CLINICAL REVIEW

Application Type	NDA
Submission Number	22-371
Submission Code	N000
Letter Date	August 1, 2008
Major Amendment Date	April 29, 2009
PDUFA Goal Date	September 1, 2009
Reviewer Name	Susan Limb, MD
Review Completion Date	July 15, 2009
Established Name	Azelastine hydrochloride
(Proposed) Trade Name	Astepro® Nasal Spray 0.15%
Therapeutic Class	Intranasal antihistamine
Applicant	MEDA
Priority Designation	S
Formulation	Intranasal solution
Dosing Regimen	1 or 2 sprays each nostril BID 2 sprays each nostril QD
Indications	Seasonal allergic rhinitis Perennial allergic rhinitis
Intended Population	Patients 12 years of age and older

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1 Executive Summary

The clinical recommendation for this application is Approval. The application contains adequate evidence to support the proposed indication for MP03-36 (sweetened 0.15% azelastine hydrochloride intranasal 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 the following indications and dosing regimens:

- 1 or 2 sprays BID for the SAR indication in patients 12 years of age and older
- 2 sprays QD for the SAR indication in patients 12 years of age and older
- 2 sprays BID for the PAR indication in patients 12 years of age and older.

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 currently carries a PAR indication, and the Applicant is not seeking a VMR indication for MP03-36.

The NDA was initially submitted on August 1, 2008, with a PDUFA date of June 1, 2009; however, a major amendment to the NDA was submitted on April 29, 2009, and the PDUFA clock was extended by 3 months. A clinical review of the original NDA submission was completed on April 1, 2009. The clinical recommendation for the original application was approval with the exception that the once daily dosing regimen in patients with SAR was not supported. In the major amendment, the Applicant submitted the results of an additional clinical trial (Study MP443) as support for the once daily dosing regimen. The clinical development program included 5 clinical trials in patients with SAR (Studies MP433, MP438, MP439, MP440, and MP443) and 3 clinical trials in patients with PAR (Studies MP434, MP435, and MP436) as shown in Table 1. Study MP443 was submitted as part of the major amendment dated April 29, 2009, and is reviewed in detail in Section 3. A review of the other individual trials as well as a more complete discussion of the risk:benefit assessment, other safety data, and the proposed pediatric plan can be found in the Medical Officer review dated April 1, 2009.

SAR indication
Twice daily dosing regimen

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. A summary of the major efficacy findings for the clinical program can be found in the tables located in Section 2 with details in the Medical Officer review dated April 1, 2009 and Section 3 of this review. The primary support for the twice-daily SAR indication comes from Studies MP433 and MP438, two 2-week, randomized, placebo-controlled, double-blind trials. Each trial 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) (**Table 2**). Secondary endpoints were also supportive of efficacy. Support for the twice daily dosing interval comes from the results of the secondary endpoint, mean change from baseline combined AM and PM Instantaneous Total Nasal Symptom Score (iTNSS) (**Table 4**). Of these two studies, only Study MP438 demonstrated a statistically significant difference from placebo for the AM iTNSS; however, further support for the twice-daily dosing interval is obtained from the PAR trial, Study MP434 (**Table 6**), which is discussed below. 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 SAR findings is not required. Each trial also included an active comparator: Astelin in MP433 and Astepro in MP438. In each trial 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.

Once daily dosing regimen

Studies MP439 and MP440 were clinical trials in patients with SAR which were intended to demonstrate the efficacy of a 2 sprays once daily dose. The primary endpoint used in these two trials was the same endpoint used in the other SAR trials, the change from baseline in combined AM and PM rTNSS, and these results were statistically significant over placebo (**Table 2**). However, a key secondary endpoint was the mean change from baseline in AM iTNSS, which was intended to assess the efficacy of MP03-36 at the dose trough and demonstrate the adequacy of the proposed dosing interval (**Table 3**). 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 but in the absence of replication, the efficacy of the once-daily dosing interval was not confirmed. Comments regarding the lack of replication to support the once daily dosing regimen were conveyed in the 74-day filing letter dated October 14, 2008. The Applicant subsequently submitted a major amendment dated April 29, 2009, which contained the results of an additional clinical trial in patients with SAR, MP443. Study MP443 was conducted in support of a once-daily dosing regimen and replicated the results of Study MP440, providing support for a 2 spray once-daily dosing regimen in patients with SAR with statistically significant rTNSS (**Table 2**) and AM iTNSS scores (**Table 3**). However, it is worth noting that both Studies MP440 and MP443 were 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; a more heterogeneous SAR patient population may not experience such a robust effect.

One spray dose

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. Neither Astelin nor Astepro have a 1 spray once daily dose approved, so there is no data to support a 1 spray once daily regimen.

PAR indication

The primary support for the PAR indication comes from Study MP434, a 4-week, randomized, placebo-controlled, double-blind trial 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 (**Table 5**). Secondary endpoints, including the combined AM and PM iTNSS which demonstrated the adequacy of the twice-daily dosing regimen, were also supportive of efficacy (**Table 6**). As mentioned above, one PAR and one SAR trial can support both indications; therefore, replication of the PAR findings is not required. Study MP435 was a PAR trial intended to support a once daily dose, but this trial 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. Furthermore, 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. Study MP436 was an open-label, active-controlled, long-term safety study and contained minimal efficacy data.

Safety

The safety of MP03-36 in SAR and PAR patients 12 years of age and older is supported by the submitted clinical trial 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 trials, as well as long-term safety data from an open-label, active-controlled trial 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. Refer to the Medical Officer review dated April 1, 2009 for a detailed review of the safety in original NDA. The additional safety data from the clinical trial submitted in the major amendment (Study MP443) did not suggest any new safety signal.

In summary, the application provides adequate support for the SAR indication (1 or 2 sprays twice daily and 2 sprays twice daily) and the PAR indication (2 sprays twice daily) in patients 12 years of age and older for MP03-36. 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; 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 2 sprays once daily; and 3) 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.

2 Summary Tables

Table 1 shows the clinical development program for MP03-36. Study MP443 was submitted on April 29, 2009, and was considered a major amendment. Review of the original NDA can be found in the Medical Officer review dated April 1, 2009. Study MP443 is reviewed in detail in Section 3.

Table 1 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)	R, DB, PC	2 sprays per nostril once daily: • MP03-36 • Placebo	2 weeks	• SAR trial for once-daily dose
MP443	505 ≥12 yrs (mountain cedar)	R, DV, 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

Table 2 shows the primary efficacy results for the clinical trials in patients with SAR.

Table 2 Primary efficacy results for SAR trials: 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	18.6	-3.9	-0.9	0.08	-1.7, 0.1
MP03-36 BID	153	18.2	-4.3	-1.3	0.01	-2.1, -0.3
Astelin BID	153	17.9	-3.9	-0.9	0.07	-1.8, 0.1
Placebo BID	153	18.1	-3.0			
MP03-36 vs. Astelin‡				-0.4	0.45‡	-1.27, 0.57 ‡
MP438						
MP03-36 BID	177	17.7	-5.1	-3.0	<0.001	-3.9, -2.1
Astepro 0.1% BID	169	18.2	-4.2	-2.1	<0.001	-3.0, -1.2
Placebo BID	177	17.7	-2.1			
MP03-36 vs. MP03-33‡					0.06‡	-1.82, 0.02 ‡
MP439						
MP03-36 QAM	238	17.4	-3.4	-1.0	0.008	-1.7, -0.3
Placebo QAM	242	17.4	-2.4			
MP440						
MP03-36 QAM	266	18.5	-3.3	-1.4	<0.001	-2.1, -0.8
Placebo QAM	266	18.0	-1.9			
MP443						
MP03-36 QAM	251	18.5	-3.4	-1.4	<0.001	-2.1, -0.7
Placebo QAM	254	18.8	-2.0			

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

Table 3 shows the results for AM iTNSS in the once daily clinical trials in patients with SAR.

Table 3 Once-daily SAR trials: The change from baseline for AM iTNSS

Study Treatment groups	N	LE mean baseline	Mean change from baseline	Treatment difference from placebo	P-value vs placebo	95% CI†
MP439						
MP03-36 QAM	238	8.1	-1.3	-0.2	0.15	-0.6, 0.1
Placebo QAM	242	8.3	-1.1			
MP440						
MP03-36 QAM	266	8.7	-1.4	-0.7	<0.001	-1.0, -0.4
Placebo QAM	266	8.3	-0.7			
MP443						
MP03-36 QAM	251	8.9	-1.4	-0.6	<0.001	-0.9, -0.3
Placebo QAM	254	8.9	-0.8			

* 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.
† 95% confidence interval for active minus placebo treatment difference

Table 4 shows the results for combined AM and PM iTNSS in the twice daily clinical trials in patients with SAR.

Table 4 Twice daily SAR trials: The change from baseline for combined AM and PM iTNSS

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	18.0	-3.4	-0.4	0.49	-1.3, 0.6
MP03-36 BID	153	17.3	-3.7	-0.7	0.14	-1.7, 0.3
Astelin BID	153	17.1	-3.9	-0.9	0.08	-1.8, 0.1
Placebo BID	153	17.2	-3.0			
MP03-36 vs. Astelin‡				0.2	0.75‡	-0.8, 1.1 ‡
MP438						
MP03-36 BID	177	16.3	-4.2	-2.6	<0.001	-3.5, -1.7
Astepro 0.1% BID	169	16.3	-3.4	-1.8	<0.001	-2.7, -0.9
Placebo BID	177	16.4	-1.6			
MP03-36 vs. MP03-33‡					0.09‡	-1.7, 0.1 ‡

* 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.
† 95% confidence interval for active minus placebo treatment difference
‡ MP03-36 vs. active comparator post-hoc analysis performed by Agency

Table 5 shows the primary efficacy results in the clinical trials in patients with PAR.

Table 5 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	15.8	-4.0	-0.9	0.03	-1.7, -0.07
Astepro 0.1% BID	194	15.5	-3.8	-0.7	0.08	-1.5, 0.09
Placebo BID	192	14.7	-3.1			
MP435						
MP03-36 QAM	53	15.2	-4.9	-1.2	0.30	-3.5, 1.1
MP03-36 QPM	50	15.1	-3.9	-0.9	0.42	-3.0, 1.3
Placebo QAM	23	15.2	-3.7			
Placebo QPM	27	14.3	-3.0			

* 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.

Table 6 shows the results for combined AM and PM iTNSS in Study MP434 in patients with PAR. The results for Study MP435 are not shown because the primary endpoint failed to show a statistical significance compared to placebo.

Table 6 Twice daily PAR trial: Change from baseline in combined AM and PM iTNSS*

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	14.3	-3.4	-0.9	0.03	-1.6, -0.1
Astepro 0.1% BID	194	13.9	-3.3	-0.8	0.045	-1.6, -0.02
Placebo BID	192	13.3	-2.5			
MP03-36 vs. Astepro 0.1%‡				-0.1	0.86‡	-0.8, 0.7‡

* 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.
‡ MP03-36 vs. active comparator post-hoc analysis performed by Agency

3 Individual Study Report: Study MP443

3.1 Study Protocol: MP443

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 30, 2008
- Study completion date: February 13, 2009
- Study report date: April 24, 2009
- Location: 7 study sites in the US

Objectives/Rationale

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

Study design overview

MP443 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. Tolerability was assessed by adverse events, focused nasal examinations, and vital signs assessments.

Study population

506 patients (251 in the MP03-36 arm; 255 in the placebo arm) 12 years of age and older with a minimum 2-year history of allergy to Texas mountain cedar pollen with a positive skin test during the previous year were enrolled.

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 (Visit 1)
- Randomization visit:

    - Have a 12-hour rTNSS ≥8 on 3 separate assessments (1 of which was within 2 days of Day 1/Visit 2 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

- Presence of nasal mucosal erosion, nasal ulceration, or septal perforation (Grades 1b to 4) at either the screening or randomization visit
- Use of any investigational drug within 30 days prior to Visit 1
- 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 14 days prior to Visit 1
- Respiratory tract infection requiring oral antibiotics within 2 weeks prior to Visit 1
- 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
- Clinical significant arrhythmia or symptomatic cardiac condition
- Known history of drug or alcohol abuse within last 2 years
- Surgical or medical condition which may alter pharmacokinetics of study drug
- Clinically relevant abnormal physical findings within 1 week of randomization that may interfere with the objectives of the study or preclude compliance, per investigator's judgment
- Planned travel outside the study area during the study period
- Participation in Studies MP439 or MP440

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.

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. Patients were randomized to active treatment of placebo in a 1:1 ratio.

Blinding

MP03-36 and placebo were supplied in 30 cc HDPE metered-dose nasal spray bottles were masked to disguise the drug's identity. Additional space for subject identification information and date dispensed was provided.

Administration

At Visit 1, patients received a 7-day supply of placebo nasal spray. Patients were observed taking the initial dose of placebo spray to ensure proper technique. At Visit 2, patients received a 14-day supply of study drug nasal spray. Unused medication was returned at Visit 3 and Visit 4 for compliance assessment.

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.

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 or a serious systemic infection, and SLIT were prohibited. Immunotherapy was permitted if a stable maintenance regimen had been reached at least 30 days prior to Visit 1. The medications listed in Table 7 were not permitted during the study period and required the specified washout periods prior to Visit 1.

Table 7 Study MP443: Medications prohibited during treatment period
Antihistamines (OTC and prescription, including ophthalmic)
Cromolyn compounds
Intranasal therapies, including intranasal saline
Oral and intranasal anticholinergic agents
Leukotriene inhibitors
Corticosteroids (oral, topical, inhaled)
All eye drops (prescription and OTC)
Ephedrine or pseudoephedrine
Decongestants including cold preparations
Tricyclic antidepressants
Monoamine oxidase inhibitors
Immunosuppressives/immunomodulators
IgE antagonist
Radiation therapy

Assessments and evaluations

Table 8 shows the schedule of assessments and evaluations performed in Study MP443.

Table 8 Study MP443: Assessments and evaluations

Procedure	Lead-in period	Treatment period		
	Visit 1 Day -7 Screening	Visit 2 Day 1 Randomization	Visit 3 Day 7	Visit 4 Day 14 or early termination
TNSS qualification	X	X		
Inclusion/exclusion criteria	X	X		
Skin test[a]	X			
Physical exam/history	X			
Nasal exam	X	X	X	X
Vital signs[b]	X	X	X	X
Urine pregnancy test	X	X		X
Patient instruction	X	X	X	
Dispense placebo lead-in meds	X			
Dispense TNSS diary	X	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

[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 at Visit 2 to subjects 18 years and older

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 rTNSS 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 12-hr rTNSS individual symptom scores
- Daily change from baseline in 12hr rTNSS and iTNSS
- Change from baseline in 12hr rTOSS (Total Ocular Symptom Score) and iTOSS
    - Itchy eye, watery eye, red eye
- Change from baseline in 12h rTOSS individual symptoms
- Change from baseline in 12h rPND (Post-Nasal Drip severity score) for the 14-day study period
- Change from baseline Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) in subjects 18 years and older
    - 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, emotional)
    - Each domain rated on a 7-point scale with 0 being not troubled by rhinitis during the past week and 6 being extremely troubled/all of the time

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. Nasal irritation was graded on the following scale:

- 0 = no abnormal findings
- Grade 1A = focal nasal mucosal inflammation, erythema, or hyperemia
- Grade 1B = superficial nasal mucosal erosion
- Grade 2 = moderate nasal mucosal erosion
- Grade 3 = nasal mucosal ulceration
- Grade 4 = nasal septum perforation

Epistaxis was also categorized as none, mild, moderate, and severe.

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.

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 post-baseline TNSS was missing, the last non-missing post-baseline 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.

3.2 Results

Protocol amendments

- Amendment 1 (December 17, 2008) – Criteria for recording AEs was corrected to any that occurred after signing of informed consent instead of post-dosing of lead-in medication. Additional minor corrections were made in the medically acceptable forms of contraception.

Study patients

A total of 506 patients were randomized to double-blind treatment. A total of 478 (94.5%) subjects completed the study while 28 (5.5%) subjects discontinued early.

Table 9 Study MP443: Patient disposition

Disposition	MP03-36	Placebo	Total
Randomized	251	255	506
Completed	238 (94.8)	240 (94.1)	478 (94.5)
Discontinued	13 (5.2)	15 (5.9)	28 (5.5)
Adverse event	5 (2.0)	4 (1.6)	9 (1.8)
Abnormal test result	-	-	-
Treatment failure	2 (0.8)	2 (0.8)	4 (0.8)
Non-compliance	2 (0.8)	4 (1.6)	6 (1.2)
Withdrew consent	3 (1.2)	2 (0.8)	5 (1.2)
Lost to follow-up	-	-	-
Protocol violations	-	2 (0.8)	2 (0.4)
Other	1 (0.4)	1 (0.4)	2 (0.4)
ITT[a]	251 (100)	254 (99.6)	505 (99.8)
Per protocol population[b]	237 (94.4)	238 (93.3)	475 (93.9)
Safety population[c]	251 (100.0)	255 (100.0)	506 (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: MP443 CSR, Section 10.1

Protocol deviations

One placebo patient had a protocol deviation which resulted in exclusion from the ITT population (no post-baseline efficacy evaluation available). Fourteen patients in the MP03-36 group and 16 patients in the placebo group had protocol violations which resulted in exclusion from the PP population. These violations were primarily due to failure to complete the study. One patient (302-074) in the MP03-36 arm was cited as being pregnant or lactating. A complete listing of the violations can be found in the Appendix 16.2.3.2 of the Applicant's complete study report.

Reviewer's comment: The protocol deviations are unlikely to have impacted the overall results and conclusions of Study MP443. The nature of the deviations and the total number in each treatment group were similar.

Treatment exposure and compliance

Table 10 Study MP443: Duration of exposure and compliance

	MP03-36 N=251	Placebo N=255
Duration (days)		
N	251	255
Mean	14.2	14.2
SD	1.7	1.9
Median	14.0	15.0
Range	3-17	1-17
Total number of doses		
N	251	255
Mean	14.1	14.1
SD	1.8	2.0
Median	14.0	14.0
Range	3-17	1-17
# Patients ≥80% compliance [N,%]	251 (100)	254 (99.6)

Source: MP443 CSR, Section 11.3, Table 7 and Section 12.1, Table 16

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.

Demographics and baseline characteristics

Table 11 Study MP443: Patient demographics and baseline characteristics

Variables	MP03-36 N=251	Placebo N=254
Age (Mean, Range)	38.0 (12-74)	38.5 (12-75)
Gender (male, %)	94 (37.5)	104 (40.9)
Race		
Caucasian	217 (86.5)	225 (88.6)
Black	28 (11.2)	29 (11.4)
Hispanic	82 (32.7)	99 (39.0)
Asian	2 (0.8)	-
Native American	1 (0.4)	-
Native Hawaiian or Pacific Islander	2 (0.8)	-
Other	1 (0.4)	-
Total score		
Mean, SD	18.5 (3.2)	18.8 (3.3)
Range	8-24	9-24
Duration of SAR (yrs)		
Mean, SD	17.7 (12.0)	18.7 (11.9)
Range	3-69	3-59

Source: MP443 CSR, Section 11.2.1, Table 6

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.

Efficacy endpoint outcomes

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

Table 12 Study MP443: Change from baseline combined (AM plus PM) 12-hour rTNSS[a]

Treatment	Baseline	Change from baseline	P-value vs placebo, 95% CI	Treatment difference from placebo
MP03-36 QD N=251	18.5	-3.4	<0.001 (-2.1, -0.7)	-1.4
Placebo QD N=254	18.8	-2.0		

[a] Based on ITT population

The values shown in the table are taken from the Agency's statistical re-analysis and vary slightly from the values presented in the Applicant's submission. The differences do no alter the conclusions of the review.

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 13 Study MP443: Change from baseline in AM iTNSS[a]

Treatment	Baseline	Change from baseline	P-value vs placebo, 95% CI	Difference from placebo
MP03-36 QD N=251	8.9	-1.4	<0.001 (-0.9, -0.3)	-0.6
Placebo QD N=254	8.9	-0.8		

[a] Based on ITT population
The values shown in the table are taken from the Agency's statistical re-analysis and vary slightly from the values presented in the Applicant's submission. The differences do no alter the conclusions of the review.

Table 14 Study MP443 Change from baseline combined (AM plus PM) iTNSS[a]

Treatment	Baseline	Change from baseline	P-value vs placebo, 95% CI	Difference from placebo
MP03-36 QD N=251	17.4	-3.0	<0.001 (-2.0, -0.7)	-1.4
Placebo QD N=254	17.6	-1.6		

[a] Based on ITT population
The values shown in the table are taken from the Agency's statistical re-analysis and vary slightly from the values presented in the Applicant's submission. The differences do no alter the conclusions of the review.

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

Individual nasal symptom scores

Table 15 Study MP443: 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	Difference from placebo	P-value vs placebo[b], 95% CI
Itchy Nose	MP03-36	4.5 (1.1)	-0.9	-0.4	<0.001
	Placebo	4.6 (1.1)	-0.5		
Runny nose	MP03-36	4.7 (1.0)	-1.0	-0.5	<0.001
	Placebo	4.7 (1.1)	-0.5		
Sneezing	MP03-36	4.2 (1.2)	-1.0	-0.4	<0.001
	Placebo	4.3 (1.1)	-0.6		
Congestion	MP03-36	5.1 (0.9)	-0.8	-0.3	0.004
	Placebo	5.1 (0.8)	-0.5		

[a] Least-square mean and standard deviation
[b] P-value calculated from repeated measures ANCOVA model and baseline as a covariate.
Source: MP443 CSR Section 11.4.1.2, Table 11

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 statistically superior to placebo for daily change from baseline rTNSS on Days 2 through 14 ($p \leq 0.01$) and for daily change from baseline AM and combined iTNSS on Days 2 to 14 ($p \leq 0.01$).

Reflective and instantaneous TOSS

The rTOSS (itchy eyes, watery eyes, red eyes) showed statistically significant improvement from baseline for MP03-36 over placebo (-2.2 vs. -1.3; $p<0.001$) at the end of the 2-week treatment period. The treatment difference was -1.1. For the individual ocular symptoms, the rTNSS scores were also statistically significant ($p \leq 0.004$).

The change in combined iTOSS from baseline was also statistically significant from MP03-36 compared to placebo (-2.0 vs. -1.1; $p<0.001$; treatment difference = -0.9).

Reflective PND

The change from baseline rPND was statistically significant for MP03-36 compared to placebo (-0.7 vs. -0.4; $p=0.002$; treatment difference =-0.3).

RQLQ change from baseline

The overall RQLQ score and the RQLQ scores for each of the individual domains were improved from baseline in MP03-36 group compared to placebo ($p<0.001$ and $p \leq 0.014$, respectively). However, the treatment difference for the overall score was 0.38 (-1.12 vs -0.74), which is less than the generally accepted MCID of 0.5. For the individual domains, the treatment difference ranged from 0.28 to 0.5.

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

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
Five patients in the MP03-36 arm withdrew secondary to an AE, compared to 4 patients in the placebo group. The AEs cited at the time of discontinuation included: 1) nasal discomfort and sneezing; 2) bronchitis; 3) hypertension (BP 146/97 → 148/110 mmHg); 4) eye allergy; and 5) influenza. In the placebo group, the discontinuations were secondary to two cases of sinusitis, one case of nasal mucosal disorder and epistaxis, and one patient reported asthma, eczema, bronchitis, and sinusitis.

Reviewer's comment: The AEs cited as reasons for discontinuation do not raise any new safety concerns.

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 and MP03-36 observed in the other clinical trials. No cases of sedation, somnolence, or fatigue were reported in the study. The most commonly occurring AEs are summarized in the table below.

Table 16 Study MP443: Adverse events occurring in ≥1% MP03-36 treatment group

Preferred Term [N(%)]	MP03-36 (N=251)	Placebo (N=255)
Any AE	43 (17.1)	28 (11.0)
Nasal discomfort	9 (3.6)	-
Dysgeusia	6 (2.4)	2 (0.8)
Headache	5 (2.0)	-
Sneezing	5 (2.0)	-
Epistaxis	4 (1.6)	4 (1.6)
Sinusitis	-	3 (1.2)

Source: MP443 CSR, Section 12.2.3.1, Table 18

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; one patient randomized to receive MP03-36 had a positive pregnancy test at the end of study visit. The outcome of the pregnancy is pending. 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.). Two patients in the MP03-36 arm had superficial nasal mucosal ulceration at Day 14 compared to 1 patient in the placebo arm. No nasal ulcerations or septal perforations were reported in either treatment arm. Overall, 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 is less than 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%). No sedation or somnolence were reported in this study.

3.3 Study summary and conclusions

The results of MP443 support the efficacy and safety of once-daily MP03-36 for the treatment of SAR, confirming the results of Study MP440. In contrast to Study MP439, the iTNSS scores support the 24-hr dosing interval. It is worth noting that both Studies MP440 and MP443 were 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 may be more exaggerated in this particular SAR population and patients with other forms of SAR may not experience as robust an effect. The overall safety profile for the once-daily dosing regimen was similar to the profile observed in other studies in the clinical development program.

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/s/

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I concur.