CLINICAL REVIEW

Application Type	NDA
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Priority or Standard	s
Submit Date(s)	August 6, 2012
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Division / Office	DPARP/ODEII/OND
Reviewer Name(s)	Xu Wang, M.D., Ph.D.
Review Completion Date	April 25, 2013
Established Name	Azelastine hydrochloride nasal spray
Trade Name	Astepro Nasal Spray
Therapeutic Class	Antihistamine
Applicant	MEDA Pharmaceuticals
Formulation(s)	Intranasal solution
Dosing Regimen	One or two sprays per nostril twice daily
Indication(s)	Relief of the symptoms of seasonal and perennial allergic rhinitis
Intended Population(s)	Patients 6 years of age and older

Template Version: March 6, 2009

Table of Contents

Tables

Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend an Approval action for this pediatric supplemental NDA. The application contains adequate efficacy and safety data to support the proposed indication for Astepro Nasal Spray 0.15% and 0.10% "for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 6 years of age and older." The test drug product, Astepro Nasal Spray 0.15% and 0.10%, has been approved previously "for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older." This pediatric supplemental NDA is in response to one of the 2 post-marketing requirements (PMRs) issued at the time of approval, in which the Applicant was required to conduct pediatric studies in patients 6 months to <6 years and 6 years to <12 years of age.

Evidence of efficacy comes from the pediatric clinical study MP441, in which 486 perennial allergic rhinitis (PAR) patients, with or without concomitant seasonal allergic rhinitis (SAR), 6 to <12 years of age received Astepro Nasal Spray 0.15%, 0.10%, or placebo one spray per nostril twice daily for 28 days. The primary efficacy endpoint is the mean change from baseline in combined AM and PM 12-hour reflective total nasal symptom score (rTNSS) for the entire 28-day treatment period. The study MP441 showed that the mean changes from baseline in combined AM and PM 12-hour rTNSS for Astepro Nasal Spray 0.15% and 0.10% were -3.45 and -3.37, respectively. Compared with the placebo, these rTNSS changes were statistically significant with the p-value of 0.005 and 0.015 for Astepro Nasal Spray 0.15% and 0.10%, respectively. There was no trend for a better efficacy of higher strength (0.15%) versus lower strength (0.10%) of Astepro Nasal Spray. The general trend across the secondary efficacy endpoints is consistent with the primary efficacy result, showing both Astepro Nasal Spray treatment groups numerically benefiting over placebo.

This pediatric supplemental NDA contains adequate data to support the safety of Astepro Nasal Spray 0.15% and 0.10% in patients 6 to <12 years of age. The evidence for safety is based primarily on the assessment performed in the pediatric study MP441. There were no deaths or serious adverse events occurred during the 28-day treatment period. The patients who reported any adverse events were 23.7%, 25.6% and 23.5% in Astepro Nasal Spray 0.15%, 0.10%, and placebo group, respectively. The most common adverse events reported were epistaxis, nasal discomfort, and dysgeusia. These common adverse events are all described in the current product label for Astepro Nasal Spray 0.15% and 0.10%, and are consistent with the post-marketing safety profiles for Astepro Nasal Spray. In the pediatric clinical study MP441, no cases of nasal ulceration or septal perforation were reported.

In summary, the application provides adequate support for the proposed pediatric indication for Astepro Nasal Spray 0.15% and 0.10% in patients 6 to <12 years of age at the dosing regimen of one spray per nostril twice daily.

1.2 Risk Benefit Assessment

The risk benefit assessment supports Astepro Nasal Spray 0.15% and 0.10% for the indication of the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 6 to <12 years of age. Astepro Nasal Spray 0.15% and 0.10%, has been approved previously "for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older." This pediatric supplemental NDA is in response to a PMR, in which the pediatric clinical study MP441 was conducted in pediatric PAR patients with or without concomitant SAR 6 to <12 years of age. The adverse event profile observed in the study appears to be similar to the profile observed in Astepro clinical studies in PAR and SAR patients 12 years of age and older. The efficacy data provide sufficient support for the benefit of Astepro Nasal Spray 0.15% and 0.10% in PAR patient with or without concomitant SAR.

Furthermore, there are no intranasal antihistamine drug products approved for PAR in pediatric patients 6 to <12 years of age in the US, so the approval of Astepro Nasal Spray 0.15% and 0.10% in the pediatric patients for this indication fills a niche in allergic rhinitis armamentarium.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for post-marketing risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for post-marketing requirements and commitments. There is one existing PMR for NDA 22-203 to study Astepro Nasal Spray in patients 6 months to <6 years with allergic rhinitis, and the study report is to be submitted by September 2014.

2 Introduction and Regulatory Background

2.1 Product Information

Astepro (azelastine hydrochloride) is a selective, H1 antihistamine administered as an intranasal spray. Astepro Nasal Spray is formulated as metered-spray solutions of 2 strengths (0.10% and 0.15%) for intranasal administration. Astepro Nasal Spray 0.10% contains 0.10% azelastine hydrochloride in an isotonic aqueous solution containing sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium, benzalkonium chloride (125 mcg/mL), and purified water (pH 6.4). Astepro Nasal Spray 0.15% contains 0.15% azelastine hydrochloride in an isotonic aqueous solution containing sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium, benzalkonium chloride (125 mcg/mL), and purified water (pH 6.4). After priming, each metered spray delivers a 0.137 mL mean volume containing 137 mcg and 205.5 mcg of azelastine hydrochloride (equivalent to 125 mcg and 187.6 mcg of azelastine base) for 0.10% and 0.15% formulation, respectively. The 30-mL (net weight 30 gm of solution) bottle for both formulations provides 200 metered sprays.

Astepro Nasal Spray is currently approved for the indication of the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older at the following dosing regimen:

- Seasonal Allergic Rhinitis
  The recommended dose of Astepro Nasal Spray 0.10% and 0.15% is 1 or 2 sprays per nostril twice daily for seasonal allergic rhinitis. Astepro Nasal Spray 0.15% may also be administered as 2 sprays per nostril once daily.
- Perennial Allergic Rhinitis
  The recommended dose of Astepro Nasal Spray 0.15% for perennial allergic rhinitis is 2 sprays per nostril twice daily.

This pediatric supplemental NDA is to support the indication of Astepro Nasal Spray 0.10% and 0.15% in pediatric patients 6 to <12 years of age.

Azelastine hydrochloride nasal spray is approved and marketed for the treatment of symptoms of allergic rhinitis in more than 80 countries worldwide. No reports were received regarding marketing authorization withdrawals, suspensions, failures to obtain marketing authorization renewal, restrictions on distribution or clinical trial suspensions related to azelastine hydrochloride nasal spray.

2.2 Tables of Currently Available Treatments for Proposed Indications

Aside from Astepro Nasal Spray, there is another azelastine hydrochloride nasal spray, Astelin (NDA 20-114, approved November 1, 1996), for the treatment of the symptoms

of SAR in patients 5 years of age and older and vasomotor rhinitis in patients 12 years of age and older. In addition, there is also another intranasal antihistamine product, olopatadine, 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 6 years of age and older. In addition, six long-acting oral antihistamines are currently available for allergic rhinitis indication. A summary of these antihistamines is provided in Table 1 below.

Table 1 Available antihistamine treatment for allergic rhinitis

Drug	Indications*	Dose	Age range
Azelastine hydrochloride spray (Astelin®)	SAR VMR	1 to 2 sprays/nostril twice daily 2 sprays/nostril twice daily	5 to 11 years: 1 spray/nostril; 12 years and older: 2 sprays/nostril 12 years and older for VMR
Olopatadine nasal spray (Patanase®)	SAR	1 to 2 sprays/nostril twice daily	6 to 11 years: 1 spray/nostril; 12 years and older: 2 sprays/nostril
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; VMR = vasomotor rhinitis
† 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 hydrochloride was originally marketed as 0.10% intranasal spray for the treatment of the symptoms of SAR and VMR (Astelin, NDA 20-114, approved November 1, 1996). The Applicant later developed 2 sweetened azelastine hydrochloride intranasal sprays: Astepro Nasal Spray 0.10%, NDA 22-203, approved October 15, 2008, and Astepro Nasal Spray 0.15%, NDA 22-371, approved August 31, 2009. The Agency decided to combine the 2 NDAs into one under NDA 22-203 for administrative purposes. Azelastine hydrochloride 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 label, the study did not show an effect on cardiac repolarization as represented by the corrected QT interval (QTc) of the electrocardiogram.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Since the approval of Astepro Nasal Spray 0.10% and 0.15%, the Division has had multiple communications with the Applicant regarding the required pediatric program triggered by the Pediatric Research Equity Act (PREA). In the Approval Letter issued to NDA 22-371 for Astepro Nasal Spray 0.15%, 2 PMRs were specified for pediatric studies under PREA for the treatment of perennial and/or seasonal allergic rhinitis in pediatric patients 6 to <12 years of age (PMR 1535-1) and 6 months to <6 years of age (PMR 1535-2). The Division combined Astepro Nasal Spray 0.10% (NDA 22-203) and Astepro Nasal Spray 0.15% (NDA 22-371) into one NDA for administrative purposes, and requested that all submissions related to Astepro Nasal Spray PMRs be submitted under NDA 22-203 [NDA 22-371, Approval Letter, August 31, 2009].

The Applicant subsequently submitted the pediatric clinical study protocol for PAR patients 6 to <12 years of age (PMR 1535-1) on October 21, 2009, under IND 69,785. The Division has multiple communications with the Applicant thereafter with regard to the study protocol, and on April 20, 2010 communicated with the Applicant with following key comments:

> "…a pediatric PAR trial that enrolls a substantial subset of patients with concomitant SAR may be used to support both PAR and SAR indications. However, we highlight the following considerations and caveats to this approach:
>
> - The trial should demonstrate a statistically significant improvement for azelastine versus placebo for the PAR population. Subgroup analysis of the PAR patients with concomitant SAR should be supportive of efficacy, if not statistically significant. An acceptable safety profile must be shown for the PAR population as a whole, as well as the subgroup of patients with

PAR and SAR.
- The trial must be conducted in such a way that minimizes confounding by seasonal allergens, i.e. a statistical win is based on improvement in PAR, not improvement in SAR.
- Both the diagnoses of PAR and SAR should be objectively confirmed. Diagnosis of SAR by history alone is not adequate. We refer you to the April 2000 Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products for guidance on appropriate patient selection criteria."

On September 10, 2010 the Applicant submitted the protocol amendment for study MP441. The amended pediatric study protocol MP441 was acceptable [IND 69,785, Pediatric Study Protocol MP441, Medical Officer Review, Jennifer Rodriguez Pippins, M.D., M.P.H., September 14, 2010].

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission included complete study report of the study MP441, proposed labeling, and appropriate case report forms. The study reports were appropriately indexed and organized to allow review. Review of the application did not raise any data integrity concerns. There was no basis for suspect any irregularities in this pediatric clinical study. In addition, Astepro Nasal Spray 0.15% and 0.10% are approved products for the treatment of allergic rhinitis with extensive post-marketing experience. Because of these reasons, no DSI audit was recommended.

3.2 Compliance with Good Clinical Practices

The Applicant states that the clinical trials were conducted in compliance with good clinical practice (GCP), US Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR including parts 50 and 56 concerning informed consent and IRB regulations), and with the Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, South Africa, 1996, Edinburg 2000, Washington DC, 2002).

Prior to trial initiation, the clinical study protocol and the written informed consent form were reviewed and approved by the IRB. As minors being defined as those less than 18 years of age are legally unable to provide informed consent, the parent(s) or legal guardian of these study subjects provided informed consent for study participation. The pediatric subjects were then informed of the study procedures and personally signed and dated a separately designed, written assent form. Pediatric participants were made

aware of their rights to decline participation or to withdraw from the study at any time. The IRB used for this study was New England Institutional Review Board of Wellesley, MA. Written informed consent was obtained prior to any study-related activity [m5, MP441, page 18].

3.3 Financial Disclosures

The Applicant provided the list and descriptions for 39 investigators participating in the study MP441. The financial disclosure did not raise any questions about the integrity of the data provided in this Supplemental NDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Astepro Nasal Spray 0.15% and 0.10% used in this pediatric supplemental NDA are the same drug products that are currently marketed. There are no CMC issues related to this pediatric supplemental NDA.

4.2 Clinical Microbiology

There was no clinical microbiology review for this pediatric supplemental NDA.

4.3 Preclinical Pharmacology/Toxicology

There was no pre-clinical pharmacology/toxicology review for this pediatric supplemental NDA.

4.4 Clinical Pharmacology

No new clinical pharmacology studies were submitted in this application. There was no clinical pharmacology review for this pediatric supplemental NDA.

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 pediatric supplement. The approved product labeling summarized following results of pharmacology studies conducted in the Astepro Nasal Spray development program. In a placebo-controlled trial (95 patients with allergic rhinitis), there was no evidence of an effect of azelastine hydrochloride nasal spray (2 sprays per nostril twice daily for 56 days) on cardiac repolarization as represented by the corrected QT interval (QTc) of the electrocardiogram. Following multiple dose oral administration of azelastine 4 mg or 8 mg twice daily, the mean change in QTc was 7.2 msec and 3.6 msec, respectively. Interaction studies investigating the cardiac repolarization effects of concomitantly administered oral azelastine hydrochloride and erythromycin or ketoconazole were conducted. Oral erythromycin had no effect on azelastine pharmacokinetics or QTc based on analysis of serial electrocardiograms. Ketoconazole interfered with the measurement of azelastine plasma levels; however, no effects on QTc were observed.

4.4.3 Pharmacokinetics

No new pharmacodynamic data is included in this pediatric supplement. Based on the data from PK studies in adult subjects in the Astepro Nasal Spray development program, the systemic bioavailability of azelastine hydrochloride is approximately 40% after intranasal administration. The mean azelastine peak plasma concentration (C_{max}) is 200 pg/mL and 409 pg/mL, reached at 3 and 4 hours (tmax), after intranasal administration of 2 sprays per nostril of Astepro Nasal Spray 0.1% and 0.15%, respectively. *In vitro* studies with human plasma indicate that the plasma protein binding of azelastine and its metabolite, desmethylazelastine, are approximately 88% and 97%, respectively. Azelastine is oxidatively metabolized to the principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. The intranasal administration of Astepro Nasal Spray has the elimination half-life of 22 to 25 hours for azelastine and 52 to 57 hours for desmethylazelastine. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as unchanged azelastine. Following oral administration, pharmacokinetic parameters were not influenced by hepatic impairment, age and gender.

In the PMR study 1535-2, the PK data from patients 6 months to <6 years of age will be measured. The study report of PMR study 1535-2 is to be submitted by September 2014.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 Clinical study report in this pediatric supplement

Trial #	Trial type	Treatment group	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects	Materials submitted
MP441	Pediatric supplement	1. MP03-36, Astepro Nasal Spray(0.15%), one spray per nostril BID (822 mcg) 2. MP03-33, Astepro Nasal Spray(0.10%), one spray per nostril BID (548 mcg) 3. Placebo (vehicle) one spray per nostril BID	28 days	RD, DB, PC, multicenter	489	Symptomatic PAR, 6 to <12 years old	Study report

5.2 Review Strategy

There is only one clinical study report submitted in this pediatric supplemental NDA (Table 2). The clinical review was based primarily on the study report 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 Adverse Events (SAE) were reviewed to the extent of their relevance to the review. A brief literature review was also performed by the reviewer to identify any new safety signals with azelastine.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study MP441

Table 3 Summary of Study (MP441)

Protocol #	MP441
Title	Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of MP03-36 (0.15 % solution) and MP03-33 (0.10 % solution) in Children Ages ≥ 6 to < 12 with Perennial Allergic Rhinitis (PAR)
Study dates	Study initiated: November 12, 2009 Study completed: April 9, 2011 Date of final study report: February 22, 2012

Sites	There were 39 study sites in the United States
IRB	The Institutional Review Boards (IRB) used for this study was: Sterling Institutional Review Board, 6300 Powers Ferry Road, Suite 600-351, Atlanta, GA 30339. Prior to study initiation, the clinical study protocol and the written informed consent forms were reviewed and approved by the IRB.
Ethics	The study report states that the study was conducted in compliance with good clinical practice (GCP) as described in the International Committee on Harmonisation (ICH) Harmonized Triparties Guidelines for GCP 1996, US Code of Federal Regulations (CFR) parts 50 and 56 concerning informed consent and IRB regulations; and Declaration of Helsinki, concerning medical research in humans. Samples of written informed consent forms are provided in the study report.
Source references	Unless otherwise indicated, all source references are to: Study report MP441 and related information [m5, Clinical Study Report, Study MP441, pages 1-904]

5.3.1.1 Protocol

Objective

The objective of this clinical trial was to evaluate the safety and efficacy of MP03-36 (0.15 % formulation) and MP03-33 (0.10 % formulation) compared with placebo at a dosage of one spray per nostril twice daily in pediatric subjects 6 to < 12 years with perennial allergic rhinitis (PAR). The Total Nasal Symptom Score (TNSS), consisting of nasal congestion, runny nose, sneezing and nasal itching, was the primary efficacy variable.

The study also evaluated the Total Ocular Symptom Score (TOSS) and the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ). TOSS consists of scores of eye symptoms of itchy eyes, watery eyes and red eyes. PRQLQ is a five-domain, 23 item QOL questionnaire assessing nasal and ocular symptoms, practical problems, activity limitations, and other problems.

Safety was assessed on the basis of reported adverse experiences, nasal examinations, and vital signs assessments.

Study Design

This is a phase 3, randomized, placebo-controlled, parallel-group, double-blind study in pediatric subjects 6 to <12 years of age with symptomatic PAR. The study flow chart is shown in Figure 1 below. Subjects were seen on an outpatient basis at four visits. The study started with a washout period from prohibited medications if needed, followed by a 7-day, single-blind Placebo Lead-in Period during which subjects or in the case of younger children, caregivers, recorded symptom scores twice daily in order to qualify for randomization to the double-blind treatment period. Symptoms were recorded in a diary prior to the morning (AM) and evening (PM) doses of study medications on each day of the study. At Visit 2, subjects who satisfied the symptom severity requirements and continue to meet all of the study inclusion/exclusion criteria would be randomized to one of the following three treatment groups for the double-blind Treatment Period. Subjects/caregivers then continued to record 12-hour (AM and PM) reflective TNSS and

TOSS, instantaneous TNSS and TOSS in the diary for the 4-week, double-blind Treatment Period. Symptoms were assessed prior to the AM dose of study medication (upon awakening) and at approximately 12 hours after the AM dose. Subjects returned to the clinic at Visit 3 for an interim evaluation. After completing the 4-week double-blind Treatment Period, subjects returned to the clinic on Visit 4 for an end-of-study evaluation. The study evaluation schedule is listed in Table 4 below. All study personnel remained blinded to the identity of the assigned treatment until after the database was locked, the random code applied, and the statistical analyses were complete.

The study was conducted outside the seasonal allergy season for each subject at each site to reduce the possibility of symptoms due to seasonal pollens. Subjects were enrolled in 39 study sites in the United States.

Figure 1 Study flow chart [m5, Clinic Study Report Study MP441, page 35]

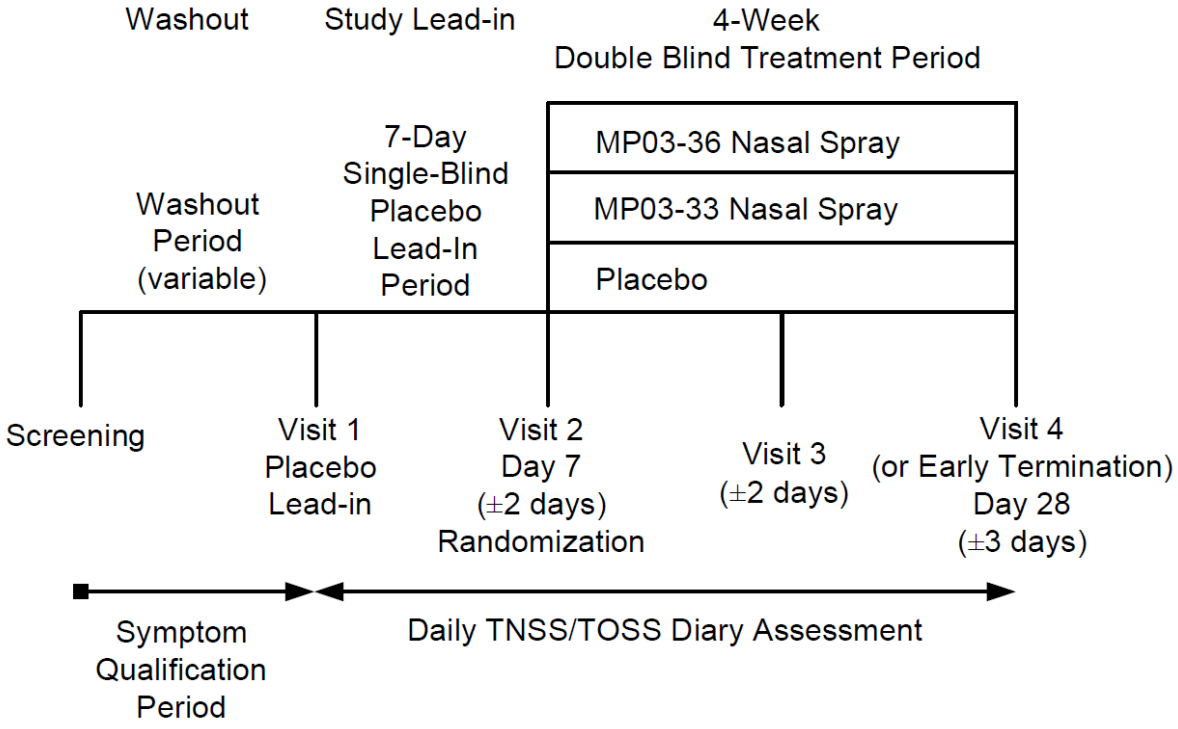

Table 4 Study evaluation schedule [m5, Clinic Study Report Study MP441, page 36]

PROCEDURE	LEAD-IN PERIOD	TREATMENT PERIOD		
	VISIT 1[d]	VISIT 2 D1 (±2 days)	VISIT 3[c]	VISIT 4 (EARLY TERMINATION) D28 (±3 days)[c]
	Screening	Randomization		
Written informed consent and pediatric assent	X			
TNSS qualification	X	X		
Inclusion/Exclusion criteria	X	X		
Skin test	X			
Physical examination/medical history	X			
Nasal examination, direct visual	X	X	X	X
Vital signs	X	X	X	X
Urine pregnancy test[a]	X	X	X	X
Assess concomitant medications	X	X	X	X
Instruct Subjects/caregivers on proper use of study medications and completion of Subject Diary	X	X	X	X
Dispense placebo lead-in medication	X			
Dispense Subject Diary	X	X	X	
PRQLQ		X		X
Weigh and dispense lead-in study medication	X			
Collect and weigh used lead-in medication		X		
Weigh and dispense double-blind study medication		X		
Collect and weigh used study medication			X	X
Collect Subject Diary		X	X	X
Adverse events assessment[b]		X	X	X
Call IVRS	X	X		X

a: Pubescent females only.
b: Any AE that occurs subsequently to the initial dose of the study drug during the lead-in period is recorded.
C: Visit 3, 4 windows are calculated from visit 2.
D: Appropriate washout from prohibited medications.

Subjects

A total of 489 symptomatic PAR patients aged 6 to <12 years of age were randomized

to receive the treatment for 28 days. Subjects were stratified so that approximately equal numbers of subjects in the age ranges 6 to <9 years of age and 9 to <12 years of age would be randomized.

Subjects with a history of seasonal allergic rhinitis were skin tested with SAR allergens appropriate for each site. Mixed allergen extracts were used. The allergens used and the average cross-sectional wheal diameter was recorded on the CRF. Skin test results obtained within the previous year could be used.

The sample size for this study was determined based on the change from baseline in AM and PM combined TNSS observed in a previous study using one spray per nostril twice daily regimens of MP03-33 (0.10% formulation) in subjects with PAR. Considering a reduction of 1.5 units in AM and PM combined TNSS with a standard deviation of 4.1, it was determined that a sample size of approximately 158 subjects per treatment group would be required to demonstrate efficacy with 1 spray per nostril twice daily compared to placebo in the MP03-33 (0.10% formulation) group and demonstrate an observable dose-response difference between MP03-33 (0.10% formulation) and MP03-36 (0.15% formulation).

Inclusion criteria:

- Male and female subjects 6 to <12, inclusive at the screening visit
- At least a 1-year history of PAR
- The parent must provide written informed consent and the child must provide written assent.
- The presence of IgE-mediated hypersensitivity to dust mite, cockroach, mold, cat or dog dander, confirmed by a positive response to skin prick testing at the screening visit. A positive response was defined as a wheal diameter of ≥5 mm larger than the negative control for the skin prick test. Histamine control must also be positive with a wheal diameter ≥5 mm larger than the control.
- Screening Visit: Have a 12-hour reflective TNSS of at least 6 out of a possible 12 and a congestion score of ≥2 or a rhinorrhea score of ≥2
- Randomization Visit: At Visit 2, to be eligible for entry into the double-blind treatment period, subjects/caregivers must record:
  1) at least 3 symptom assessments (either AM or PM score) during the past 3 days of the Lead-in Period or the Day of Randomization (Visit 2/Day 1):
     a) a 12-hour reflective TNSS ≥ 6
     b) a 12-hour reflective congestion score of ≥2 or a rhinorrhea score of ≥2
  2) the total of the seven Lead-in symptom assessments during the past 3 days of the Lead-In Period including the Day of Randomization (Visit 2/Day 1):
     a) a 12-hour reflective TNSS ≥ 42
     b) a 12-hour reflective congestion score of ≥14 or a rhinorrhea score of ≥14 h. Must have taken at least 10 doses of study medication during the placebo Lead-in Period

- General good health and free of any disease or concomitant treatment that could interfere with the interpretation of the study results as determined by the investigator
- Subjects receiving immunotherapy injections (antigen desensitization) must be on a stable maintenance regimen for at least 30 days before the first study visit. Subjects receiving sublingual immunotherapy are excluded. A 6 month washout period is required following the last dose of sublingual immunotherapy.

Exclusion criteria:

- On nasal examination, subjects with superficial nasal mucosal erosion, moderate nasal mucosal erosion, nasal mucosal ulceration, nasal septum perforation
- Other nasal disease(s) likely to affect deposition of intranasal medication, such as acute sinusitis, rhinitis medicamentosa or clinically significant polyposis or nasal structural abnormalities.
- Nasal surgery or sinus surgery within the previous year
- Chronic sinusitis
- The use of any investigational drug within 30 days prior to the study. No investigational products are permitted for use during the conduct of this study
- Presence of any hypersensitivity to drugs similar to azelastine and to either sorbitol or sucralose (Splenda® brand sweetener)
- Females who are pregnant or nursing
- Females of childbearing potential who are not abstinent and not practicing a medically acceptable method of contraception
- Respiratory tract infections within two weeks prior to the screening visit
- Subjects with significant pulmonary disease including asthma. Subjects with intermittent asthma who only require short-acting inhaled bronchodilators are eligible for enrollment.
- Chronic obstructive sleep apnea syndrome (clinical diagnosis)
- Existence of any surgical or medical condition, which in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism, or excretion of study drug or that might significantly affect the subject's ability to complete this trial.
- Clinically relevant abnormal physical findings within 1 week of randomization which, in the opinion of the investigator, would interfere with the objectives of the study or that may preclude compliance with the study procedures.
- Overnight absences from home for more than 3 nights
- Family members of research center or private practice personnel who are directly involved in this study are excluded
- Members of the same family cannot enroll in the study at the same time
- Subjects who have used the medications or therapies that could interfere with symptom evaluation within the time period specified (Table 5).
- Any behavioral condition which could affect subject's ability to accurately report symptoms to the caregiver such as developmental delay, attention deficit disorder, and autism.

Table 5 Prohibited therapies and medications [m5, MP441, page 34]

Medication/Therapy	Time Prior to Visit 1
Oral, topical nasal, topical ophthalmic antihistamines (OTC and Rx) including but not limited to: Claritin® (loratadine); Clarinex® (desloratadine); Zyrtec® (cetirizine); Xyzal® (levocetirizine); Allegra® (fexofenadine); Astelin® (azelastine hydrochloride) Nasal Spray; Astepro® (azelastine hydrochloride 0.10 %) Nasal Spray; Patanase® Nasal Spray; Patanol®; Pataday® (olopatadine); Optivar® (azelastine hydrochloride ophthalmic solution), Benedryl® (diphenydramine); Zaditor® or Alaway® (ketotifen); and OTC sleep, and diet aids, and cold preparations	5 days
Cromolyn compounds, including Tilade® (nedocromil)	14 days
Oral and intranasal anticholinergic agents including ipratropium nasal spray (Atrovent®)	5 days
Oral antibiotics for Respiratory Tract Infections	14 days
Leukotriene inhibitors, antagonists	14 days
Inhaled (oral) corticosteroids	30 days
Inhaled (nasal) corticosteroids	14 days
Systemic steroids (includes: oral, injected, IV)	30 days
Ocular corticosteroids	7 days
All ocular mast cell stabilizers	14 days
Ephedrine, phenylepherine, and pseudoephedrine containing products including herbal preparations, eg, Ma Huang and cold preparations	5 days
Tricyclic Antidepressants	30 days
Monoamine oxidase inhibitors	14 days
Immunosuppressives/immunomodulators, eg, anti-TNF agents	30 days
IgE antagonist (Xolair®)	130 days
Sublingual immunotherapy	6 months

Stopping criteria:
Subject participation would be terminated for any of the following reasons. If a subject discontinued prior to the completion of the study, a follow-up contact (telephone or visit) was to be arranged as appropriate. There would be no replacement for subjects who discontinued early.

- Non-compliance with study drug administration or diary symptom evaluations
- Lost to follow-up
- Subject withdrew consent
- Subject is pregnant
- Administration of nasal, orally inhaled, or systemic corticosteroids

- Subjects who develop a respiratory tract infection (upper or lower) regardless of etiology
- Patients who require antibiotics for the treatment of serious systemic infection; (patients who receive prophylactic antibiotics that were started at least 7 days prior to the screening visit may be enrolled in the study and continued on their antibiotics)
- Adverse Event(s)
- Abnormal test procedure result(s)
- Unsatisfactory therapeutic effect
- Protocol violation

The reason for discontinuation of study medication and the date of last dose were recorded in the subject's medical record and in the subject's CRF. All End of Study procedures were completed, diary pages and study medication collected and a detailed explanation of the reason for discontinuation of study medication were recorded in the subject's medical record and in the CRF. Randomized subjects who discontinued the study medication for any reason were not replaced.

Reviewer's comment:
Patient inclusion/exclusion criteria were appropriate for defining a population of patients with symptomatic PAR with or without SAR history.

Treatments
There were three treatment groups in this study. The treatments were provided by MEDA Pharmaceuticals. MP03-36 (0.15% solution), MP03-33 (0.10% solution), and placebo were packaged in 30-mL high- density polyethylene (HDPE) bottles with a metered-dose nasal spray pump closure. After priming (pressing and releasing the spray pump for 6 times), each metered spray delivers a 0.137 mL mean volume of solution containing either 205.5 mcg (0.15% solution) or 137 mcg (0.10% solution) of azelastine hydrochloride or placebo vehicle.

- MP03-36, Astepro Nasal Spray (0.15% solution)
  Mode of Administration: Topical/intranasal spray
  Dose: 822 mcg of azelastine hydrochloride, total daily dose
  Regimen: 1 spray per nostril twice daily
  Duration of Treatment: 4 weeks

- MP03-33, Astepro Nasal Spray (0.10% solution)
  Mode of Administration: Topical/intranasal spray
  Dose: 548 mcg of azelastine hydrochloride, total daily dose
  Regimen: 1 spray per nostril twice daily
  Duration of Treatment: 4 weeks

- Placebo (vehicle) nasal spray
  Mode of Administration: Topical/intranasal spray

Dose: vehicle only
Regimen: 1 spray per nostril twice daily
Duration of Treatment: 4 weeks

Information regarding the dispensing and return of the study medication were recorded in the subject's medical record. The study staff was to maintain an ongoing record of the dispensing and return of all study medication for each subject. Treatment compliance was evaluated at each clinical visit. Subjects/caregivers recorded each dose of study medication in the Subject Diary. At each clinical visit, the study site staff reviewed the amount of study medication returned, the amount of medication as recorded on the Diary and assessed the subject's compliance. All bottles were weighed (without the caps) prior to dispensing and when returned and the end of the study. Any discrepancies between the Subject Diary and the actual amount of returned study medication would be resolved before the subject leaved the clinic. Comments related to treatment compliance were recorded on the comment section of the source documents and the CRF.

Efficacy

Severity of symptoms of allergic rhinitis, including rhinorrhea (nasal discharge/runny nose), nasal congestion/stuffiness, nasal itching, sneezing, was individually scored twice daily by the subject or caregiver during the Screening and Treatment Periods and was based on the subject's status over the previous 12 hours (reflective or PRIOR) and on the subject's status as the diary was being completed (instantaneous or NOW).

Severity of symptoms will be graded as follows:

0 = None: No symptom evident;
1 = Mild: Symptom was clearly present but minimal awareness; easily tolerated;
2 = Moderate: Definite awareness of symptom, which was bothersome but tolerable;
3 = Severe: Symptom was hard to tolerate; cause interference with activities of daily living and/or sleeping.

Primary efficacy endpoint for this trial was the change from Baseline in 12-hour reflective total nasal symptom score (rTNSS) for the entire 28-day treatment period compared to placebo. Subjects or in the case of younger children, caregivers, recorded both Am and PM 12 hour rTNSS (how symptoms were over the previous 12 hours). For the primary efficacy endpoint, the AM and PM rTNSS were summed for each day (maximum score of 24) and then averaged over the 28 day treatment period.

The study also evaluated the Total Ocular Symptom Score (TOSS) and the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ). TOSS consists of scores of eye symptoms of itchy eyes, watery eyes and red eyes. The severity of ocular symptoms was scored as the nasal symptoms. The maximum combined AM and PM TOSS is 18. PRQLQ is a five-domain, 23 item QOL questionnaire assessing nasal and ocular symptoms, practical problems, activity limitations, and other problems.

Secondary efficacy endpoints of this study included change from baseline in instantaneous TNSS for the entire 28-day study period compared to placebo; change from baseline in 12-hour reflective TOSS and instantaneous TOSS for the entire 28-day study period compared to placebo; and change from baseline to Visit 4 in the PRQLQ compared to placebo.

Efficacy analyses were performed on an intent-to-treat (ITT) population of all randomized subjects who receive at least one dose of study medication with at least one post baseline observation. The treatment groups were compared using an analysis of covariance (ANCOVA) model with baseline as a covariate. The treatment comparison was based on the least squares means from this model using the pooled standard deviation. For weekly summaries, missing values were imputed using the last observation carried forward (LOCF) method, while the primary analysis were completed using a repeated measures mixed model. Secondary efficacy endpoints were analyzed using an ANCOVA model, with the variable specific baseline as a covariate, as described for the primary endpoint. The analyses of secondary efficacy endpoints were supportive in nature and were not corrected for multiplicity.

Safety
Safety evaluation:

- Reported adverse experiences (incidence, type, and severity of adverse events)
- Nasal examinations
- Vital signs assessments

Safety assessment was performed on all randomized subjects who received at least one dose of study medication.

6 Review of Efficacy

Efficacy Summary

The supplemental NDA submission contains adequate data to support the proposed indication for Astepro Nasal Spray 0.15% and 0.10% for the relief of the symptoms of PAR and SAR in patients 6 to <12 years of age. Evidence of efficacy comes from the pediatric efficacy and safety study MP441, in which 486 PAR patients (with or without SAR) 6 to <12 years of age received Astepro Nasal Spray 0.15%, 0.10%, or placebo one spray per nostril twice daily for 28 days. The primary efficacy endpoint was the mean change from baseline in combined AM and PM 12-hour reflective total nasal symptom score (rTNSS) for the entire 28-day treatment period. The secondary efficacy endpoints included the change from baseline in 12-hour instantaneous total nasal symptom score (iTNSS), the change from baseline in 12-hour reflective and instantaneous total ocular symptom score (rTOSS and iTOSS), and change from baseline in the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ).

The study MP441 showed that the mean changes from baseline in combined AM and PM 12-hour rTNSS for Astepro Nasal Spray 0.15% and 0.10% were -3.45 and -3.37, respectively. Compared with the placebo, these rTNSS changes were statistically significant with the P value of 0.005 and 0.015 for Astepro Nasal Spray 0.15% and 0.10%, respectively. There was no trend for a better efficacy of higher strength (0.15%) versus lower strength (0.10%) of Astepro Nasal Spray. The general trend across all of the secondary efficacy endpoints was consistent with the primary efficacy result, showing both Astepro Nasal Spray treatment groups numerically benefiting over placebo.

The Applicant was seeking the indication for the relief of the symptoms of both PAR and SAR based on one pediatric study in PAR patients with or without concomitant SAR. In previous communications with the Applicant the Division stated that "a pediatric PAR trial that enrolls a substantial subset of patients with concomitant SAR may be used to support both PAR and SAR indications. However, the trial should demonstrate a statistically significant improvement for azelastine versus placebo for the PAR population. Subgroup analysis of the PAR patients with concomitant SAR should be supportive of efficacy, if not statistically significant." [IND 69,785, MO Review by Susan Limb, M.D., April 14, 2010]. Subgroup analyses were performed in study MP441. The primary efficacy endpoint, mean change from baseline in combined AM and PM 12-hour rTNSS, in subgroups of patients with and without concomitant SAR was numerically benefiting in Astepro Nasal Spray 0.15% and 0.10% groups over placebo. The statistical significance was shown in some comparisons (p=0.028 in SAR positive group for Astepro 0.10% vs placebo and p=0.014 in SAR negative group for Astepro 0.15% vs placebo) but not in other comparisons (p=0.870 in SAR positive group for Astepro 0.15% vs placebo and p=0.204 in SAR negative group Astepro 0.10% vs placebo).

6.1 Indication

This is a pediatric supplemental NDA for an approved drug product Astepro Nasal Spray.

Currently, the FDA approved indication in the product labeling (Section 1.1) is "Astepro Nasal Spray is an H_1-receptor antagonist indicated for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older."

In the present pediatric supplement, the Applicant seeks the indication be approved as "Astepro Nasal Spray is (b) (4) indicated for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 6 years of age and older."

6.1.1 Methods

See Section 5.3 for a description of the design and conduct of study MP441. The design and conduct of the study were appropriate and consistent with recommendations made in the *Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products.*

6.1.2 Demographics

Table 6 summarized demographic data for intent-to-treat (ITT) subject population in study MP441. The demographic characteristics and baseline total nasal symptom score and total ocular symptom score of subjects who received Astepro Nasal Spray 0.15%, 0.10%, or placebo were similar. Approximately half of the PAR patients who participated in the study had concomitant SAR positive skin test. Patient inclusion/exclusion criteria, described in Section 5.3 of the review, were appropriate for defining a population of patients with moderate to severe PAR with or without concomitant SAR. In general, patient recruitment was performed appropriately, and the patients enrolled in study MP441 appeared to be representative of PAR patients in the general population.

Table 6 Summary of demographics and baseline characteristics, ITT Population [m5, MP441, page 58]

Demographics		**MP03-36^ (N=159)**	**MP03-33^ (N=166)**	**Placebo (N=161)**
Age (years)	Mean	8.8	8.8	8.7
	Range	6 – 11	6 – 12	6 – 12
	6 to <9 (%)	68 (42.8)	72 (43.4)	71 (44.1)
	9 to <12 (%)	91 (57.2)	94 (56.6)	90 (55.9)
Sex	Male (%)	86 (54.1)	101 (60.8)	93 (57.8)
	Female (%)	73 (45.9)	65 (39.2)	68 (42.2)
Race	Caucasian (%)	131 (82.4)	129 (77.7)	119 (73.9)
	Black (%)	17 (10.7)	25 (15.1)	20 (12.4)
	Others* (%)	11 (6.9)	12 (7.2)	22 (13.7)
Baseline Mean rTNSS (SD)		16.7 (3.39)	16.5 (3.40)	16.3 (3.09)
Baseline Mean rTOSS (SD)		7.2 (4.86)	6.8 (4.93)	7.3 (4.83)
Duration of PAR (years)	Mean	5.4	5.8	5.3
	Range	1 - 11	1 - 11	1 - 11
SAR Skin Test (%)	Positive	77 (48.4)	83 (50.0)	92 (57.1)
	Negative	43 (27.0)	43 (25.9)	37 (23.0)
	Not Done	39 (24.5)	40 (24.1)	32 (19.9)

* Others include Asian, American Indian or Pacific Islanders, and unknowns.
^ MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation

6.1.3 Subject Disposition

As shown in Table 7, over 90% of subjects completed the 28-day study. Overall, there were 8% subjects who discontinued early. The small number of the early discontinuations would not have a significant influence on the efficacy data obtained from study MP441.

Table 7 Subject disposition [m5, MP441, pages 52 - 54]

Disposition	MP03-36^	MP03-33^	Placebo	Total
All Randomized Subjects	161	166	162	489
Ages 6 to < 9 years	70	72	71	213
Ages 9 to <12 years	91	94	91	276
Safety Population[a]	161	166	162	489
Ages 6 to < 9 years	70	72	71	213
Ages 9 to <12 years	91	94	91	276
ITT Population[b] (%)	159 (98.8)	166 (100.0)	161 (99.4)	486 (99.4)
Ages 6 to < 9 years	68 (97.1)	72 (100.0)	71 (100.0)	211 (99.9)
Ages 9 to <12 years	91 (100.0)	94 (100.0)	90 (98.9)	275 (99.6)
Completed Study (%)	148 (91.9)	156 (94.0)	146 (90.1)	450 (92.0)
Ages 6 to < 9 years	64 (91.4)	67 (93.1)	64 (90.1)	195 (91.5)
Ages 9 to <12 years	84 (92.3)	89 (94.7)	82 (90.1)	255 (92.4)
Discontinued Early (%)	13 (8.1)	10 (6.0)	16 (9.9)	39 (8.0)
Adverse Event	2 (1.2)	0	6 (3.7)	8 (1.6)
Treatment Failure	1 (0.6)	0	2 (1.2)	3 (0.6)
Subj. Withdrew Consent	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.8)
Others[c]	9 (5.6)	8 (4.8)	7 (4.3)	24 (5.0)

^ MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation
a: Safety population includes all subjects who received as least one dose of study medication.
b: Intent-to treat (ITT) population includes subjects who had at least one post baseline efficacy observation.
c: Others include protocol violation, non-compliance, lost to follow-up, administrative problems, and other unspecified reasons.

6.1.4 Treatment Compliance

The duration of exposure and compliance were summarized in Table 8 as assessed by patient diary daily recorded doses and confirmed by bottle weights measured on Days 1, 14, and 28 days. The treatment compliance was measured by the study medication usage recorded in the patient diary. The non-compliance was defined as the study medication usage that was outside the 80% to 120% range of the scheduled medication usage. The treatment compliance appeared high (97% to 99%) and comparable in 3 treatment groups. The small non-compliance rates in treatment and placebo groups were unlikely to have impact on the study results.

Table 8 Duration of exposure and compliance [m5, MP441, page 114]

	MP03-36^ (N=161)	MP03-33^ (N=166)	Placebo (N=162)
Duration of Exposure (Days)			
Mean (SD)	27.9 (4.12)	28.3 (3.59)	27.7 (4.66)
Median (Min – Max)	29.0 (1 – 35)	29.0 (4 – 35)	29.0 (3 – 35)
Average Daily Sprays			
Mean (SD)	3.9 (0.19)	3.0 (0.13)	3.9 (0.37)
Median (Min – Max)	3.9 (2 – 4)	3.9 (3 – 4)	3.9 (2 – 8)
# Patients ≥80% Compliance* (%)	156 (96.9)	165 (99.4)	160 (98.8)

^ MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation
* Compliance is calculated as total number of doses/diary recorded doses.

6.1.5 Analysis of Primary Endpoint

The primary efficacy endpoint is the mean change from baseline in combined AM and PM 12-hour reflective total nasal symptom score (rTNSS) for the entire 28-day treatment period. Subjects or in the case of younger children, caregivers, recorded symptom scores twice daily in a diary prior to the morning (AM) and evening (PM) doses of study medications on each day of the study. The AM/PM reflective symptom score measures the symptom of the patients during a period of 12 hours prior to the dose administration. This is an acceptable primary efficacy measurement, and has been used to evaluate the efficacy of Astepro Nasal Spray in clinical trials for PAR and SAR patients 12 years of age and older.

Table 9 below shows that the mean changes from baseline in combined AM and PM 12-hour rTNSS for Astepro Nasal Spray 0.15% and 0.10% were -3.45 and -3.37, respectively. Compared with the placebo, these rTNSS changes were statistically significant with the P value of 0.005 and 0.015 for Astepro Nasal Spray 0.15% and 0.10%, respectively. There was no trend for a better efficacy of higher strength (0.15%) versus lower strength (0.10%) of Astepro Nasal Spray.

Table 9 Change from baseline in rTNSS over 28-day treatment period [m5, MP441, page 63]

Treatment[a]	LS Mean[b] Baseline (SD)	LS Mean[b] Change (SD)	Mean % Change	Comparison	Treatment Difference	ANCOVA *P* value[c] 95% CI
MP03-36 (n = 159)	16.60 (3.387)	-3.45 (4.032)	20.2	MP03-36 vs P	-0.97	.005 (-1.65, -0.29)
MP03-33 (n = 166)	16.35 (3.397)	-3.37 (4.374)	20.5	MP03-33 vs P	-0.89	.015 (-1.61, -0.17)
Placebo (n = 161)	16.09 (3.094)	-2.48 (3.933)	15.0	—	—	—

a: MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation
b: Least-Square Mean
c: P value was based on a repeated measures ANCOVA model

The Applicant was seeking the indication for the treatment of the symptoms of both PAR and SAR based on one pediatric study in PAR patients. In previous communications with the Applicant the Division stated that "a pediatric PAR trial that enrolls a substantial subset of patients with concomitant SAR may be used to support both PAR and SAR indications. However, the trial should demonstrate a statistically significant improvement for azelastine versus placebo for the PAR population. Subgroup analysis of the PAR patients with concomitant SAR should be supportive of efficacy, if not statistically significant." [IND 69,785, MO Review by Susan Limb, M.D., April 14, 2010]. Table 10 and 11 show the results of subgroup analyses for subjects with and without concomitant SAR. The primary efficacy endpoint, mean change from baseline in combined AM and PM 12-hour rTNSS, in subgroups of patients with and without concomitant SAR was numerically benefiting in Astepro Nasal Spray 0.15% and 0.10% groups over placebo. The statistical significance was shown in some comparisons (p=0.028 in SAR positive group for Astepro 0.10% vs placebo and p=0.014 in SAR negative group for Astepro

0.15% vs placebo) but not in other comparisons (p=0.870 in SAR positive group for Astepro 0.15% vs placebo and p=0.204 in SAR negative group Astepro 0.10% vs placebo). Given the fact that Astepro Nasal Spray 0.15% and 0.10% have shown statistically significant improvement in the primary efficacy endpoint for the PAR population, the numerical benefit of Astepro Nasal Spray treatment over placebo for PAR patients with and without concomitant SAR provides support of efficacy for both PAR and SAR patients.

Table 10 Change from baseline in rTNSS over 28-day treatment period in SAR negative patients [m5, MP441, page 66]

Treatment[a]	LS Mean[b] Baseline (SD)	LS Mean[b] Change (SD)	Mean % Change	Comparison	Treatment Difference	ANOVA *P* value[c] 95 % CI[d]
MP03-36 (n = 43)	15.54 (3.297)	-3.42 (3.446)	23.8	MP03-36 vs P	-2.44	.014 (-4.36, -0.51)
MP03-33 (n = 43)	16.32 (3.538)	-2.28 (4.922)	13.8	MP03-33 vs P	-1.30	.204 (-3.32, 0.72)
Placebo (n = 37)	16.40 (3.290)	-0.98 (3.870)	10.1	—	—	—

a: MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation
b: Least-Square Mean
c: P value was based on a repeated measures ANCOVA model

Table11 Change from baseline in rTNSS over 28-day treatment period in SAR positive patients [m5, MP441, page 66]

Treatment[a]	LS Mean Baseline (SD)	LS Mean[b] Change (SD)	LS Mean % Change	Comparison	Treatment Difference	ANOVA *P* value[c] 95 % CI[d]
MP03-36 (n = 77)	17.74 (3.386)	-2.78 (4.007)	16.7	MP03-36 vs P	-0.10	.870 (-1.31, 1.11)
MP03-33 (n = 83)	17.02 (3.187)	-3.98 (3.968)	23.9	MP03-33 vs P	-1.30	.028 (-2.45, -0.15)
Placebo (n = 92)	16.57 (2.831)	-2.68 (3.820)	16.0	—	—	—

a: MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation
b: Least-Square Mean
c: P value was based on a repeated measures ANCOVA model

6.1.5 Analysis of Secondary Endpoints

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 the relief of non-nasal symptoms. The secondary endpoints assessed in study MP441 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 adjustment for multiplicity. Assessment of secondary endpoints, therefore, is focused on the numerical differences and the trends, rather than the statistical significances.

Change from baseline for individual reflective nasal symptom components

TNSS is a composite symptom score of itching nose, nasal congestion, running nose, and sneezing. Table 12 demonstrated that for each of the nasal symptoms Astepro Nasal Spray 0.15% and 0.10% had numerically better improvement for the individual rTNSS symptom components compared with placebo.

Table 12 Change from baseline in reflective individual nasal symptom score over 28-day treatment period [m5, MP441, pages 331 - 334]

Individual symptom	Treatment[a]	Baseline score[b] (SD)	Mean change from baseline	P-value (vs placebo)[c]
Itchy Nose	MP03-36	3.98 (1.38)	-0.83	0.104
	MP03-33	3.90 (1.42)	-0.82	0.052
	Placebo	4.02 (1.35)	-0.68	
Nasal Congestion	MP03-36	5.05 (0.97)	-0.86	0.237
	MP03-33	5.05 (0.87)	-0.99	0.049
	Placebo	4.93 (0.96)	-0.70	
Running Nose	MP03-36	4.29 (1.28)	-1.06	0.136
	MP03-33	4.22 (1.30)	-1.03	0.126
	Placebo	4.12 (1.27)	-0.76	
Sneezing	MP03-36	3.29 (1.57)	-0.63	0.136
	MP03-33	3.18 (1.63)	-0.62	0.116
	Placebo	3.02 (1.46)	-0.44	

a: MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation
b: Least-Square Mean
c: P value was based on a repeated measures ANCOVA model

Change from baseline for iTNSS

The AM and PM instantaneous nasal symptom scores were generally supportive of the BID dosing regimen. The change from baseline combined AM and PM iTNSS over the 28-day treatment period in study MP441 (Table 13) showed that Astepro Nasal Spray 0.15% and 0.10% had numerically better improvement for iTNSS compared with placebo, supporting for the BID dose interval for Astepro Nasal Spray.

Table 13 Change from baseline in iTNSS over 28-day treatment period [m5, MP441, page 381]

Treatment[a]	LS Mean[b] baseline (SD)	Mean change From baseline (SD)	Mean % change	Comparison	Treatment difference	ANOVA P value[c]
MP03-036 (n=159)	14.92 (4.34)	-2.71 (3.91)	17.6	MP03-36 vs P	-0.33	0.435
MP03-033 (n=165)	14.36 (4.13)	-3.00 (4.42)	17.4	MP03-33 vs P	-0.62	0.160
Placebo (n=161)	14.09 (4.29)	-2.37 (3.95)	13.1			

a: MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation
b: Least-Square Mean
c: P value was based on a repeated measures ANCOVA model

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

Astepro is currently one of two approved antihistamines administered via intranasal spray for the 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 study. Nasal exam findings were evaluated in Section 7.3.5 of this review.

7.3 Major Safety Results

7.3.1 Deaths

No patient died during the study.

7.3.2 Nonfatal Serious Adverse Events

There was no serious adverse event (SAE) reported in this study.

7.3.3 Dropouts and/or Discontinuations

A total of 39 subjects discontinued early from the study. Eight subjects (6 with placebo and 2 with MP03-36) discontinued early due to adverse events that were listed below in Table 22. Review of the adverse events leading to the early discontinuation showed that the AEs were mild or moderate in severity. The AEs were abated or completely recovered after withdrawal from the study. These AE cases did not reveal a new safety signal for the trial medication.

Table 22 Dropouts or early discontinuations in the study [m5, MP441, pages 52, 56, 81]

	MP03-36^ (N=161)	MP03-33^ (N=166)	Placebo (N=162)	Total (N=489)
Discontinued early (%)	13 (8.1)	10 (6.0)	16 (9.9)	39 (8.0)
Adverse event (%)	2 (1.2)	0	6 (3.7)	8 (1.6)
Sinus infection	1 (0.6)	-	-	1 (0.2)
Nasal Itching	1 (0.6)	-	-	1 (0.2)
Otitis media	-	-	1 (0.6)	1 (0.2)
Irritability	-	-	1 (0.6)	1 (0.2)
Vomiting	-	-	1 (0.6)	1 (0.2)
Croup	-	-	1 (0.6)	1 (0.2)
Asthma	-	-	1 (0.6)	1 (0.2)
Acute URI	-	-	1 (0.6)	1 (0.2)
Treatment Failure	1 (0.6)	0	2 (1.2)	3 (0.6)
Withdrew consent	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.8)
Administrative problems	3 (1.9)	3 (1.8)	4 (2.5)	10 (2.0)
Lost to follow-up	3 (1.9)	1 (0.6)	0	4 (0.8)

Non-compliance	0	1 (0.6)	0	1 (0.2)
Protocol violation*	1 (0.6)	3 (1.8)	3 (1.9)	7 (1.4)
Other	2 (1.2)	0	0	2 (0.4)

^ MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation
* Protocol violation includes “Did not complete the study”, “Had inadequate diary data”.

7.3.4 Significant Adverse Events

No significant adverse events were identified in the study.

7.3.5 Submission Specific Primary Safety Concerns

No unusual or unexpected adverse events occurred, there were no deaths and no serious adverse events reported. No systemic or local adverse effects were reported with greater frequency in patients who received Astepro Nasal Spray 0.10% and 0.15% than that in patients who received placebo in this supplemental NDA.

Somnolence, a common adverse reaction to many antihistamines, was reported by only one subject who received MP03-33 in the 28-day study.

Focused nasal exam was performed in the study to assess local toxicity that may be associated with intranasal inhalation of the test medication. 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 mucosal ulceration or septal perforation was reported in the study. The common local observations were physical findings consistent with allergic rhinitis (e.g. epistaxis, nasal irritation, mucosal edema, mucosal erythema, and nasal discharge). The overall rate and severity of common adverse events related to local toxicity appeared comparable among MP03-36, MP03-33, and placebo.

In the Astepro development program, the Applicant conducted a one year long term safety study for Astepro Nasal Spray 0.15% in patients 12 years of age and older with PAR. The study report was reviewed and no new safety signals were identified [NDA 22-203, Medical Officer Review for the Long Term Safety Study MP436, Susan Limb, M. D., March 15, 2010].

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 23 shows all adverse events that occurred in ≥1% of subjects in any treatment group. A total of 23.7%, 25.9%, and 23.5% of subjects reported any adverse event in MP03-36, MP03-33, and placebo, respectively. The most common adverse event was epistaxis, accounting for 4.3%, 4.8%, and 3.1% for subjects receiving MP03-36, MP03-

33, and placebo, respectively. The slightly higher incidences of nasal discomfort and dysgeusia were reported in MP03-36 group (4.3% and 3.7%, respectively) than those in MP03-33 and placebo groups. In general, the incidence and profile of adverse events did not reveal a new safety signal for the trial medication.

Table 23 Adverse events occurred ≥1% of subjects in any treatment group [m5, MP441, page 79]

Preferred Term[a] (%)	MP03-36^ (N=161)	MP03-33^ (N=166)	Placebo (N=162)
Any adverse event[b]	38 (23.7)	43 (25.9)	38 (23.5)
Epistaxis	7 (4.3)	8 (4.8)	5 (3.1)
Nasal discomfort	7 (4.3	1 (0.6)	0
Dysgeusia	6 (3.7)	4 (2.4)	1 (0.6)
URI	4 (2.5)	4 (2.4)	3 (1.9)
Sneezing	4 (2.5)	3 (1.8)	2 (1.2)
Oropharyngeal pain	3 (1.9)	1 (0.6)	2 (1.2)
Pyrexia	2 (1.2)	2 (1.2)	3 (1.9)
Abdominal discomfort	2 (1.2)	0	0
Nasopharyngitis	1 (0.6)	5 (3.0)	3 (1.9)
Headache	1 (0.6)	3 (1.8)	4 (2.5)
Vomiting	1 (0.6)	0	5 (3.1)
Otitis media	1 (0.6)	0	2 (1.2)
Rash	0	2 (1.2)	1 (0.6)
Nausea	0	1 (0.6)	4 (2.5)

^ MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation
a: Coded using MedDRA dictionary V. 14.0
b: A subject with multiple AEs is counted only once in "Any Adverse Event" category.

7.4.2 Laboratory Findings

Other than urine pregnancy tests administered at Screening, laboratory assessments were not performed during this study. There were no pregnancies in the study.

7.4.3 Vital Signs

Vital signs (blood pressure, pulse rate, and respiratory rate) were assessed at Screening, Baseline, 2 weeks, and 4 weeks (Final Visit). Table 24 showed the values and changes of the vital signs from baseline to the end of the study. There were no trends suggesting an adverse effect of Astepro Nasal Spray 0.10% and 0.15% on vital signs.

Table 24 Changes from baseline in vital signs [m5, MP441, pages 704 - 707]

Vital signs, mean (SD)	MP03-36^ (N=161)	MP03-33^ (N=166)	Placebo (N=162)
Systolic BP (mmHg)			
Baseline	101.0 (8.89)	100.7 (9.78)	99.8 (9.22)
Endpoint*	100.2 (9.18)	101.1 (9.27)	100.4 (9.10)
Change	-0.8	0.4	0.6
Diastolic BP (mmHg)			
Baseline	64.3 (7.10)	63.3 (7.68)	62.7 (7.28)
Endpoint*	62.8 (6.85)	62.4 (7.02)	62.0 (6.99)

Change	-1.5	-0.9	-0.7
Pulse rate (bpm)			
Baseline	81.8 (9.97)	81.3 (10.21)	81.2 (8.92)
Endpoint*	82.9 (7.92)	80.1 (9.68)	82.0 (9.46)
Change	1.1	-1.2	0.8
Resp. rate (per min)			
Baseline	17.7 (2.13)	17.7 (2.20)	17.4 (2.11)
Endpoint*	17.3 (1.89)	17.5 (2.15)	17.1 (2.01)
Change	-0.4	-0.2	-0.3

^ MP03-36 = 0.15% formulation, MP03-33 = 0.10% formulation
***** Measured at week 4 or on the day of early termination

7.4.4 Electrocardiograms (ECGs)

Electrocardiogram was not performed in the study.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies conducted in this supplemental NDA.

7.4.6 Immunogenicity

The drug product, azelastine, does not have any recognized immunogenicity potential.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Formal exploration for dose response and adverse events was not performed under this supplemental NDA. Review of the adverse events incidence and profile of MP03-36 (0.15% formulation) and MP03-33 (0.10% formulation) does not suggest a dose-dependence for the common adverse events reported.

7.5.2 Time Dependency for Adverse Events

It appears no time dependency for adverse reactions reported in the 28-day study for Astepro Nasal Spray 0.15% and 0.10%.

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. However, the relatively small number of patients in the demographic subgroups of age, sex, gender, and race in the study limits the assessment for adverse reactions occurring at such low frequencies.

7.5.4 Drug-Disease Interactions

No apparent interactions between Astepro Nasal Spray and past or concurrent illness were identified in the study.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction study was included in this supplemental NDA. The current product label for Astepro 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.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No formal studies were done in humans evaluating the carcinogenic effect of Astepro Nasal Spray. There were no patients who developed malignancy while receiving Astepro Nasal Spray for the treatment of seasonal and perennial allergic rhinitis.

A 2-year carcinogenicity study in rodents did not show evidence of carcinogenicity at oral doses approximately 150 and 60 times the maximum recommended daily intranasal dose in human. Azelastine hydrochloride was not mutagenic in *in vitro* and *in vivo* laboratory studies.

7.6.2 Human Reproduction and Pregnancy Data

There was no pregnancy reported during the clinical study submitted under this supplemental NDA. There are no adequate and well controlled studies in pregnant women receiving Astepro Nasal Spray. The currently approved labeling categorizes Astepro Nasal Spray as Pregnancy C, and states that “Astepro Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.”

7.6.3 Pediatrics and Assessment of Effects on Growth

This is a pediatric supplemental submission in response to the PMR 1535-1 issued in the Approval Letter of NDA 22-371 on August 31, 2009. The Pediatric Review Committee (PeRC) meeting on April 3, 2013 discussed this pediatric supplemental

NDA. PeRC agreed that the submission had fulfilled the requirements specified in the PMR 1535-1, and suggested that the pediatric information from the study MP441 be incorporated in the product labeling sections.

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose, drug abuse potential, withdrawal and rebound were not assessed in the study in this supplemental NDA. There is no pharmacological basis to expect that Astepro Nasal Spray has drug abuse potential, withdrawal and rebound. With the extensive marketing history of the product, no clinical data suggest that Astepro Nasal Spray is associated with overdose, drug abuse, withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

There are no additional submission and safety issues for this supplemental NDA. On November 16, 2012, the Applicant submitted the periodic adverse events report for Astepro (azelastine hydrochloride) Nasal Spray 0.10% and 0.15%, covering the reporting period of July 15, 2012 to October 14, 2012 [NDA 22-203, SD 333]. There were 42 non-serious adverse events and no serious AE reported during the reporting period. The periodic report did not reveal new safety signals.

8 Postmarket Experience

The Applicant submitted a summary of the post-marketing experience for Astepro Nasal Spray covering the time period from October 15, 2008 to October 15, 2010. The data were presented as table of the reports to the manufacture using MedDRA preferred terms, along with case report forms. A total of 117 adverse events were reported to the manufacture during the reporting period. There were 4 serious adverse events (one pneumonia, one oropharyngeal pain, one hypoaesthesia oral, and one nasal discomfort). The common adverse events included dysgeusia, throat irritation, nasal discomfort, sneezing, and epistaxis. In general, the post-marketing safety profile was similar to the safety profile observed in clinical trials and no new safety issues were identified during the post-marketing period for Astepro Nasal Spray.

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, review] yielded 19 references. Brief review of the other references did not indicate any new safety signals. A comprehensive literature review is not performed because there were no questions raised by the data submitted by the Applicant that could have been answered by such a review.

9.2 Labeling Recommendations

A full labeling review was conducted. The proposed label is of the PLR format. At the time of this review, labeling discussions are ongoing among the Applicant and the Agency. Major labeling recommendations include the revision of the indication for pediatric patients 6 to <12 years of age and additional efficacy and safety data based on the pediatric study MP441 in correspondent labeling sections.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not held for this supplemental NDA. Astepro Nasal Spray is already approved in two strength formulations, 0.1% and 0.15%, for the treatment of PAR and SAR in patients 12 years of age and older. No new safety or efficacy concerns were identified in this pediatric supplement. Given the pre-existing efficacy and safety data available for intranasal azelastine and the information on MP03-36 and MP03-33 provided in the application, an AC discussion was not warranted.

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/s/

XU WANG
04/25/2013

ANTHONY G DURMOWICZ
04/29/2013