in patients with moderate-to-severe SAR. The study consisted of a 1-week placebo lead-in period followed by a 2-week double-blind treatment period for those patients qualifying with a minimum symptom score.

10.3.1.4 Study population

500 subjects (250 per treatment arm) 12 years of age and older with a minimum 2-year history of SAR with a positive skin test to a prevalent local fall pollen.

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).
- Must have taken ≥5 doses of study medication during the Lead-in Period
- ≥2 year history of SAR
- IgE-mediated hypersensitivity to local fall pollen confirmed by skin prick or intradermal teating within the last year.

  - ≥3mm wheal larger than control on SPT *OR*
  - ≥7mm 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

10.3.1.5 Study treatments

Treatment groups

- MP03-36 two sprays per nostril once daily (AM) (822 mcg total daily dose)
- Vehicle placebo two sprays per nostril once daily (AM)

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.

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.

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.

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.

10.3.1.6 Study procedures

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 medications listed in Table 37 were not permitted during the study period and required minimum washout periods prior to Day -7.

Assessments and evaluations

Table 56 Study MP439: Assessments and evaluations

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
Dispense study medication		X		
AE assessment		X	X	X
Collect TNSS diary		X	X	X
Collect used study medication		X		X

[a] May be omitted if patient had positive skin test for fall 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 to subjects 18 years of age and older

10.3.1.7 Efficacy parameters

Primary efficacy variable

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 0-3 scale (none to severe): runny nose,

sneezing, itchy nose, and nasal congestion. The highest possible combined score on this scale was 24 (maximum AM rTNSS of 12 + maximum PM rTNSS of 12).

Secondary efficacy variables

- End of 24-hr dosing interval – mean change from baseline in iTNSS for the entire 14-day study period compared to placebo to determine if the duration of efficacy lasted 24 hours
- Change from baseline in 12-hr rTNSS individual symptom component scores
- Change from baseline for daily 12-hr iTNSS and rTNSS
- Change from baseline for daily SSCS (postnasal drip, itchy eyes, cough, headache)
- Change from baseline to Day 14 in RQLQ for subjects 18 years of age and older

10.3.1.8 Safety parameters

Adverse experiences

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

Laboratory assessments

Prick-puncture allergen skin testing was performed at Screening. No blood laboratory tests were routinely assessed during the study. Urine pregnancy tests were performed in all female subjects at screening and at Day 14/Early termination.

Physical exams

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

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.

10.3.1.9 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 ANCOVA 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. Safety analyses were performed on all randomized patients who received at least one dose of study medication.

A sample size of 234 patients per treatment arm was calculated so that the study would have 90% power to detect a treatment difference of 1.15 units, based on the results of a previous study of MP03-36 versus placebo. Assuming a 5% dropout rate, 250 per treatment arm was the

target enrollment. Descriptive statistics were used to report the frequency of adverse events and the distribution of vital sign measurements.

10.3.2 Results

10.3.2.1 Protocol amendments

The protocol was amended once on July 20, 2007.

- PM dosing was changed to AM
- The enrollment target was reduced from 1040 to 500.
- Inclusion criteria were relaxed to allow inclusion of subjects who had taken a minimum of 5 doses during the lead-in period.
- 1 study site was excluded because double-blind study drug was dispensed during the placebo lead-in period. A separate AE listing for this site was provided for the safety analysis.

10.3.2.2 Study patients

A total of 481 patients were randomized to double-blind treatment. A total of 467 completed the study and 14 patients discontinued early.

Table 57 Study MP439: Patient disposition

Disposition	MP03-36	Placebo	Total
Randomized	239	242	481
Completed	233 (97.5)	234 (96.7)	467 (97.1)
Discontinued	6 (2.5)	8 (3.3)	14 (2.9)
Adverse event	2 (0.8)	1 (0.4)	3 (0.6)
Abnormal test result	0	0	0
Treatment failure	0	3 (1.2)	3 (0.6)
Non-compliance	0	1 (0.4)	1 (0.2)
Withdrew consent	0	1 (0.4)	1 (0.2)
Lost to follow-up	1 (0.4)	0	1 (0.2)
Administrative problems	0	0	0
Other	3 (1.3)	2 (0.8)	5 (1.0)
ITT[a]	238 (99.6)	242 (100)	480 (99.8)
Per protocol population[b]	219 (91.6)	213 (88.0)	432 (89.8)
Safety population[c]	239 (100.0)	242 (100.0)	481 (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: Module 5, Vol 40, Section 10.1, Table 3

10.3.2.3 Protocol deviations

A major protocol violation resulted in the exclusion of 1 study site due to patients being mistakenly given double-blind study drug instead of placebo during the 7-day lead-in period. These subjects were excluded from the ITT analysis.

The other most common protocol deviations were patients who failed to meet minimum TNSS criteria. A full listing of protocol deviations is provided in the Applicant's Appendix 16.2.3.2. Other protocol deviations included <80% or >120% compliance based on diaries and failure to complete the study for various reasons.

Reviewer's comment: The protocol deviations are unlikely to have impacted the overall results and conclusions of Study MP439. If anything, the failure of patients to meet minimum rTNSS criteria would most likely have made it more difficult to show a treatment effect from study drug.

10.3.2.4 Treatment exposure and compliance

The duration of exposure and compliance are summarized in Table 58 Study MP439: Duration of exposure and compliance as assessed by patient diary daily recorded doses and confirmed by bottle weights measured on Days 1, 7, and 14.

Table 58 Study MP439: Duration of exposure and compliance

	MP03-36 N=239	Placebo N=242	Total N=481
Duration (days)			
N	238	242	480
Mean	14.7	14.4	14.5
SD	1.40	1.75	1.59
Median	15.0	15.0	15.0
Range	2-18	2-18	2-18
Total number of doses			
N	239	242	481
Mean	14.3	14.2	14.2
SD	1.82	1.84	1.83
Median	15.0	15.0	15.0
Range	1-17	2-18	1-18
# Patients ≥80% compliance [N,%]	236 98.7	240 99.2	476 99.0

Source: Module 5, Vol 40, Section 11.3 and 12.1, Tables 6 and11

10.3.2.5 Datasets 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.

10.3.2.6 Demographics and baseline characteristics

Table 59 Study MP439: Patient demographics and baseline characteristics			
Variables	**MP03-36 (N=238)**	**Placebo (N=242)**	**Total (N=480)**
Age (Mean, Range)	35.5 (12-78)	35.3 (12-75)	35.4 (12-78)
Gender (male, %)	84 (35.3)	80 (33.1)	164 (34.2)
Race			
Caucasian	186 (78.2)	179 (74.0)	365 (76.0)
Black	38 (16.0)	49 (20.2)	87 (18.1)
Hispanic	25 (10.5)	27 (11.2)	52 (10.8)
Asian	3 (1.3)	3 (1.2)	6 (1.3)
Native American	1 (0.4)	0	1 (0.2)
Native Hawaiian or Pacific Islander	2 (0.8)	3 (1.2)	5 (1.0)
Other	8 (3.4)	8 (3.3)	16 (3.3)
Total score			
Mean, SD	17.1 (3.54)	17.7 (3.31)	17.7 (3.42)
Range	9-24	6-24	6-24
Duration of SAR (yrs)			
Mean, SD	19.2 (12.57)	18.6 (12.82)	18.9 (12.68)
Range	2-56	2-62	2-62

Source: Module 5, Volume 40, Section 11.2.1, Table 5

The patients ranged in age from 12 to 78 years with a mean age of 35 years. The average duration of SAR in the study was 19 years.

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

10.3.2.7 Efficacy endpoint outcomes

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

Table 60 Study MP439: Change from baseline combined (AM plus PM) 12-hour rTNSS[a]				
Treatment	**Baseline (SD)[b]**	**Change from baseline**	**P-value vs placebo, 95% CI**	**Treatment difference from placebo**
MP03-36 N=238	17.7 (3.5)	-3.6 (4.5)	0.005 (-1.80, -0.31)	-1.0
Placebo N=242	17.7 (3.3)	-2.6 (4.2)	-	-

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 40, Section 11.4.1.1, Table 7

Results of the primary efficacy analysis are presented in the table above. MP03-36 showed a statistically significant benefit over baseline.

Secondary efficacy endpoints

End of 24-h dosing and combined iTNSS

The end of 24-h dosing interval as assessed by the overall AM iTNSS did not show a statistically significant difference between MP03-36 and placebo, as shown in Table 11. However, the

combined AM and PM iTNSS over the 14-day period did show a difference between MP03-36 and placebo (-3.0 vs. -2.2; p=0.023) as did overall PM iTNSS scores (-1.7 vs. -1.1; p=0.011).

Table 61 Study MP439: End of 24-hour dosing interval efficacy as measured by the change from baseline in AM iTNSS over the 14-day treatment period[a]

Treatment	Baseline (SD)[b]	Change from baseline	P-value vs placebo, 95% CI
MP03-36 N=238	8.2 (2.5)	-1.4 (2.3)	0.112 (-0.67, 0.07)
Placebo N=242	8.4 (1.9)	-1.1 (2.1)	-

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 40, Table 14.2.7.1

Reviewer's comment: The end of 24-h dosing assessment was intended to demonstrate the efficacy of a once-daily MP03-36 regimen. Although the combined iTNSS and PM iTNSS show a statistically significant benefit over placebo, the AM iTNSS which is measuring symptoms at drug trough do not show a statistically significant difference. These results suggest that although once-daily dosing of MP03-36 is better than placebo for more than half of the 24 hour dosing interval, towards the end of the dosing interval this benefit wanes considerably. Based on these results, the once-daily dose is not supported.

Individual nasal symptom scores

Table 62 Study MP439: 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], 95% CI
Itchy Nose	MP03-36	4.4 (1.2)	-0.9 (1.3)	0.002 (-0.5, -0.1)
	Placebo	4.5 (1.2)	-0.6 (1.2)	
Runny nose	MP03-36	4.4 (1.1)	-1.0 (1.4)	0.018 (-0.5, -0.04)
	Placebo	4.4 (1.0)	-0.7 (1.2)	
Sneezing	MP03-36	4.0 (1.3)	-1.0 (1.3)	0.001 (-0.6, -0.1)
	Placebo	3.9 (1.3)	-0.6 (1.2)	
Congestion	MP03-36	5.0 (1.1)	-0.9 (1.3)	0.002 (-0.5, -0.1)
	Placebo	5.0 (0.9)	-0.7 (1.1)	

[a] Least-square mean and standard deviation
[b] P-value calculated from repeated measures ANCOVA model and baseline as a covariate.
Source: Module 5, Vol 40, Section 11.4.1.1, Table 9

Reviewer's comment: The individual symptom scores support the efficacy for MP03-36 over placebo for all 4 individual symptom components of the TNSS.

Daily symptom scores

MP03-36 was numerically superior to placebo for daily change from baseline combined AM and PM rTNSS on Days 2 through 14, although the differences were not consistently statistically superior. Similar results were recorded for daily change from baseline combined AM and PM

iTNSS (p=0.002 to 0.487), with p-values <0.05 observed on Days 2-6 and 12-14. However, the statistically significant results for daily change in combined iTNSS scores appear to be driven mainly by the PM iTNSS scores. Statistically significant treatment differences for daily PM iTNSS in favor of MP03-36 over placebo were observed on each study day with the exception of Days 9 to 11 (p<0.001 to 0.263). The mean daily treatment difference in change from baseline PM iTNSS for Days 2 through 14 was -0.53 in favor of MP03-36. In contrast, the daily change in AM iTNSS, the results were more variable. Statistically significant differences were observed only on Day 6 and 12, and numerical trends favoring MP03-36 over placebo were not observed on all study days. The mean daily treatment difference in change from baseline AM iTNSS for Days 2 through 14 was -0.29.

Reviewer's comment: Review of the daily change in iTNSS scores further indicates that once daily dosing is not sufficient to provide consistent symptom relief over the entire dosing interval. Twice daily dosing appears to be the optimal regimen.

Secondary symptom complex score (SSCS)
The SSCS (itchy eyes, postnasal drip, cough, headache) showed statistically significant improvement from baseline for MP03-36 over placebo (p=0.025).

RQLQ change from baseline
The overall improvement in the RQLQ was significant for MP03-36 compared to placebo (p-0.048).

Reviewer's comment: The secondary efficacy analyses support the efficacy of MP03-36 over placebo in general, although the support for the once-daily dosing regimen is not convincing.

10.3.2.8 Safety outcomes

Adverse events

Deaths and serious adverse events
No deaths or SAEs were reported during the study.

Discontinuations from the study due to adverse events.
Two patients in the MP03-36 group withdrew prematurely due to AEs (upper respiratory tract infection in Patient 925-05; dysgeusia, burning sensation in the nasal/sinus area, and numbness in the throat in Patient 929-03). One patient in the placebo group withdrew due to an AE, citing sore throat, cough, and nasal congestion.

Common adverse events
The most common adverse events reported for MP03-36 were dysgeusia and nasal discomfort. In general, the common adverse events reported were consistent with the safety profile of the commercially marketed Astelin. Fatigue and somnolence were reported in 2 and 1 patients, respectively, in the MP03-36 arm compared to none in the placebo group. The AEs are summarized in the table below.

Table 63 Study MP439: Adverse events occurring in ≥1% MP03-36 treatment group

Preferred Term [N(%)]	MP03-36 (N=239)	Placebo (N=242)
Any AE	33 (13.8)	25 (10.3)
Dysgeusia	8 (3.3)	2 (0.8)
Nasal discomfort	6 (2.5)	4 (1.7)
Headache	3 (1.3)	5 (2.1)
Pharyngolaryngeal pain	3 (1.3)	4 (1.7)
Sinus headache	4 (1.7)	1 (0.4)
Epistaxis	3 (1.3)	2 (0.8)
Blood pressure increased	1 (1.3)	0

Source: Vol 40, Section 12.2.3.1, Table 14

Vital signs
Increased blood pressure was reported in 3 patients in the MP03-36 group; the increases did not warrant medical intervention. No clinically relevant mean changes from baseline were noted for either treatment group.

Clinical laboratory evaluations
Pregnancy tests were performed as part of routine screening; no pregnancies were reported. No other formal laboratory evaluations were performed.

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.). No nasal ulcerations or septal perforations were reported. Seven MP03-36 patients reported mild epistaxis; no moderate or severe epistaxis was reported. One case of severe mucosal crusting was reported; the majority had mild or no crusting observed.

Reviewer's comment: The types of adverse events reported for MP03-36 are consistent with the known safety profile of intranasal azelastine. The rate of dysgeusia was improved compared to the rate reported in the Astelin product label (19.7%), although the rate was still higher than in the placebo group despite the addition of taste-masking agents. The rate appears less than the rate reported in other studies using the twice-daily dosing regimen of MP03-36 (~8%).

10.3.3 Study summary and conclusions
The results of MP0439 are generally supportive of MP03-36's efficacy and safety in SAR; however, the study does not provide conclusive support for the once-daily dosing regimen. Although the once-daily dosing regimen did win over placebo in terms of the primary efficacy variable, it did not win over placebo for the secondary variable intended to assess the adequacy of the dosing interval, the end-of-24hr iTNSS. These results suggest that although once-daily dosing is better than placebo, the optimal dosing regimen for the most consistent efficacy over

the dosing interval is twice-daily. The overall safety profile for the once-daily dosing regimen was similar to that of the twice-daily regimen seen in other studies.

10.4 Individual Study Report: Study MP440

10.4.1 Study Protocol: MP440

10.4.1.1 Administrative information

- Title: Randomized, double-blind, placebo-controlled trial of the safety and efficacy of MP03-36 in patients with seasonal allergic rhinitis
- Study initiation date: December 13, 2007
- Study completion date: February 21, 2008
- Study report date: June 19, 2008
- Location: 6 study sites in the US

10.4.1.2 Objectives/Rationale

- Evaluate the efficacy of MP03-36 two sprays once daily (AM) versus placebo once-daily in SAR

10.4.1.3 Study design overview

MP440 was a randomized, double-blind, placebo-controlled, parallel-group study in patients with moderate-to-severe allergy to Texas mountain cedar. The study consisted of a 1-week, single-blind, placebo lead-in period followed by a 2-week double-blind treatment period for those patients qualifying with a minimum symptom score. Patients recorded symptom scores twice daily for the duration of the treatment period and completed the RQLQ on Days 1 and 14. Interim evaluation was performed on Day 7 and end-of-study evaluation was performed on Day 14 or at the time of early termination, if applicable.

10.4.1.4 Study population

536 patients (268 in each treatment arm) 12 years of age and older with a minimum 2-year history of SAR and a positive skin test to Texas mountain cedar pollen during the previous year were enrolled.

<u>Inclusion criteria</u>

- 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 assessments (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 assessments (1 of which was within 2 days of Day 1 and can include the morning of Day 1).
- ≥2 year history of SAR during Texas mountain cedar season
- IgE-mediated hypersensitivity to Texas mountain cedar pollen confirmed by skin prick within the last year.
  - ≥3mm wheal larger than control on SPT
- General good health
- Stable immunotherapy, if applicable, for at least 30 days before first study visit. Patients on sublingual immunotherapy (SLIT) were excluded. A 6-month washout period was required following the last dose of SLIT.

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
- Nasal or sinus surgery within the previous year
- Chronic sinusitis – more than 3 episodes per year
- 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
- Participation in Studies MP433, MP438, or MP439

Reviewer's comment: Texas mountain cedar allergen is a potent allergen that appears to cause particularly intense rhinitis symptoms in sensitized patients. Accordingly, it is expected that a treatment difference would be more exaggerated in this particular SAR population and results from a study conducted in mountain cedar allergic patients may not necessarily be generalizable to a wider SAR patient population.

10.4.1.5 Study treatments

Treatment groups

- MP03-36 (0.15% azelastine) 2 sprays per nostril once daily in AM (822 mcg total daily dose)
- Vehicle placebo 2 sprays per nostril once daily in AM

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.

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.

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.

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.

10.4.1.6 Study procedures

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 medications listed in Table 37 were not permitted during the study period and required the specified washout periods prior to Day -7.

Assessments and evaluations
Table 64 shows the schedule of assessments and evaluations performed in Study MP440.

Table 64 Study MP440: Assessments and evaluations				
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 used study medication		X		X

[a] May be omitted if patient had positive skin test for mountain cedar 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 to subjects 18 years and older

10.4.1.7 Efficacy parameters

Primary efficacy endpoint

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 0-3 scale (none to severe): runny nose, sneezing, itchy nose, and nasal congestion. The highest possible combined score on this scale was 24 (maximum AM rTNSS of 12 + maximum PM rTNSS of 12).

Secondary efficacy endpoints

- End-of-24hr dosing interval: Change from baseline in AM iTNSS for the entire 14-day period compared to placebo to determine if the duration of efficacy lasts 24 hours
- Change from baseline in combined AM and PM iTNSS
- Change from baseline in 12-hr rTNSS individual symptom scores
- Daily change from baseline in 12hr rTNSS and iTNSS
- Change from baseline in 12hr rSSCS (Secondary Symptom Complex Score: postnasal drip, itchy eye, cough severity, headache severity)
- Change from baseline in 12h rSSCS individual symptoms
- Change from baseline Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) in subjects 18 years and older

10.4.1.8 Safety parameters

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

Laboratory assessments
Prick-puncture allergen skin testing for mountain cedar pollen was performed at Screening. No blood laboratory tests were routinely assessed during the study. Urine pregnancy tests were administered to all female subjects with no exceptions.

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

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.

10.4.1.9 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 ANCOVA model. Missing TNSS values were imputed using the last observation carried forward (LOCF). If a postbaseline TNSS was missing, the last non-missing postbaseline TNSS was used. 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. Safety analyses were performed on all randomized patients who received at least one dose of study medication.

A sample size of 234 patients was calculated so that the study would have 90% power to detect a change of 1.42 units in the AM and PM combined TNSS from baseline for MP03-36 compared to placebo. The treatment difference was based on prior efficacy results from Study MP435. Descriptive statistics were used to report the frequency of adverse events and the distribution of vital sign measurements.

10.4.2 Results
10.4.2.1 Protocol amendments

- Amendment 1 (November 8, 2007) – added a urine pregnancy test for female subjects who qualified at Day 1, added clarification to contraceptive use during the placebo lead-in period, added clarification that interruption of treatment was at investigator discretion, deleted text regarding new nasal mucosal lesions
- Amendment 2 (November 20, 2007) – changed the placebo lead-in period to 7 days, added clarification that all eye drops were prohibited, added clarification that 30 days applied to hormonal therapy only

- Memo to File (December 4, 2007) – added clarification to supervisory staff for Day 1 dosing, added clarification that a 3rd-party dispenser was not required

10.4.2.2 Study patients

A total of 536 patients were randomized to double-blind treatment. A total of 499 subjects completed the study while 37 subjects discontinued early.

Table 65 Study MP440: Patient disposition

Disposition	MP03-36	Placebo	Total
Randomized	268	268	536
Completed	249 (92.9)	250 (93.3)	499 (93.1)
Discontinued	19 (7.1)	18 (6.7)	37 (6.9)
Adverse event	4 (1.5)	3 (1.1)	7 (1.3)
Abnormal test result	0	0	0
Treatment failure	3 (1.1)	2 (0.7)	5 (0.9)
Non-compliance	4 (1.5)	0	4 (0.7)
Withdrew consent	2 (0.7)	1 (0.4)	3 (0.6)
Lost to follow-up	2 (0.7)	3 (1.1)	5 (0.9)
Administrative problems	0	0	0
Other	4 (1.5)	9 (3.4)	13 (2.4)
ITT[a]	266 (99.3)	266 (99.3)	532 (99.3)
Per protocol population[b]	242 (90.3)	245 (91.4)	487 (90.9)
Safety population[c]	268 (100.0)	268 (100.0)	536 (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 55, Section 10.1, Table 3

10.4.2.3 Protocol deviations

Four subjects (2 in each treatment group) were not evaluable for the ITT. The reason for exclusion was not having a post-baseline efficacy evaluation. A full listing of protocol deviations is provided in the Applicant's Appendiz 16.2.3.2.

Reviewer's comment: The protocol deviations are unlikely to have impacted the overall results and conclusions of Study MP440. The nature of the deviations and the total number in each treatment group were similar.

10.4.2.4 Treatment exposure and compliance

Table 66 Study MP440: Duration of exposure and compliance		
	MP03-36 N=268	**Placebo N=268**
Duration (days)		
N	266	265
Mean	14.0	14.3
SD	2.2	1.6
Median	15.0	15.0
Range	2-16	4-19
Total number of doses		
N	266	268
Mean	13.9	14.0
SD	2.4	2.1
Median	15.0	15.0
Range	2-16	1-19
# Patients ≥80% compliance [N,%]	258 96.3	262 97.8

Source: Module 5, Vol 55, Section 11.3 and 12.1, Tables 6 and11

10.4.2.5 Datasets 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.

10.4.2.6 Demographics and baseline characteristics

Table 67 Study MP440: Patient demographics and baseline characteristics		
Variables	**MP03-36 N=266**	**Placebo N=266**
Age (Mean, Range)	40.9 (12-80)	40.0 (12-81)
Gender (male, %)	91 (34.2)	95 (35.7)
Race		
Caucasian	231 (86.8)	241 (90.6)
Black	26 (9.8)	13 (4.9)
Hispanic	84 (31.6)	80 (30.1)
Asian	1 (0.4)	4 (1.5)
Native American	1 (0.4)	0
Native Hawaiian or Pacific Islander	0	1 (0.4)
Other	7 (2.6)	7 (2.6)
Total score		
Mean, SD	18.5 (3.28)	18.0 (3.33)
Range	7-24	6-24
Duration of SAR (yrs)		
Mean, SD	18.3 (12.6)	18.3 (13.1)
Range	2-60	2-70

Source: Module 5, Vol 55, Section 11.2.1, Table 5

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

10.4.2.7 Efficacy endpoint outcomes

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

Table 68 Study MP440: Change from baseline combined (AM plus PM) 12-hour rTNSS[a]

Treatment	Baseline (SD)[b]	Change from baseline	P-value vs placebo, 95% CI	Treatment difference from placebo
MP03-36 N=266	18.5 (3.3)	-3.5 (4.2)	<0.001 (-2.2, -0.9)	-1.5
Placebo N=266	18.0 (3.3)	-2.0 (3.5)	-	-

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 55, Section 11.4.1.1, Table 7

Results of the primary efficacy analysis are presented in the table above. MP03-36 showed a statistically significant benefit over placebo.

Secondary efficacy endpoints

End of 24-h dosing and combined iTNSS

The dosing interval as assessed by change from baseline in AM iTNSS at the end of the 24-hour dosing interval demonstrated a statistically significant benefit for MP03-36 over placebo. Similarly, the combined AM and PM iTNSS over the 14-day period also showed a statistically significant difference between MP03-36 and placebo

Table 69 Study MP440: Change from baseline in AM iTNSS[a]

Treatment	Baseline (SD)[b]	Change from baseline	P-value vs placebo, 95% CI
MP03-36 N=266	8.7 (2.0)	-1.4 (2.1)	<0.001 (-1.1, -0.4)
Placebo N=266	8.3 (2.0)	-0.6 (1.9)	

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 55, Table 14.2.7.1

Table 70 Study MP440Change from baseline combined (AM plus PM) iTNSS[a]

Treatment	Baseline (SD)[b]	Change from baseline	P-value vs placebo, 95% CI	% Change from baseline	P-value vs. placebo, 95% CI
MP03-36 N=266	17.1 (4.1)	-3.0 (4.3)	<0.001 (-2.1, -0.8)	-16.7 (27.4)	<0.001 (-12.6, -3.7)
Placebo N=266	16.3 (4.1)	-1.4 (3.6)		-8.4 (24.9)	

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 55, Section 14.2.6.2

Reviewer's comment: The AM and combined iTNSS scores support the efficacy of the once-daily MP03-36 regimen.

Individual nasal symptom scores

Table 71 Study MP440: 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], 95% CI
Itchy Nose	MP03-36	4.6 (1.2)	-0.9 (1.3)	<0.001 (-0.7, -0.3)
	Placebo	4.5 (1.2)	-0.5 (1.1)	
Runny nose	MP03-36	4.7 (1.1)	-0.9 (1.3)	0.002 (-0.5, -0.1)
	Placebo	4.6 (1.1)	-0.6 (1.2)	
Sneezing	MP03-36	4.1 (1.3)	-1.0 (1.4)	<0.001 (-0.7, -0.3)
	Placebo	3.9 (1.4)	-0.5 (1.2)	
Congestion	MP03-36	5.1 (0.9)	-0.7 (1.1)	0.002 (-0.4, -0.1)
	Placebo	5.1 (0.8)	-0.5 (0.9)	

[a] Least-square mean and standard deviation
[b] P-value calculated from repeated measures ANCOVA model and baseline as a covariate.
Source: Vol 55, Section 11.4.1.1, Table 9

Reviewer's comment: The individual symptom scores support the efficacy for MP03-36 over placebo for all 4individual symptom components of the TNSS.

Daily symptom scores
MP03-36 was numerically superior to placebo for daily change from baseline rTNSS on Days 2 through 14 ($p \leq 0.24$), although the difference was not statistically significantly superior on Day 10 ($p=0.08$). For daily change from baseline iTNSS, MP03-36 was consistently superior compared to placebo ($p \leq 0.046$) for Days 2 through 14. Similar results were observed for the daily change from baseline AM iTNSS ($p \leq 0.025$).

Secondary symptom complex scores
The SSCS (itchy eyes, postnasal drip, cough, headache) showed statistically significant improvement from baseline for MP03-36 over placebo (-2.81 vs. -1.52; $p<0.001$) at the end of the 2-week treatment period.

RQLQ change from baseline
The overall RQLQ score was improved from baseline in MP03-36 group compared to placebo ($P=0.023$).

Reviewer's comment: The secondary efficacy analyses support the efficacy of MP03-36 once daily over placebo.

10.4.2.8 Safety outcomes

Adverse events

Deaths and serious adverse events
No deaths or SAEs were reported during the study.

Discontinuations from the study due to adverse events
Four patients in the MP03-36 arm withdrew secondary to an AE, compared to 3 patients in the placebo group. The AEs cited at the time of discontinuation included: 1) sinusitis; 2) bronchitis, pyrexia, cough, 3) sinus congestion, and 4) sinusitis. In the placebo group, the discontinuations were secondary to two cases of upper respiratory tract infection and once case of bronchitis.

Reviewer's comment: SAR predisposes patients to sinusitis. It seems unlikely that MP03-36 would independently worsen sinusitis, although this effect cannot be ruled out. Sinusitis is an AE associated with azelastine nasal spray and is cited in the current Astelin product label.

Common adverse events
The most common adverse events reported for MP03-36 were dysgeusia and nasal discomfort. In general, the common adverse events reported were consistent with the safety profile of the commercially marketed Astelin. Sedation and somnolence were reported in 2 and 2 patients, respectively, in the MP03-36 arm compared to none in the placebo group. Fatigue was not reported in the MP03-36 group while one patient in the placebo arm reported this AE. The most commonly occurring AEs are summarized in the table below.

Table 72 Study MP440: Adverse events occurring in ≥1% MP03-36 treatment group

Preferred Term [N(%)]	MP03-36 (N=268)	Placebo (N=268)
Any AE	57 (21.3)	33 (12.3)
Dysgeusia	12 (4.5)	0
Nasal discomfort	12 (4.5)	0
Epistaxis	5 (1.9)	6 (2.2)
Sinusitis	5 (1.9)	1 (0.4)
Nausea	4 (1.5)	1 (0.4)
Pyrexia	3 (1.1)	1 (0.4)
Sneezing	3 (1.1)	0

Source: Module 5, Vol 55, Section 12.2.3.1, Table 13

Vital signs
No clinically relevant mean changes from baseline were noted for either treatment group.

Clinical laboratory evaluations
Pregnancy tests were performed as part of routine screening; no pregnancies were reported. No other formal laboratory evaluations were performed.

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.). No nasal ulcerations or septal perforations were reported. No clear differences between treatment groups were reported.

Reviewer's comment: The types of adverse events reported for MP03-36 are consistent with the known safety profile of intranasal azelastine. The rate of dysgeusia was improved compared to the rate reported in the Astelin product label (19.7%), although the rate was still higher than in the placebo group despite the addition of taste-masking agents. The rate appears less than the rate reported in other studies using the twice-daily dosing regimen of MP03-36 (~8%).

10.4.3 Study summary and conclusions

The results of MP440 support the efficacy and safety of once-daily MP03-36 for the treatment of SAR. In contrast to Study MP439, the iTNSS scores support the 24-hr dosing interval. However, it is worth noting that this study was conducted in patients with allergy to Texas mountain cedar allergen, a potent allergen that appears to cause particularly intense rhinitis symptoms in sensitized patients. Accordingly, it is expected that a treatment difference would be more exaggerated in this particular SAR population and results from a study conducted in mountain cedar allergic patients may not necessarily be generalizable to a wider SAR patient population. The overall safety profile for the once-daily dosing regimen was similar the profile observed in other studies in the clinical development program.

10.5 Individual Study Report: Study MP434

10.5.1 Study Protocol: MP434

10.5.1.1 Administrative information

- Title: Randomized, double-blind, placebo-controlled trial of the safety and efficacy of MP03-36 and MP03-33 in patients with PAR
- Study initiation date: February 5, 2007
- Study completion date: October 8, 2007
- Study report date: June 26, 2008
- Location: 43 centers in the continental US

10.5.1.2 Objectives/Rationale

- Evaluate the efficacy of MP03-36 compared to placebo for the treatment of PAR
- Compare the efficacy of MP03-33 to placebo for the treatment of PAR

Reviewer's comment: Although MP03-33 was included as a comparator, a direct statistical comparison of MP03-36 to MP033 is not made and was not considered one of the primary objectives of the protocol.

10.5.1.3 Study design overview

Study MP434 was a randomized, double-blind, placebo-controlled, parallel group study in patients with moderate to severe PAR. The study was conducted in the winter to minimize confounding due to seasonal pollen allergens. The study consisted of a 1-week placebo lead-in period followed by a 4-week double-blind treatment period for those patients qualifying with a minimum symptom score.

10.5.1.4 Study population

581 patients were randomized and results from 535 patients (180 in MP03-33, 180 in the MP03-36 group, and 175 in placebo) were included in the ITT analysis.

Inclusion criteria

- 12 years of age and older
- Written informed consent/pediatric assent
- Screening visit: Have a 12-hour rTNSS (AM or PM) ≥6 out of a possible 12 and a congestion score of 2 or 3 on Day -7
- Randomization visit:
    - Have a 12-hour rTNSS ≥6 on 3 separate symptom assessments (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 symptom assessments (1 of which was within 2 days of Day 1 and can include the morning of Day 1).
- Must have taken ≥10 doses of study medication during the Lead-in Period

- ≥2 year history of PAR
- IgE-mediated hypersensitivity to dust mite, cockroach, mold, cat, or dog dander confirmed by skin prick or intradermal teating within the last year.
    - ≥3mm wheal larger than control on SPT *OR*
    - ≥7mm wheal larger than control on IDT
- General good health
- Stable immunotherapy, if applicable, for at least 30 days before first study visit. Patients on sublingual immunotherapy (SLIT) were excluded. A minimum 6-month washout period following the last dose of SLIT was required.

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
- Positive skin test to any seasonal pollens anticipated during the study period (e.g. Texas mountain cedar)
- Presence of any nasal ulceration or nasal septal perforation at screening or randomization
- Other nasal diseases which may affect deposition of intranasal medication
- Nasal/sinus surgery within past year
- Asthma (except mild, intermittent asthma) or other significant pulmonary disease
- Arrhythmia
- 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
- Overnight absences from home for more than 3 nights
- Prior participation in Study MP430 or MP433

10.5.1.5 Study treatments

Treatment groups

- MP03-36 2 sprays twice daily (1644 mcg total daily dose)
- MP03-33 2 sprays twice daily (1096 mcg total daily dose)
- Vehicle placebo 2 sprays twice daily

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.

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.

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 28-day supply of study drug nasal spray.

Treatment compliance
Patients were instructed to record each dose of study drug taken in the TNSS diary. On Days 1, 14, and 28, 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.

10.5.1.6 Study procedures

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 medications listed in Table 37 were not permitted during the study period and required the specified washout periods prior to Day -7.

Assessments and evaluations

Table 73 shows the schedule of assessments and evaluations performed in Study MP434.

Table 73 Study MP434: Assessments and evaluations

Procedure	Lead-in period	Treatment period		
	Day -7 Screening	Day 1 Randomization	Day 14	Day 28 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[d]	X			
Patient instruction	X	X	X	
Dispense placebo lead-in meds	X			
Dispense study medication		X		
Dispense TNSS diary	X	X	X	
RQLQ[c]		X		X
Dispense study medication		X		
AE assessment		X	X	X
Collect TNSS diary		X	X	X
Collect used study medication		X		X

[a] May be omitted if patient had positive skin test for a relevant allergen 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 to subjects 18 years and older
[d] All female subjects. Exception: hysterectomy or at least 2 years menopausal or prepubescent adolescents

10.5.1.7 Efficacy parameters

Primary efficacy endpoint

The primary efficacy variable was the change from baseline in 12-hour combined (AM plus PM) reflective TNSS (rTNSS) to Day 28 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 0-3 scale (none to severe): runny nose, sneezing, itchy nose, and nasal congestion. The highest possible combined score on this scale was 24 (maximum AM rTNSS of 12 + maximum PM rTNSS of 12).

Secondary efficacy endpoints

- Change from baseline in iTNSS for the entire 28-day study period
- Change from baseline in 12-hr rTNSS individual symptom scores
- Daily scores – both 12hr rTNSS and iTNSS compared to placebo
- Change from baseline in 12-hr rSSCS for the entire 28-day period. The SSCS was scored on a 0-3 scale (none to severe) for the following symptoms: postnasal drip, itchy eye, cough, and headache.
- Change from baseline in individual 12-hr SSCS symptoms over the entire 28-day period compared to placebo
- Change from baseline to Day 28 in the RQLQ in subjects 18 years of age and older

10.5.1.8 Safety parameters

Adverse experiences

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

Laboratory assessments
Prick-puncture allergen skin testing for dust mite, cockroach, mold, and cat/dog dander was performed at Screening if testing had not been performed within the previous year. No blood laboratory tests were routinely assessed during the study. Urine pregnancy tests were administered to all female subjects with the exception of patients who had underwent hysterectomy, were at least 2 years post-menopausal, or were prepubescent.

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

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.

10.5.1.9 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 4-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 ANCOVA model. If significant, the MP03-33 vs. placebo comparison was to be performed. Missing TNSS values were imputed using the last observation carried forward (LOCF). If a postbaseline TNSS was missing, the last non-missing postbaseline TNSS was used. 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. Safety analyses were performed on all randomized patients who received at least one dose of study medication.

A sample size of 180 patients was calculated so that the study would have 90% power to detect a change of 1.5 units in the AM and PM combined TNSS from baseline for MP03-33 compared to placebo and to demonstrate an "observable" dose-response difference between MP03-33 and MP03-36. The study was not powered to show a statistically significant difference between the two active treatments. The treatment difference was based on prior efficacy results for MP03-33. Descriptive statistics were used to report the frequency of adverse events and the distribution of vital sign measurements.

Reviewer's comment: A formal comparison of MP03-36 versus MP03-33 was not included in the SAP.

10.5.2 Results
10.5.2.1 Protocol amendments

- Amendment 1, November 28, 2006, was the protocol as originally submitted to the FDA

- Amendment 2, January 11, 2007, clarified inclusion/exclusion criteria, TNSS qualifications, and the components of the direct visual nasal exam.

10.5.2.2 Study patients

A total of 581 patients were randomized, of whom 535 completed the 4-week study. Forty-six patients discontinued early.

Table 74 Study MP434: Patient disposition

Disposition	MP03-33	MP03-36	Placebo	Total
Randomized	197	192	192	581
Completed	180 (91.4)	180 (93.8)	175 (91.1)	535 (92.1)
Discontinued	17 (8.6)	12 (6.3)	17 (8.9)	46 (7.9)
Adverse event	4 (2.0)	7 (3.6)	3 (1.6)	14 (2.4)
Abnormal test result	0	0	0	0
Treatment failure	0	1 (0.5)	1 (0.5)	2 (0.3)
Non-compliance	0	0	3 (1.6)	3 (0.5)
Withdrew consent	2 (1.0)	1 (0.5)	4 (2.1)	7 (1.2)
Lost to follow-up	4 (2.0)	0	1 (0.5)	5 (0.9)
Administrative problems	0	0	0	0
Other	7 (3.6)	3 (1.6)	5 (2.6)	15 (2.6)
ITT[a]	194 (98.5)	192 (100.0)	192 (100.0)	578 (99.5)
Per protocol population[b]	173 (87.8)	172 (89.6)	166 (86.5)	511 (88.0)
Safety population[c]	197 (100.0)	192 (100.0)	192 (100.0)	581 (100.0)

[a] All patients who were randomized and had at least one post-baseline observation.
[b] All patients who completed the 4-week treatment period per protocol.
[c] All randomized patients who received at least one dose of study medication.
Source: Module 5, Vol 70, Section 10.1, Table 3

10.5.2.3 Protocol deviations

Three patients were not evaluable for the ITT population because they did not have post-baseline efficacy evaluations and 1 of the 3 also did not meet all entrance criteria. The most common protocol deviations were patients who were non-compliant with the diary or study medications (n=9 in the MP03-36 group; n=4 in the MP03-33 group; n=9 in placebo) and patients who did not meet lead-in rTNSS criteria (n=3 in the MP03-36; n=6 in the MP03-33 group; n=3 in the placebo). A full listing of the protocol deviations for Study MP434 is included in Appendix 16.2.3.2 in the study report.

Reviewer's comment: The protocol deviations noted are unlikely to have impacted the overall results and conclusions of Study MP434.

10.5.2.4 Treatment compliance

The duration of exposure and compliance are summarized in Table 75 as assessed by patient diary daily recorded doses and confirmed by bottle weights measured on Days 1, 14, and 28.

Table 75 Study MP434: Duration of exposure and compliance			
	MP03-33 (N=194)	**MP03-36 (N=192)**	**Placebo (N=192)**
Duration (days)			
N	193	192	191
Mean	27.9	27.4	27.5
SD	3.8	5.0	4.2
Median	29.0	29.0	28.0
Range	1-38	2-36	2-35
Total number of doses			
N	196	192	192
Mean	53.8	53.4	52.8
SD	9.5	10.0	9.6
Median	56.0	56.0	56.0
Range	1-76	3-71	3-70
# Patients ≥80% compliance [N,%]	189 95.9	187 97.4	184 95.8

Source: Module 5, Vol 70, Section 11.3 and 12.1, Tables 6 and 11

10.5.2.5 Datasets 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 4-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.

10.5.2.6 Demographics and baseline characteristics

The patients ranged in age from 12 to 84 years with a mean age of 37 years. The average duration of PAR in the study was 20 years.

Table 76 Study MP434: Patient demographics and baseline characteristics			
Variables	**MP03-33 (N=194)**	**MP03-36 (N=192)**	**Placebo (N=192)**
Age (Mean, Range)	36.9 (12-64)	35.6 (12-71)	38.1 (12-84))
Gender (male, %)	58 (29.9)	65 (33.9)	62 (32.3)
Race			
Caucasian	160 (82.5)	159 (82.8)	172 (89.6)
Black	28 (14.4)	26 (13.5)	11 (5.7)
Hispanic	32 (16.5)	36 (18.8)	29 (15.1)
Asian	2 (1.0)	3 (1.6)	2 (1.0)
Native American	1 (0.5)	1 (0.5)	0
Native Hawaiian or Pacific Islander	2 (1.0)	1 (0.5)	2 (1.0)
Other	1 (0.5)	2 (1.0)	5 (2.6)
Total score			
Mean, SD	15.6 (3.80)	15.9 (3.89)	17.9 (3.30)
Range	5-24	6-24	8-24
Duration of SAR (yrs)			
Mean, SD	19.0 (12.69)	19.6 (12.82)	20.2 (13.45)
Range	2-52	2-59	2-64

Source: Module 5, Volume 70, Section 11.2.1, Table 5

Reviewer's comment: In terms of demographics, the treatment groups appear similar in terms of age, gender, and overall racial make-up, although there were fewer Blacks in the placebo arm.

The significance of this disproportion is not clear. Baseline symptom scores and history of PAR appear comparable.

10.5.2.7 Efficacy endpoint outcomes

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

Results of the primary efficacy endpoint are shown in the table below. Baseline TNSS scores were the highest in the MP03-36 group, followed by the MP03-33 and placebo groups. According to the Applicant's analysis, MP03-36 did not show a statistically significant difference from placebo for the primary efficacy endpoint, change from baseline to Day 14 in combined 12-h rTNSS. In keeping with the gatekeeping protocol, the comparison for MP03-33 versus placebo was not calculated. Numerically, both performed better than placebo and MP03-36 appeared to have an advantage over MP03-33. The Applicant did not perform subgroup analyses of the primary endpoint, but did provide a per-protocol analysis. When looking at the PP analysis, the results were statistically significant for MP03-36 versus placebo (p=0.018).

In contrast, reanalysis by the Agency's statistical review demonstrated a statistically significant treatment benefit for MP03-36 over placebo. These results are displayed below. Further details about the Agency's findings can be found in the Dr. Ted Guo's statistical review.

Table 77 Study MP434: Change from baseline combined (AM plus PM) 12-hour rTNSS[a]

Treatment	Baseline (SD)[b]	Change from baseline	P-value vs placebo, 95% CI	Treatment difference from placebo
MP03-33 N=194	15.6 (3.8)	-3.8 (4.0)	*Not calculated*	-0.5
MP03-36 N=192	15.9 (3.9)	-4.1 (4.3)	0.061 (-1.57, 0.04)	-0.8
Placebo N=192	14.9 (4.0)	-3.3 (4.4)	-	-

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 70, Section 11.4.1.1, Table 7

Reviewer's endpoint: The Applicant states that more severe symptoms at baseline in the MP03-36 group combined with a robust placebo effect at 8 study sites may account for the failure of MP03-36 to demonstrate a statistically significant difference from placebo according to the Applicant's analysis. The validity of this statement is not confirmed. A more severe symptom status at baseline could be interpreted conversely, i.e. there was more room for symptom improvement which MP03-36 failed to demonstrate.

However, based on the Agency's primary endpoint analysis, Study MP434 showed support for the efficacy of MP03-36 twice daily for the treatment of PAR. This reanalysis is consistent with the analysis performed in the other PAR and SAR studies, according to Dr. Guo's review, using a statistical model based on ANCOVA with treatment and center as fixed effect and the TNSS at baseline as a covariate. This is the same approach that was used for the pivotal SAR studies, MP433 and MP438. In comparison, the Applicant used a repeated measure model

that included effects of treatment, center, days (2-28), and treatment-by-days interaction with baseline as covariate in the analysis of MP434's results. Therefore, the clinical review has relied on the Agency's reanalysis values in determining the efficacy of MP03-36 in PAR.

Secondary efficacy endpoints

Instantaneous TNSS

Results for change from baseline in iTNSS over the 28-day treatment period are shown below.

Table 78 Study MP434: Change from baseline combined (AM plus PM) 12-hour iTNSS[a]

Treatment	Baseline (SD)[b]	Change from baseline	P-value vs placebo, 95% CI	Treatment difference from placebo
MP03-33 N=194	13.9 (4.6)	-3.4 (3.9)	0.102 (-1.4, 0.1)	-0.7
MP03-36 N=192	14.3 (4.6)	-3.5 (4.2)	0.044 (-1.6, -0.02)	-0.8
Placebo N=192	13.3 (4.6)	-2.7 (4.1)	-	-

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 70, Section 11.4.1.1, Table 8

Individual nasal symptom scores

Table 79 Study MP434: 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], 95% CI
Itchy Nose	MP03-33 N=194	3.9 (1.4)	-0.9 (1.1)	0.610 (-13.3, 7.8)
	MP03-36 N=192	4.0 (1.4)	-0.9 (1.3)	0.299 (-0.4, 0.1)
	Placebo N=192	3.7 (1.4)	-0.8 (1.3)	-
Runny nose	MP03-33 N=194	3.8 (1.3)	-1.0 (1.2)	0.375 (-0.4, 0.1)
	MP03-36 N=192	3.9 (1.3)	-1.2 (1.3)	0.039 (-0.5, -0.01)
	Placebo N=192	3.7 (1.4)	-0.9 (1.4)	-
Sneezing	MP03-33 N=194	3.3 (1.5)	-0.9 (0.2)	0.130 (-0.4, 0.05)
	MP03-36 N=192	3.3 (1.5)	-1.0 (1.3)	0.065 (-0.45, 0.01)
	Placebo N=192	2.9 (1.5)	-0.7 (1.2)	-
Congestion	MP03-33 N=194	4.7 (0.9)	-0.9 (1.1)	0.552 (-0.3, 0.2)
	MP03-36 N=192	3.9 (1.4)	-0.9 (1.3)	0.299 (-0.4, 0.1)
	Placebo N=192	3.7 (1.4)	-0.8 (1.3)	-

[a] Least-square mean and standard deviation
[b] P-value calculated from repeated measures ANCOVA model and baseline as a covariate.
Source: Module 5, Vol 70, Section 11.4.1.1, Table 9

Reviewer's comment: The secondary endpoints numerically favor MP03-36 over placebo, but the results are not statistically significant. There is no clear dose-response between MP03-33 and MP03-36.

Daily symptom scores

The daily change from baseline in the 12h rTNSS generally favored MP03-36 and MP03-33 over placebo but the results were not consistent over the 28-day treatment period. MP03-36 appeared more efficacious overall compared to MP03-33, but these were not statistically significant differences. Similar results were seen for the daily change from baseline in iTNSS as well.

Reflective SSCS

The MP03-36 group showed a statistically significant improvement in rSSCS compared to placebo over the 28-day treatment period (-2.92 vs. -1.79; p=0.002). For individual symptoms in the rSSCS, MP03-36 was superior to placebo in terms of itchy eyes, cough, and headache ($p<0.001$ to p=0.028) but not for post-nasal drip (p=0.29). The results for rSSCS were not statistically significant for the comparison between MP03-33 versus placebo.

RQLQ

The RQLQ scores were statistically significantly different at baseline between the treatment groups, with the MP03-36 group having the highest mean score (3.29), followed by the MP03-33 group (3.18) and the placebo group (2.98). The overall score for the RQLQ change from baseline compared to placebo was statistically improved for the MP03-33 group (p=0.04) but not for the MP03-36 group compared to placebo (p=0.292).

Reviewer's comments: The secondary efficacy endpoints provide some evidence of efficacy but the results are not consistent for MP03-36 compared to placebo. In addition, the results do not suggest a clear dose-related efficacy, when comparing MP03-36 to MP03-33.

10.5.2.8 Safety outcomes

Adverse events

Deaths and serious adverse events
There were no deaths or SAEs reported during the study.

Discontinuations from the study due to adverse events
Thirteen patients withdrew from the study due to adverse events. The 7 AEs reported in the MP03-36 group included nasal discomfort, sneezing, lacrimation, streptococcal pharyngitis, contact dermatitis, conjunctivitis, and upper respiratory tract infection. Two patients in the MP03-33 group withdrew secondary to influenza and dysgeusia. The 3 patients who discontinued early in the placebo group cited nasal discomfort, pharyngolaryngeal pain, otitis media, and bronchial hyperreactivity. One patient in the MP03-33 group was reported as having a nasal septum perforation, which the investigators deemed unlikely to be related to treatment because the patient reported that the perforation had been present since 1997, well before the study. However, the perforation was not reported on screening form. Another patient became pregnant and withdrew but this event was not classified as an AE.

Reviewer's comment: Although the septal perforation was not documented at screening, it seems unlikely that a patient would develop a perforation in a short-term study and the patient's self-report of a pre-existing perforation appears to be the more plausible explanation.

Common adverse events
The most common adverse event reported for both MP03-36 and MP03-33 was nasal discomfort (6.8% and 3.6%, respectively) followed by dysgeusia (4.7% and 5.6%, respectively). In general, common adverse events were consistent with adverse events noted in the clinical trials to support the approval for Astelin. These AEs are summarized in the table below.

Table 80 Study MP434: Adverse events occurring in 1% or more of either active treatment group

Preferred Term [N(%)]	MP03-33 (N=197)	MP03-36 (N=192)	Placebo (N=192
Any AE	48 (24.4)	46 (24.0)	39 (20.3)
Nasal discomfort	7 (3.6)	13 (6.8)	7 (3.6)
Dysgeusia	11 (5.6)	9 (4.7)	1 (0.5)
Headache	4 (2.0)	1 (0.5)	6 (3.1)
Epistaxis	4 (2.0)	2 (1.0)	3 (1.6)
Upper respiratory tract infection	1 (0.5)	2 (1.0)	4 (2.1)
Sneezing	0	5 (2.6)	0
Nasal mucosal disorder	1 (0.5)	2 (1.0)	2 (1.0)
Pregnancy	3 (1.5)	1 (0.5)	0
Back pain	1 (0.5)	2 (1.0)	0
Contact dermatitis	1 (0.5)	2 (1.0)	0
Viral gastroenteritis	1 (0.5)	2 (1.0)	0
Nasopharyngitis	1 (0.5)	1 (0.5)	1 (0.5)
Diarrhea	2 (1.0)	0	1 (0.5)
Pharyngolaryngeal pain	0	0	3 (1.6)
Fatigue	0	2 (1.0)	0
Somnolence	0	2 (1.0)	0
Nausea	2 (1.0)	0	0

Source: Module 5, Vol 70, Section 12.2.3.1, Table 13

Reviewer's comment: The types of adverse events reported for MP03-36 are consistent with the known safety profile of intranasal azelastine. There is no clear dose relationship for adverse events for MP03-36 versus MP03-33 overall, although there did appear to be fatigue and sedation in the MP03-36 group compared to none in the MP03-33 and placebo groups. In general, the overall 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%.

Vital signs

No notable derangements in mean vital signs were noted in any of the treatment groups during the 28-day treatment period (Source Volume 70, Section 14.3.5).

Physical examinations

General physical examinations were performed at Screening. Focused nasal exams were performed at Screening, Randomization, Day 14, and Day 28/Termination Day. No significant changes in the focused nasal exam were recorded in any of the treatment groups for the 28-day treatment period. The most common observations were physical findings consistent with allergic rhinitis (e.g. boggy turbinates, pale mucosa, watery mucosa, etc.). One patient was recorded as having a nasal septal perforation predating the study who should not have been randomized as noted above and was discontinued from the study. Nasal mucosal disorder was reported in 1 MP03-33 patient, 2 MP03-36 patients, and 2 placebo patients.

10.5.3 Study summary and conclusions

Based on the Agency's primary endpoint analysis, Study MP434 showed support for the efficacy of MP03-36 twice daily for the treatment of PAR. This reanalysis is consistent with the analysis performed in the other PAR and SAR studies. Therefore, the clinical review has relied on the Agency's reanalysis values in determining the efficacy of MP03-36 in PAR. The types of adverse events reported for MP03-36 are consistent with the known safety profile of intranasal azelastine. There is no clear dose relationship for adverse events for MP03-36 versus MP03-33. In general, the overall 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.

10.6 Individual Study Report: Study MP435

10.6.1 Study Protocol: MP435

10.6.1.1 Administrative information

- Title: Randomized, double-blind, placebo-controlled trial of the safety and efficacy of MP03-36 in patients with perennial allergic rhinitis
- Study dates: January 18, 2007 to May 17, 2007
- Location: 15 centers in the continental US
- Study report date: June 5, 2008

10.6.1.2 Objectives/Rationale

- Proof-of-concept study intended to evaluate the efficacy of MP03-36 2 sprays per nostril once daily (AM or PM) to placebo 2 sprays per nostril once daily

10.6.1.3 Study design overview

According to the Applicant, Study MP435 was a randomized, double-blind, placebo-controlled clinical trial in patients with moderate-to-severe PAR. The study had 1 week placebo run-in period followed by a 4-week double-blind treatment period. The study was conducted in the winter to minimize confounding from seasonal pollen allergens. Patients with a minimum qualifying symptom score during the run-in period were randomized to receive MP03-36 2 sprays per nostril in the AM or PM or placebo 2 sprays per nostril in the AM or PM.

10.6.1.4 Study population

The goal enrollment was 150 patients (50 per active treatment group; 25 per placebo group), 12 years of age and older with a minimum 2-year history of PAR with positive skin prick test to dust mite, cockroach, mold, or cat/dog dander.

Inclusion criteria

- 12 years of age and older
- Written informed consent/pediatric assent
- Screening visit: Have a 12-hour rTNSS (AM or PM) ≥6 out of a possible 12 and a congestion score of 2 or 3 on Day -7
- Randomization visit:

  - Have a 12-hour rTNSS ≥6 on 3 separate symptom assessments (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 symptom assessments (1 of which was within 2 days of Day 1 and can include the morning of Day 1).
- Must have taken ≥10 doses of study medication during the Lead-in Period
- ≥2 year history of PAR
- IgE-mediated hypersensitivity to dust mite, cockroach, mold, cat, or dog dander confirmed by skin prick or intradermal teating within the last year.
  - ≥3mm wheal larger than control on SPT *OR*
  - ≥7mm wheal larger than control on IDT
- General good health
- Stable immunotherapy, if applicable, for at least 30 days before first study visit. Patients on sublingual immunotherapy (SLIT) were excluded. A minimum 6-month washout period following the last dose of SLIT was required.

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
- Positive skin test to any seasonal pollens anticipated during the study period (e.g. Texas mountain cedar)
- Presence of any nasal ulceration or nasal septal perforation at screening or randomization
- Other nasal diseases which may affect deposition of intranasal medication
- Nasal/sinus surgery within past year
- Asthma (except mild, intermittent asthma) or other significant pulmonary disease
- Arrhythmia
- 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
- Overnight absences from home for more than 3 nights
- Prior participation in Study MP433

10.6.1.5 Study treatments

Treatment groups

- MP03-36 2 sprays per nostril once daily AM (MAM)
- MP03-36 2 sprays per nostril once daily PM (MPM)
- Placebo 2 sprays per nostril once daily AM (PAM)

- Placebo 2 sprays per nostril once daily PM (PPM)

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.

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.

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 28-day supply of study drug nasal spray.

Treatment compliance
Patients were instructed to record each dose of study drug taken in the TNSS diary. On Days 1, 14, and 28, 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.

10.6.1.6 Study procedures

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 medications listed in Table 37 were not permitted during the study period and required the specified washout periods prior to Day -7.

Assessments and evaluations

Table 81 shows the schedule of assessments and evaluations performed in Study MP435.

Table 81 Study MP435: Assessments and evaluations				
Procedure	**Lead-in period**	**Treatment period**		
	Day -7 Screening	**Day 1 Randomization**	**Day 14**	**Day 28 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[d]	X			
ECG	X			
Laboratory tests				
Patient instruction	X	X	X	
Dispense placebo lead-in meds	X			
Dispense study medication		X		
Dispense TNSS diary	X	X	X	
RQLQ[c]		X		X
AE assessment		X	X	X
Collect TNSS diary		X	X	X
Collect used study medication		X		X

[a] May be omitted if patient had positive skin test for a relevant allergen 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 to subjects 18 years and older
[d] All female subjects. Exception: hysterectomy or at least 2 years menopausal or prepubescent adolescents

10.6.1.7 Efficacy parameters

Primary efficacy endpoint

The primary efficacy variable was the change from baseline in 12-hour combined (AM plus PM) reflective TNSS (rTNSS) to Day 28 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 0-3 scale (none to severe): runny nose, sneezing, itchy nose, and nasal congestion. The highest possible combined score on this scale was 24 (maximum AM rTNSS of 12 + maximum PM rTNSS of 12).

Secondary efficacy endpoints

- End of 24-hours dosing interval: Mean change from baseline in iTNSS for the 28-day study period compared to placebo (key secondary endpoint)
- Change from baseline in iTNSS for the entire 28-day study period
- Change from baseline in 12-hr rTNSS individual symptom scores
- Daily scores – both 12hr rTNSS and iTNSS compared to placebo
- Change from baseline in 12-hr rSSCS for the entire 28-day period. The SSCS was scored on a 0-3 scale (none to severe) for the following symptoms: postnasal drip, itchy eye, cough, and headache.
- Change from baseline in individual 12-hr SSCS symptoms over the entire 28-day period compared to placebo
- Change from baseline to Day 28 in the RQLQ in subjects 18 years of age and older

10.6.1.8 Safety parameters

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

Laboratory assessments
Prick-puncture allergen skin testing for dust mite, cockroach, mold, and cat/dog dander was performed at Screening if testing had not been performed within the previous year. No blood laboratory tests were routinely assessed during the study. Urine pregnancy tests were administered to all female subjects with the exception of patients who had underwent hysterectomy, were at least 2 years post-menopausal, or were prepubescent.

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

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.

10.6.1.9 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 4-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 ANCOVA model. Missing TNSS values were imputed using the last observation carried forward (LOCF). If a postbaseline TNSS was missing, the last non-missing postbaseline TNSS was used. 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. Safety analyses were performed on all randomized patients who received at least one dose of study medication. No adjustments for multiplicity were made.

No formal sample size calculation was made since this study was intended as a proof of concept study. Based on prior experiences, however, the Applicant estimated that a sample size of 150 patients randomized 2:2:1:1 treatment groups:placebo groups would be able to convey trends in efficacy.

10.6.2 Results

10.6.2.1 Protocol amendments
No formal amendments were submitted to the FDA. The original protocol was amended to reduce the sample size.

10.6.2.2 Study patients

A total of 156 patients were randomized, of which 149 completed the study. Seven patients discontinued early.

Table 82 Study MP435: Patient disposition

Disposition	MAM	PAM	MPM	PPM
Randomized	53	24	52	27
Completed	53 (100.0)	22 (91.7)	48 (92.3)	26 (96.3)
Discontinued	0	2 (8.3)	4 (7.7)	1 (3.7)
Adverse event	0	0	1 (1.9)	0
Treatment failure	0	1 (4.2)	0	1 (3.7)
Non-compliance	0	0	0	0
Withdrew consent	0	0	0	0
Lost to follow-up	0	1 (4.2)	2 (3.8)	0
Other	0	0	1 (1.9)	0
ITT[a]	53 (100.0)	23 (95.8)	50 (96.2)	27 (100.0)
Per protocol population[b]	49 (92.5)	16 (66.7)	45 (86.5)	23 (95.2)
Safety population[c]	53 (100.0)	24 (100.0)	52 (100.0)	27 (100.0)

[a] All patients who were randomized and had at least one post-baseline observation.
[b] All patients who completed the 4-week treatment period per protocol.
[c] All randomized patients who received at least one dose of study medication.
Source: Module 5, Vol 93, Section 10.1, Table 1

10.6.2.3 Protocol deviations

Twenty-three patients deviated from the protocol. The most deviation cited was <80% or >120% compliance based on diary entries (n=7). Other protocol deviations reported included failure to complete the study (n=4), symptom scores did not meet cutoff criteria (n=2), missing post-randomization efficacy evaluation (n=2), prohibited medication use (n=2), non-compliance with TNSS diary and study medication (n=4), and final visit outside of the 28 day ± 3 days window (n=1).

Reviewer's comment: The impact of the protocol deviations noted on the overall results and conclusions of Study MP435 is unclear, but do not appear to favor or affect any one treatment group.

10.6.2.4 Treatment compliance

The duration of exposure and compliance are summarized in Table 83 as assessed by patient diary daily recorded doses and confirmed by bottle weights measured on Days 1, 14, and 28.

Table 83 Study MP435: Duration of exposure and compliance				
	MAM N=53	**PAM N=24**	**MPM N=52**	**PPM N=27**
Duration (days)				
N	53	23	51	27]
Mean	28.3	27.4	28.1	27.3
SD	1.3	3.7	3.1	3.3
Median	29.0	29.0	28.0	28.0
Range	24-31	13-30	14-38	12-30
Total number of doses				
N	53	23	51	27
Mean	27.6	27.1	27.6	27.1
SD	2.0	3.8	2.9	3.2
Median	28.0	28.0	28.0	28.0
Range	22-31	12-30	13-31	12-30
# Patients ≥80% compliance [N,%]	51 96.2	23 95.8	50 96.2	27 100

Source: Module 5, Vol 93, Section 11.3 and Table 14.1.3

10.6.2.5 Datasets 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 4-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.

10.6.2.6 Demographics and baseline characteristics

Table 84 Study MP435: Patient demographics and baseline characteristics					
Variables	**MAM N=53**	**PAM N=23**	**MPM N=50**	**PPM N=27**	**Total N=153**
Age (Mean, Range)	38.5 (12-76)	37.0 (14-62)	40.1 (12-70)	42.0 (13-67)	39.5 (12-76)
Gender (male, %)	14 (26.4)	5 (21.7)	17 (34.0)	10 (37.0)	46 (30.1)
Race/Ethnicity					
Caucasian	44 (83.0)	19 (82.6)	45 (90.0)	22 (81.5)	130 (85.0)
Black	5 (9.4)	3 (13.0)	3 (6.0)	2 (7.4)	13 (8.5)
Hispanic	10 (18.9)	5 (21.7)	13 (26.0)	4 (14.8)	32 (20.9)
Asian	0	0	0	1 (3.7)	1 (0.7)
Native American	0	0	0	1 (3.7)	1 (0.7)
Native Hawaiian or Pacific Islander	1 (1.9)	0	0	0	1 (0.7)
Other	3 (5.7)	1 (4.3)	2 (4.0)	1 (3.7)	7 (4.6)
Total score					
Mean, SD	15.3 (4.6)	16.2 (3.3)	15.3 (4.3)	14.5 (3.4)	15.3 (4.1)
Range	6-24	9-21	6-24	9-22	6-24
seymouDuration of SAR (yrs)					
Mean, SD	19.5 (13.4)	15.4 (8.6)	23.7 (15.2)	20.7 (12.2)	20.5 (13.4)
Range	3-57	4-38	3-62	3-48	3-62

Source: Module 5, Volume 93, Section 11.2.1, Table 2

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

10.6.2.7 Efficacy endpoint outcomes

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

Table 85 Study MP435 Change from baseline combined (AM plus PM) 12-hour rTNSS[a]

Treatment	Baseline (SD)[b]	Change from baseline	P-value vs placebo, 95% CI	% Change from baseline	P-value vs. placebo, 95% CI
MAM	15.5 (4.6)	-4.4 (4.5)	0.179		0.23 (-9.2, 2.2)
PAM	15.9 (3.9)	-4.1 (4.3)	0.061 (-1.57, 0.04)	-25.7 (26.7)	0.089 (-10.7, 0.75)
MPM	14.9 (4.0)	-3.3 (4.4)		-20.7 (33.8)	
PPM					

[a] Based on ITT population
[b] Least-square mean; standard deviation
Source: Module 5, Vol 70, Section 11.4.1.1, Table 7

10.6.2.8 Safety outcomes

Adverse events

Deaths and serious adverse events

There were no deaths or SAEs reported during the study.

Discontinuations from the study due to adverse events

One patient in the MPM group discontinued due to an AE of epistaxis and sinusitis after 8 days of treatment. No other discontinuations due to AEs were reported.

Common adverse events

The most common adverse events reported for MP03-36 included nasal discomfort, epistaxis, upper respiratory tract infection, headache, sneezing, asthma, viral gastroenteritis, dysgeusia, and nasal mucosal disorder. Fatigue was reported in one patient the MAM arm; no cases of somnolence or sedation were reported. In general, common adverse events were consistent with adverse events noted in the clinical trials to support the approval for Astelin and MP03-33(Astepro 0.1%). These AEs are summarized in the table below.

Table 86 Study MP435: Adverse events occurring in >1 patient who received MP03-36

Preferred term N, %	MAM N=53	PAM N=24	MPM N=52	PPM N=27
Any AE	17 (32.1)	7 (29.2)	15 (28.8)	5 (18.5)
Nasal discomfort	3 (5.7)	1 (4.2)	3 (5.8)	2 (7.4)
Epistaxis	1 (1.9)	1 (4.2)	5 (9.6)	1 (3.7)
Upper respiratory tract infection	2 (3.8)	1 (4.2)	2 (3.8)	-
Headache	1 (1.9)	1 (4.2)	3 (5.8)	-
Sneezing	1 (1.9)	-	2 (3.8)	-
Asthma	1 (1.9)	-	1 (1.9)	-
Gastroenteritis viral	1 (1.9)	-	1 (1.9)	-

Dysgeusia	-	-	2 (3.8)	-
Nasal mucosal disorder	-	-	2 (3.8)	-

Source: Module 5, Volume 93, Section 12.2.2, Text Table 15

Reviewer's comment: The types of adverse events reported for MP03-36 are consistent with the known safety profile of intranasal azelastine. In general, the overall frequency of adverse events was lower than the rates observed in the other controlled clinical trials.

Vital signs

No notable derangements in mean vital signs were noted in any of the treatment groups during the 28-day treatment period (Source: Module 5, Volume 93, Section 12.5 and Table 14.3.5).

Physical examinations

General physical examinations were performed at Screening. Focused nasal exams were performed at Screening, Randomization, Day 14, and Day 28/Termination Day. No significant changes in the focused nasal exam were recorded in any of the treatment groups for the 28-day treatment period. The most common observations were physical findings consistent with allergic rhinitis (e.g. boggy turbinates, pale mucosa, watery mucosa, etc.).

10.6.3 Study summary and conclusions

Study MP435 does not support the efficacy of once-daily dosing of MP03-36 for the PAR indication. Safety of MP03-36 dosed once daily was comparable to the safety demonstrated in the other MP03-36 PAR studies.

10.7 Individual Study Report: Study MP436

10.7.1 Study Protocol MP436

10.7.1.1 Administrative information

- Title: Active-controlled trial of the safety and tolerability of MP03-36 in patients with PAR (6-month interim report)
- Study sites: 57 US sites
- Study dates: March 9, 2007 to January 5, 2008
- Study report date: July 10, 2008

Reviewer's comment: An interim 6-month study report was submitted in the NDA. The 4-month safety update included updated adverse event data from the completed study. A full study report on the completed study was not submitted. In the discussion of adverse events, data from the 4-month safety update is incorporated into the clinical review.

10.7.1.2 Objectives/Rationale

- Evaluate the long-term safety and tolerability of MP03-36 over a 1-year period in patients with PAR

10.7.1.3 Study design overview

MP436 was a US multi-center, randomized, open-label, active-controlled, 6-month safety study of the safety and tolerability of MP03-36 in PAR patients 12 years of age and older. The study included patients from MP434 (N=145) and MP435 (N=82), as well as new enrollees (N=476). MP03-36 was compared to a commonly used intranasal corticosteroid, mometasone furoate, Nasonex® (200 mcg). A total of 703 PAR were enrolled and randomized 2:1 to treatment with MP03-36 2 sprays twice daily or Nasonex 2 sprays twice daily. The RQLQ was the main efficacy assessment performed in this study, assessed in patients 18 years of age and older. Safety assessments included adverse event screening, focused nasal exams, and vital signs.

10.7.1.4 Study population
700 patients 12 years of age and older with PAR who may benefit from continuous therapy with azelastine.

Inclusion criteria

- 12 years of age and older
- Written informed consent/pediatric assent
- Willing and able to comply with study requirements, including daily use of medication for a 1-year period even if symptoms were not bothersome
- IgE-mediated hypersensitivity to dust mite, cockroach, mold, cat, or dog dander confirmed by skin prick or intradermal teating within the last 2 years.
    - ≥3mm wheal larger than control on SPT *OR*
    - ≥7mm wheal larger than control on IDT
- General good health
- Stable immunotherapy, if applicable, for at least 30 days before first study visit. Patients on sublingual immunotherapy (SLIT) were excluded. A minimum 6-month washout period following the last dose of SLIT was required.

Exclusion criteria

- Use of any investigational drug within 30 days prior to Screening with the exception of study drug in Studies MP434 or MP435
- 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
- Presence of any nasal ulceration or nasal septal perforation at screening or randomization
- Other nasal diseases which may affect deposition of intranasal medication
- Nasal/sinus surgery within past year
- Asthma (except mild, intermittent asthma) or other significant pulmonary disease
- Arrhythmia
- Known history of drug or alcohol abuse
- Sublingual immunotherapy within previous 6 months
- Use of systemic corticosteroid or omalizumab within 30 days of screening

10.7.1.5 Study treatments

- MP03-36 (0.15% azelastine, 137 mcg/actuation) 2 sprays each nostril BID
- Nasonex® (mometasone furoate 50 mcg/actuation) 2 sprays each nostril QD

10.7.1.6 Study procedures

Concomitant medications

Medications that were considered necessary for the patient's welfare were permitted at the investigator's discretion. Oral decongestants could be used for upper respiratory infections or breakthrough rhinitis symptoms for no more than 5 consecutive days and no more than 2 courses per month. The following medications were prohibited:

- Antihistamines
- Oral and intranasal anticholinergics
- Topical or oral decongestants
- Intranasal or inhaled corticosteroids
- Systemic corticosteroids
- Omalizumab
- Leukotriene inhibitors
- Nasal saline or other intranasal medications
- Therapeutic doses of anticoagulant
- Sublingual immunotherapy

Treatment compliance

Compliance was assessed by audit of patient diaries. Any discrepancies between the diary entries and returned study medication were to be resolved at each study visit. Bottles were weighed to verify diary data. If more than 50% of the required doses were missing in the diary, investigators were to consider discontinuation of the patient from the study.

Assessments

A schedule of study visits for patients who did not participate in Studies MP434 or MP435 is provided below. Prior participants of these studies had a similar follow-up schedule but did not undergo the screening visit. In addition, patients received follow-up phone calls at Months 2, 4, 5, 7, 8, 10, and 11 to assess concomitant medications, compliance, and adverse events.

Table 87 Study MP436: Schedule of study visits and procedures

Procedure	Screening	Randomization	Month 1	Month 3	Month 6	Month 9	Month 12
Medical hx	X						
Physical exam	X	X	X	X	X	X	X
Nasal exam	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Height	X						
Body weight	X	X			X	X	X
Screening labs	X				X		X
ECG	X				X		X
Urine HCG	X		X	X	X	X	X
Concomitant rx	X	X	X	X	X	X	X
RQLQ		X	X	X	X	X	X
Dispense study med		X	X	X	X	X	X

Collect used study med			X	X	X	X	X
Dispense treatment diary		X	X	X	X	X	X
Collect Treatment diary			X	X	X	X	X
Assess compliance	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X

Source: Module 5, Volume 102, Section 9.5.1, Table 3

10.7.1.7 Efficacy parameters

Efficacy was assessed by calculating the change from baseline in the 28-item Rhinitis Quality of Life Questionnaire in patients 18 years of age and older at 6 months. Efficacy in patients 12 to 18 years of age was not assessed.

10.7.1.8 Safety parameters

- Adverse events monitoring
- Focused exams of the head and neck
- ECG
- Screening hematology, chemistry, and urinanalysis
- Urine pregnancy tests

10.7.1.9 Statistical plan

The change from baseline in RQLQ was analyzed using ANCOVA. Descriptive statistics were used for presentation of demographic and adverse event data.

10.7.2 Results

10.7.2.1 Study patients

Patient disposition

A total of 703 PAR patients were enrolled. Approximately ¾ of the patients completed the study. Ten percent of patients discontinued early due to an AE in the MP03-36 arm, compared to 6% in the Nasonex arm. The AEs cited included the following preferred terms: vertigo, eye irritation, retinal vein occlusion, dry mouth, lip dry, nausea, oral discomfort, fatigue (n=4), acute sinusitis, bronchitis, pneumonia primary atypical, sinusitis, upper respiratory tract infection, urinary tract infection, weight increased, increased appetite, arthralgia, dizziness, dysgeusia (n=5), headache, migraine, sedation (n=1), sinus headache, somnolence (n=3), anger, breathing-related sleep disorder, depression, dysphonia, epistaxis, nasal discomfort, nasal mucosal disorder, pharyngolaryngeal pain (n=3), postnasal drip, sneezing, snoring, throat irritation, and acne.

Table 88 Study MP436: Patient disposition		
Disposition	**MP03-36**	**Nasonex**
Randomized	466	237
Completed (%)	329 (71)	194 (82)
Discontinued	176 (38)	59 (25)
Adverse event	54 (11)	17 (7)
Abnormal test result	-	-
Treatment failure	18 (4)	7 (3)
Non-compliance	15 (3)	5 (2)
Withdrew consent	47 (10)	11 (5)
Lost to follow-up	28 (6)	14 (6)
Administrative problems	-	-
Other	14 (3)	5 (2)
ITT[a]	455 (98)	232 (98)
Safety population[b]	466 (100)	237 (100)

[a] All patients who were randomized and had at least one post-baseline observation.
[b] All randomized patients who received at least one dose of study medication.
Source: Module 5, Vol 102, Section 10.1, Table 4 and 4-month safety update (dated December 22, 2008)

Reviewer's comment: Overall, fewer patients in the MP03-36 arm completed the study. There was not an excess number of patients who discontinued early due to treatment failure. However, more patients in the MP03-36 group discontinued early secondary to an adverse event or withdrew consent.

10.7.2.2 Protocol deviations
The most common protocol violations were patients who had <75% compliance with study medication. Overall, there were similar rates of non-compliance between the two treatment groups.

10.7.2.3 Treatment compliance
Based on completion of patient diaries, 42% of the MP03-36 arm and 35% of the Nasonex arm were >75% compliant with study medication. Sixty-eight percent and 63%, respectively, were >50% compliant during the 6-month treatment period.

Compliance was also assessed using the RQLQ data, which indicated improvement from baseline for both treatment arms (Table 90).

10.7.2.4 Datasets analyzed
- Intent to treat population: All patients with at least one post-baseline efficacy observation.
- Safety population: All patients who received at least 1 dose of study drug.

10.7.2.5 Demographics and baseline characteristics

Table 89 Study MP436: Patient demographics and baseline characteristics			
Variables	**MP03-36 N=465**	**Nasonex N=238**	**Total N=703**
Age (Mean, Range)	39 (12-84)	39 (12-72)	39 (12-84)
Gender (male, %)	158 (34)	62 (26)	220 (31)
Race			
Caucasian	359 (77)	192 (81)	552 (78)
Black	66 (14)	29 (12)	95 (14)
Asian	15 (3)	6 (3)	21 (3)
Native American	0	0	0
Native Hawaiian or Pacific Islander	4 (1)	1 (0.4)	5 (1)
Other	21 (5)	9 (4)	30 (4)
Total score			
Mean, SD	12.5 (5.6)	12.1 (5.6)	12.4 (5.6)
Range	0.4-24.0	1.8-24.0	0.4-24.0
Duration of PAR (yrs)			
Mean, SD	20 (15)	19 (14)	20 (14)
Range	0-70	0-59	0-70

Source: Module 5, Volume 102, Section 11.2.1, Table 5

10.7.2.6 Efficacy endpoint outcomes

In terms of the overall RQLQ, both MP03-36 and Nasonex demonstrated improvement from baseline. In all of RQLQ components, (activity, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional), Nasonex was numerically superior to MP03-36 (p=0.06 to 0.18).

Table 90 Study MP436: RQLQ						
	N	**Baseline (SD)**	**N**	**Change from baseline (SD)**	**P-value vs baseline**	**P-value vs Nasonex**
Overall RQLQ						
MP03-36	333	3.0 (1.2)	230	-1.3 (1.2)	<0.001	0.06
Nasonex	174	3.0 (1.2)	143	-1.5 (1.3)	<0.001	
Activity						
MP03-36	337	3.8 (1.5)	235	-1.9 (1.7)	<0.001	0.12
Nasonex	174	3.8 (1.5)	144	-2.1 (1.8)	<0.001	
Sleep						
MP03-36	337	2.9 (1.5)	237	-1.2 (1.5)	<0.001	0.62
Nasonex	174	2.7 (1.5)	147	-1.3 (1.7)	<0.001	
Non-nose/eye sx						
MP03-36	336	2.8 (1.4)	237	-1.1 (1.3)	<0.001	0.11
Nasonex	174	2.7 (1.4)	146	-1.3 (1.4)	<0.001	
Practical problems						
MP03-36	336	3.5 (1.6)	236	-1.6 (1.5)	<0.001	0.18
Nasonex	174	3.5 (1.5)	146	-1.8 (1/8)	<0.001	
Nasal symptoms						
MP03-36	336	3.5 (1.3)	235	-1.4 (1.4)	<0.001	0.07
Nasonex	174	3.5 (1.3)	146	-1.6 (1.6)	<0.001	
Eye symptoms						
MP03-36	336	2.7 (1.6)	235	-1.2 (1.6)	<0.001	0.06
Nasonex	174	2.7 (1.5)	146	-1.5 (1.6)	<0.001	
Emotional						
MP03-36	336	2.7 (1.5)	235	-1.3 (1.5)	<0.001	0.07
Nasonex	174	2.7 (1.4)	146	-1.5 (1.5)	<0.001	

Source: Module 5, Volume 102, Section 11.4.1, Table 6

10.7.2.7 Safety outcomes

Deaths and SAEs

No deaths were reported in Study MP436. No cases of nasal ulceration or septal perforation were reported. Five SAEs in 5 patients were reported in the MP03-36 group: acute appendicitis, acute exacerbation of chronic bronchitis secondary to toxic fume injury (gas leakage), angina pectoris, and dyspnea. Two SAEs in 2 patients were reported in the Nasonex group: cystocele surgery and abdominal wall cellulitis.

Reviewer's comment: The diffuse nature of the SAEs makes it difficult to draw conclusions about cause and effect, although given the known mechanism of action of MP03-36 and the pharmacokinetics, a causal relationship seems unlikely.

Common adverse events

The frequency and nature of adverse events reported in Study MP436 were generally consistent with the known safety profile of intranasal azelastine (Table 91). The most common adverse events were dysgeusia, sinusitis, epistaxis, upper respiratory tract infection, headache, and pharyngolaryngeal pain. Fatigue and somnolence occurred at a rate of 4.1% and 3.6%, respectively. These rates were higher than those observed for the Nasonex (0.8% and 0.4%), which is an intranasal corticosteroid and not expected to cause sedation like an antihistamine.

Table 91 Study MP436: Adverse events occurring in 1% or more of the safety population

Preferred term	MP03-36 N=466 N, %	Nasonex N=237 N, %
Any AE	349 (74.9)	163 (68.8)
Dysgeusia	62 (13.3)	3 (1.3)
Sinusitis	44 (9.4)	19 (8.0)
Epistaxis	43 (9.2)	24 (10.1)
Upper respiratory tract infection	43 (9.2)	20 (8.4)
Nasopharyngitis	43 (9.2)	20 (8.4)
Headache	41 (8.8)	30 (12.7)
Pharyngolaryngeal pain	22 (4.7)	14 (5.9)
Bronchitis	19 (4.1)	6 (2.5)
Fatigue	19 (4.1)	2 (0.8)
Somnolence	17 (3.6)	1 (0.4)
Back pain	16 (3.4)	5 (2.1)
Sinus headache	15 (3.2)	4 (1.7)
Cough	15 (3.2)	12 (5.1)
Influenza	15 (3.2)	9 (3.8)
Sneezing	14 (3.0)	-
Mucosal erosion	13 (2.8)	6 (2.5)
Rhinitis allergic	11 (2.4)	4 (1.7)
Nausea	9 (1.9)	5 (2.1)
Ear pain	8 (1.7)	5 (2.1)
Dry mouth	8 (1.7)	1 (0.4)
Hypersensitivity	8 (1.7)	1 (0.4)
Gastroenteritis viral	8 (1.7)	10 (4.2)
Pharyngitis streptococcal	8 (1.7)	1 (0.4)
Insomnia	8 (1.7)	4 (1.7)
Urinary tract infection	7 (1.5)	9 (3.8)
Neck pain	7 (1.5)	3 (1.3)
Nasal congestion	6 (1.3)	5 (2.1)
Nasal dryness	6 (1.3)	6 (2.5)
Vomiting	5 (1.1)	3 (1.3)
Pyrexia	5 (1.1)	8 (3.4)
Ear infection	5 (1.1)	6 (2.5)
Viral infection	5 (1.1)	4 (1.7)
Viral upper respiratory tract infection	4 (0.9)	7 (3.0)
Dizziness	4 (0.9)	5 (2.1)
Acute sinusitis	3 (0.6)	5 (2.1)

Source: 4-month safety update, submission dated December 22, 2008

Laboratory assessments

Hematology

Changes in mean hematology parameters

No clinically relevant changes in mean hematology parameters were reported at 6-month follow-up (Table 32). Patients who discontinued early from the study had negligible mean changes as well.

Table 92 Study MP436: Changes in mean hematology parameters at 6-month follow-up

Indices	MP03-36 N=465		Nasonex N=238	
	Baseline	6-month visit	Baseline	Change from baseline
Hematocrit (%)				
N	321	321	166	191
Mean (SD)	41.6 (3.9)	41.3 (3.6)	41.5 (3.6)	41.3 (3.6)
Min-Max	26-55	32-51	32-52	34-54
Hemoglobin (g/dl)				
N	321	321	166	191
Mean (SD)	13.9 (1.4)	13.7 (1.2)	13.8 (1.3)	13.7 (1.3)
Min-Max	7-18	10-17	10-17	11-18
RBC (10^6/mcl)				
N	321	321	166	191
Mean (SD)	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)	4.5 (0.5)
Min-Max	3-6	3-6	4-6	4-6
WBC (10^3/mcl)				
N	321	321	166	191
Mean (SD)	6.7 (1.8)	6.5 (1.8)	6.5 (1.7)	6.6 (2.0)
Min-Max	3-15	3-13	2-12	2-13
Lymphocytes (%)				
N	321	321	166	191
Mean (SD)	31.0 (7.4=9)	31.3 (7.4)	31.1 (8.5)	30.1 (7.8)
Min-Max	12-67	313-57	11-61	14-57
Monocytes (%)				
N	321	321	166	191
Mean (SD)	6.2 (2.1)	6.1 (2.1)	6 (1.9)	6.1 (2.3)
Min-Max	2-17	1-20	2-13	0-15
Neutrophils (%)				
N	321	321	166	191
Mean (SD)	59.4 (9.0)	59.3 (8.4)	59.8 (9.3)	60.9 (8.9)
Min-Max	25-80	32-85	29-83	34-81
Basophils (%)				
N	321	321	166	191
Mean (SD)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)
Min-Max	0-1	0-2	0-1	0-1
Eosinophils (%)				
N	312	321	166	191
Mean (SD)	2.8 (2.6)	2.8 (2.4)	2.7 (2.2)	2.6 (2.7)
Min-Max	0-21	0-19	0-14	0-28
Platelets (10^3/mcl)				
N	318	315	166	187
Mean (SD)	274 (61)	275 (58)	274 (62)	274 (69)
Min-Max	131-450	125-453	121-524	113-581

Source: Module 5, Volume 102, Table 14.3.5.1.1

Outliers and shifts from normal to abnormal

The majority of hematology values stayed within the normal reference range for all hematology indices. No consistent patterns or clinically relevant shifts from normal to abnormal were observed for MP03-36 in comparison to the active comparator, Nasonex.

Table 93 Study MP436: Shifts from normal to abnormal hematology parameters

Indices	MP03-36 N=465 N, %		Nasonex N=238 N, %	
	Normal → Low	Normal → High	Normal → Low	Normal → High
Hematocrit	-	5 (2.3)	1 (0.7)	4 (3.0)
Hemoglobin	-	-	4 (3.0)	1 (0.7)
RBC	-	4 (1.9)	1 (0.7)	3 (2.2)

WBC	2 (0.9)	5 (2.3)	3 (2.2)	5 (3.7)
Lymphocytes	1 (0.5)	3 (1.4)	2 (1.5)	-
Neutrophils	3 (1.4)	10 (4.7)	1 (0.7)	9 (6.7)
Monocytes	16 (7.5)	2 (0.9)	15 (11.1)	4 (3.0)
Basophils	-	4 (1.9)	-	-
Eosinophils	-	7 (3.3)	-	3 (2.2)

Source: Module 5, Volume 102, Table 14.3.5.1.2

Outliers and shifts from normal to abnormal

The majority of laboratory values stayed within the normal reference range for all hematology indices. Overall, no consistent patterns or clinically relevant shifts from normal to abnormal were observed for MP03-36. However, there were an increased number of patients with shifts from normal to high for both CK and AST levels. The majority of CK elevations were slight increases over the upper limit and not clinically relevant. A few patients had more marked elevations and these are discussed in the next section. Five patients had AST elevations that were between 1 and 1.5 x ULN; the remainder were < 1x ULN, and the majority with just out of range and not clinically relevant. Other hepatic indices, included ALT, alkaline phosphatase, total bilirubin, and total protein were not indicative of a consistent pattern of hepatic injury or decreased hepatic function.

Table 94 Study MP436: Shifts from normal to abnormal laboratory parameters

Indices	MP03-36 N=465 N, %		Nasonex N=238 N, %	
	Normal → Low	Normal → High	Normal → Low	Normal → High
Albumin	-	-	-	-
Alkaline phosphatase	-	1 (0.5)	-	-
Total bilirubin	-	3 (1.4)	-	1 (0.7)
BUN	-	1 (0.5)	-	4 (2.9)
Calcium	-	-	-	-
Chloride	-	-	-	-
CK	-	15 (6.9)	1 (0.7)	5 (3.6)
Creatinine	-	11 (5.1)	-	6 (4.4)
Glucose	15 (7.2)	2 (1.0)	7 (5.1)	5 (3.7)
AST	-	15 (6.9)	-	3 (2.2)
ALT	-	12 (5.6)	-	7 (5.1)
Potassium	1 (0.5)	5 (2.3)	-	4 (2.9)
Sodium	-	-	-	1 (0.7)
Total protein	1 (0.5)	-	1 (0.7)	-
Uric acid	2 (0.9)	8 (3.7)	2 (1.5)	3 (2.2)

Source: Module 5, Volume 102, Table 14.3.5.2.2

No clinically relevant changes in mean laboratory parameters were reported at 6-month follow-up (Table 95). Patients who discontinued early from the study had negligible mean changes as well.

Table 95 Study MP436: Changes in mean laboratory parameters at 6-month follow-up

Indices	MP03-36 N=465		Nasonex N=238	
	Baseline	6-month visit	Baseline	6-month visit
Albumin (g/dl)				

N	321	323	166	194
Mean (SD)	4.4 (0.3)	4.3 (0.3)	4.4 (0.3)	4.4 (0.3)
Min-Max	4-5	4-5	4-5	4-5
Alk phosphatase (U/L)				
N	321	323	165	194
Mean (SD)	86.2 (51.2)	78.8 (41.3)	81.5 (37.0)	79.4 (34.5)
Min-Max	23-438	31-436	37-327	34-283
Total bilirubin (mg/dl)				
N	321	322	166	194
Mean (SD)	0.4 (0.2)	0.4 (0.2)	0.4 (0.3)	0.4 (0.3)
Min-Max	0-2	0-1	0-2	0-2
BUN (mg/dl)				
N	321	323	166	194
Mean (SD)	13.5 (4.0)	13.8 (3.9)	13.3 (3.9)	13.6 (3.8)
Min-Max	6-36	7-44	6-28	7-26
Calcium (mEq/L)				
N	321	323	165	194
Mean (SD)	4.8 (0.2)	4.7 (0.2)	4.8 (0.2)	4.7 (0.2)
Min-Max	4-5	4-5	4-6	4-5
Chloride (mEq/L)				
N	321	323	166	194
Mean (SD)	103 (3)	103 (2)	103 (2)	103 (3)
Min-Max	88-111	93-110	95-111	96-110
CK (U/L)				
N	321	323	166	194
Mean (SD)	138 (125)	156 (388)	130 (116)	142 (358)
Min-Max	19-1034	28-6757	32-963	25-4964
Creatinine (mg/dl)				
N	321	323	166	194
Mean (SD)	0.9 (0.2)	0.9 (0.2)	0.8 (0.2)	0.9 (0.2)
Min-Max	1-2	0-2	1-1	1-1
Glucose (mg/dl)				
N	319	316	166	192
Mean (SD)	90 (20)	91 (22)	87 (15)	93 (24)
Min-Max	52-216	53-231	49-157	43-246
AST (U/L)				
N	321	323	166	194
Mean (SD)	22 (8)	22 (10)	21 (8)	21 (8)
Min-Max	9-65	11-135	11-70	8-75
ALT (U/L)				
N	321	323	166	194
Mean (SD)	23 (15)	23 (14)	23 (17)	21 (12)
Min-Max	4-147	5-90	7-182	4-97
Potassium (mEq/L)				
N	321	323	165	194
Mean (SD)	4.3 (0.4)	4.2 (0.4)	4.3 (0.4)	4.2 (0.4)
Min-Max	3-6	3-6	3-6	3-6
Sodium (mEq/L)				
N	321	323	165	194
Mean (SD)	140 (2)	140 (2)	140 (2)	140 (2)
Min-Max	127-146	129-145	134-147	134-147
Total protein (g/dl)				
N	321	323	166	194
Mean (SD)	7.3 (0.5)	7.2 (0.4)	7.3 (0.5)	7.1 (0.4)
Min-Max	5-9	6-8	6-9	6-8
Uric acid (mg/100ml)				
N	321	323	166	194
Mean (SD)	5 (1.4)	4.9 (1.4)	4.9 (1.4)	4.7 (1.3)
Min-Max	2-10	1-11	2-9	1-9

Source: Module 5, Volume 102, Table 14.3.5.2.1

In Study MP436, 1 patient (066-005) in the MP03-36 arm discontinued due to an elevated ALT. At screening, the patient had an ALT slightly out of range (42 U/L, normal range 1-39). At the 6-month lab screening, the ALT was elevated at 74 U/L. At follow-up 2 weeks later, the ALT

had risen further to 118 U/L. Further follow-up on the patient is not available. This patient was reported in the December 22, 2008, safety update as a discontinuation due to an adverse event, not as an abnormal test result.

In addition to early discontinuations, the following individual marked outliers who received MP03-36 in Study MP436 were noted:

- Patient 021-004 had an elevated CK level of 1009 U/L at the 6-month visit. Follow-up not available.
- Patient 063-004 had an elevated CK level of 6757 U/L at the 6-month visit. Follow-up not available.

Reviewer's comment: Although a causal relationship cannot be ruled out, given the limited systemic exposure of MP03-36 and the known pharmacology of the drug, the cases of transaminitis and CK elevation appear unlikely to be related to MP03-36.

10.7.3 Study summary and conclusions

Study MP436 provides evidence of safety for chronic use of MP03-36. Although no placebo arm was included, the nature and frequency of adverse events were similar to those reported in the Astepro 0.1% and Astelin registration trials. Although the validity of cross-study comparisons is somewhat limited, there did not appear to be a dose-related association to the observed adverse effects. In comparison to the active comparator, Nasonex, certain adverse events occurred at a notably higher rate, namely dysgeusia and somnolence, which are known toxicities associated with intranasal azelastine.

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/s/

Susan L Limb
4/1/2009 08:18:22 AM
MEDICAL OFFICER

Sally Seymour
4/1/2009 08:55:10 AM
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I concur.