CLINICAL REVIEW

Application Type	NDA Supplement
Application Number(s)	22203-S010-S011
Priority or Standard	Priority
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Division / Office	DPARP/ODE II
Reviewer Name(s)	Kathleen M. Donohue, M.D., M.Sc.
Review Completion Date	January 28, 2015
Established Name	azelastine hydrochloride
(Proposed) Trade Name	Astepro
Therapeutic Class	antihistamine
Applicant	Meda Pharmaceuticals
Formulation(s)	0.1% (b) (4) nasal spray
Dosing Regimen	1 spray per nostril twice daily
Indication(s)	Seasonal Allergic Rhinitis (SAR) Perennial Allergic Rhinitis (PAR)
Intended Population(s)	Patients 2 years to 5 years with SAR Patients 6 months to 5 years with PAR

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The submitted data are adequate to support the approval of Astepro Nasal Spray 0.1% for the proposed indication of "the relief of the symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older." [redacted]

Meda Pharmaceuticals submitted a 505(b)(1) application for azelastine hydrochloride, an H_1-receptor antagonist, with the trade name Astepro®. Each actuation of the product contains 137 or 205.5 µg of azelastine hydrochloride for the 0.1% or 0.15% formulations, respectively. The proposed dosing regimen is one spray per nostril twice daily, for a total daily dose of 548 or 822 µg of azelastine hydrochloride for the 0.1% [redacted]. Azelastine hydrochloride is available in the United States as an active ingredient in multiple products including Astelin (azelastine hydrochloride 0.1%, [redacted]), which received initial U.S. approval on November 1, 1996.

This application encompasses pediatric supplements No. 010 and 011 submitted on September 24, 2014 to NDA 22-203 for Astepro Nasal Spray (azelastine hydrochloride). It includes the final study report for the pediatric study MP442, submitted to fulfill the Pediatric Research Equity Act requirement for NDA 22-203. This study also is intended to fulfill one of the studies outlined in the Written Request issued September 6, 2013. On the basis of this study, the Applicant has proposed new labeling for Astepro, expanding the seasonal allergic rhinitis indication down to 2 years of age and the perennial allergic rhinitis indication down to patients 6 months and older, 0.1% [redacted] 1 spray per nostril twice daily.

Evidence of efficacy comes from the Agency's prior findings for Astepro (NDA 22371) in seasonal and perennial allergic rhinitis in patients 6 years and older, and the supportive data contained in this submission for pediatric patients 6 months to 5 years. MP442 was an open-label, parallel-group, multicenter study that randomized 191 patients 1:1 to Astepro 0.1% or 0.15% and measured general allergy severity score, overall symptoms rated on 3-point scale from none to severe, over a 4-week period. [redacted]

The safety of Astepro in children age 6 months to 5 years was evaluated in MP442. There were no deaths in the clinical development program, and the rate of serious adverse events and adverse events leading to discontinuation were low. There were no instances of nasal ulceration or perforation, and no reports of somnolence during MP442. The most commonly reported adverse events (≥2%) were pyrexia, cough, epistaxis, sneezing, dysgeusia, rhinalgia, upper respiratory infection, vomiting, otitis media, contact dermatitis, and oropharyngeal pain. Of note, a higher proportion of participants receiving the 0.15% formulation experienced at least one treatment emergent adverse event (28.4% vs. 20.8%) compared to those receiving the lower dose formulation (MP442 Study report p. 55).

(b) (4)

1.2 Risk Benefit Assessment

(b) (4)

The data suggest a higher numerical improvement for the lower dose Astepro 0.1% (b) (4) among younger children. Overall, the safety profile for Astepro is similar to what was observed in the adult development program, however, an increased rate of overall adverse events was observed among those receiving the 0.15% formulation compared to those receiving the 0.1% formulation.

The risk/benefit assessment for the 0.1% formulation is favorable given the improvement in general allergy symptom scores and an acceptable adverse event profile. (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No post-market Risk Evaluation and Mitigation Strategies are recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

None. Study MP442 fulfills post-marketing requirement 1535-2, which is the remaining Pediatric Research Equity Act requirement for Astepro Nasal Spray. Meda has now fulfilled all of the Pediatric Research Equity Act requirements for Astepro Nasal Spray.

2 Introduction and Regulatory Background

2.1 Product Information

Azelastine is a selective, H1 antihistamine administered as an intranasal spray. It is currently marketed under two trade names, Astelin (azelastine hydrochloride 0.1% nasal spray) and Astepro (azelastine hydrochloride 0.1% and 0.15%). (b) (4)

Azelastine hydrochloride is available in several related intranasal formulations. The following summarizes each of these products:

Astelin Nasal Spray (azelastine HCl 0.1%, 137 µg/spray)

- approved 1996 for seasonal allergic rhinitis
  - Children 5 to 11 years - 1 spray per nostril twice daily (548 µg/day)
  - Adults and children 12 years of age and older -1 or 2 sprays per nostril twice daily (1096 µg/day)
- Vasomotor rhinitis in adults and children 12 years of age and older – 2 sprays per nostril twice daily (1096 µg/day)

Astepro Nasal Spray (azelastine 0.1% and 0.15%; 137 or 205.5 µg/spray); approved 2008

- seasonal allergic rhinitis
  - Children 6 to 11 years – 1 spray per nostril twice daily (548 to 822 µg/day)
  - Adults and children 12 years and older – 0.1% 1 or 2 sprays per nostril twice daily or 0.15% 2 sprays per nostril daily (548 to 1096 µg/day)
- perennial allergic rhinitis
  - Children 6 to 11 years – 1 spray per nostril twice daily (548 to 822 µg/day)
  - Adults and children 12 years and older – 0.15% 2 sprays per nostril twice daily (1644 µg/day)

(b) (4) . Also, Astepro is available in two concentrations, 0.1% and 0.15%.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Available antihistamine treatments for allergic rhinitis

Drug	Indications*	Dose	Age range
Azelastine nasal spray (Astelin)	SAR, VMR	1 to 2 sprays twice daily	≥5 years
Azelastine nasal spray (Astepro)	SAR, PAR	1 to 2 sprays twice daily	≥ 6 years
Azelastine and fluticasone nasal spray (Dymista)	SAR	1 spray per nostril twice daily	≥ 12 years
Olopatadine nasal spray (Patanase)	SAR	2 sprays twice daily	≥6 years
Desloratadine (Clarinex)	SAR, PAR, CIU	1 to 5 mg once daily	≥ 6 months
Fexofenadine (Allegra)	SAR, CIU	30 mg to 60 mg twice daily or 180 mg once daily	≥ 6 years
Levocetirizine (Xyzal)	SAR, PAR, CIU	2.5 to 5 mg once daily	≥ 6 years
Cetirizine (Zyrtec)†	Allergic rhinitis, chronic hives	2.5 to 10 mg once daily	≥ 2 years (OTC) ≥ 6 months (Rx only)
Loratadine (Claritin)‡	Allergic rhinitis, chronic hives	5 to 10 mg once daily	≥ 2 years (OTC)

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

2.3 Availability of Proposed Active Ingredient in the United States

Azelastine hydrochloride is available in the United States as an active ingredient in multiple products.

Azelastine hydrochloride 0.1% (b) (4) is available as both a branded product (Astelin) and generic. Astelin received initial U.S. approval on November 1, 1996. Azelastine hydrochloride 0.1% (b) (4) is indicated for seasonal allergic rhinitis in adults and children 5 years of age and older, and for vasomotor rhinitis in adults and adolescents 12 years of age and older.

Azelastine hydrochloride also is available as 0.1% and 0.15% (b) (4) formulations under the trade name Astepro. Both the 0.1% and 0.15% (b) (4) formulations are indicated for seasonal allergic rhinitis in patients 6 years of age and older.

2.4 Important Safety Issues with Consideration to Related Drugs

Somnolence has been noted as a class effect for antihistamines. It was observed in the clinical program for both the (b) (4) azelastine nasal sprays. Section 5.1 of the current Astelin and Astepro labels contain warnings and precautions regarding activities requiring mental alertness.

One of the first second-generation antihistamines approved for the treatment of allergic rhinitis, terfenadine, was associated with QT interval prolongation and cardiac arrhythmias, leading to its removal from the market. The current Astelin and Astepro labels contain results from a study that found no effect of intranasal azelastine on cardiac repolarization.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The early years of the pediatric program for azelastine nasal sprays predate the Agency's authorities under the Pediatric Research Equity Act.

No pediatric studies were requested or planned when the Division first approved azelastine nasal spray on November 1, 1996 for seasonal allergic rhinitis in patients age 12 and older at a dose of two sprays twice daily (Astelin, NDA 20-114). On May 30, 2000, the Division requested either a pediatric plan or waiver request when it approved a supplement to expand the seasonal allergic rhinitis indication to patients 5 to 11 years of age (Astelin, NDA 20-114, S-005). (b) (4) The Division (b) (4) issued a pediatric Written Request on September 20, 2002. (b) (4).

On February 17, 2006 the Division revisited the pediatric study plan when it approved a supplement of the one spray twice daily dosing regimen in patients 5 years of age and older (Astelin, NDA 20-114, S-014). The Pediatric Research Equity Act recently had gone into effect but the Agency's authority to enforce it was under legal challenge. Consequently, the approval letter did not explicitly list pediatric studies for seasonal allergic rhinitis as formal post-marketing commitments. Instead, the letter required that the Applicant submit a summary of the pediatric drug development plan (June 14, 2005, NDA 20-114, SE2-014).

In response, the Applicant planned a Phase 4 study in patients 2 to 4 years of age with seasonal allergic rhinitis using a related intranasal azelastine product, Astepro 0.1%. Astepro (b) (4). Studies under the age of 2 years were not planned as seasonal allergic rhinitis is not generally thought to exist in patients below 2 years of age. The Division was in agreement with this plan.

In 2008, the Division approved azelastine nasal spray 0.1% (b) (4) for seasonal allergic rhinitis in patients 12 years of age and older at a dose of 2 sprays twice daily (Astepro, NDA 22-203, approved on October 15, 2008). The application contained no new active ingredient, indication, dosage form, dosing regimen, or route of administration. Thus, the application did not trigger the Pediatric Research Equity Act, and no pediatric studies were encumbered.

Subsequently, the Applicant filed an application for a higher-strength 0.15% formulation of Astepro and proposed the addition of the perennial allergic rhinitis indication as well as a once-daily dosing regimen (NDA 22-371; later combined under one NDA number, 22-203). This triggered studies under the Pediatric Research Equity Act. Therefore, the August 14, 2009, Approval Letter outlined the following studies:

1535-1. A study of the treatment of perennial allergic rhinitis and/or seasonal allergic rhinitis in pediatric patients ages 6 years to less than 12 years of age. The study will include efficacy and safety assessments.

- Protocol Submission: November 2009
- Study Completion: June 2011
- Final Report Submission: December 2011

1535-2. A study of the treatment of perennial allergic rhinitis and/or seasonal allergic rhinitis in pediatric patients ages 6 months to less than 6 years of age. The study will include safety assessments and pharmacokinetic measurements.

- Protocol Submission: April 2012
- Study Completion: March 2014
- Final Report Submission: September 2014

1535-3. A study of the treatment of perennial allergic rhinitis and/or seasonal allergic rhinitis in pediatric patients ages 6 years to less than 12 years of age. The study will include efficacy and safety assessments.

- Protocol Submission: September 2012
- Study Completion: November 2013
- Final Report Submission: April 2014

1535-4. A study of the treatment of perennial allergic rhinitis and/or seasonal allergic rhinitis in pediatric patients ages 6 years to less than 12 years of age. The study will include pharmacokinetic measurements.

- Protocol Submission: September 2012
- Study Completion: November 2013
- Final Report Submission: April 2014

On September 6, 2013, the Agency issued a Written Request for three studies to be completed and submitted for review by September 30, 2014. The first study was for

Astepro, and the second two were for Dymista, a combination nasal spray of azelastine and fluticasone.

- *Study 1*: A randomized, open-label, parallel group, safety study in children 6 months to less than 6 years of age with perennial and/or seasonal allergic rhinitis evaluating azelastine hydrochloride (Astepro) nasal spray. The treatment duration will be 4 weeks.
- *Study 2:* A randomized, open-label, active-controlled, parallel group, long-term safety study in children 4 to 11 years of age with seasonal allergic rhinitis or perennial allergic rhinitis comparing the fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray to fluticasone propionate nasal spray. The treatment duration will be 3 months.
- *Study 3:* A randomized, double-blind, placebo-controlled, parallel group efficacy and safety study in children 4 to 11 years of age with seasonal allergic rhinitis comparing the fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray to placebo. The treatment duration will be two weeks.

Post-marketing requirement 1535-1 (Study MP441) was submitted as Supplement No. 008 to NDA 22-203 and approved on September 9, 2013, expanding the seasonal allergic rhinitis and perennial allergic rhinitis indication down to the age of 6 years. The last two studies listed, post-marketing requirement 1535-3 and 1535-4, originally were required under the assumption that an alternate device might be required to administer the product to younger patients. However, the Division released these two post-marketing requirements on April 22, 2013, once the Applicant determined that the same device could be used across all ages.

Study MP442 is submitted to fulfill the requirements of Study 1 from the Written Request and study 1535-2 under the Pediatric Research Equity Act. It was the one outstanding pediatric requirement for Astepro and is the subject of this review. Studies MP4007 and MP4008 are submitted under NDA 202-236 to fulfill the requirements of Studies 2 and 3 from the Written Request and correspond to post-marketing requirements 1888-1 and 1888-2 for Dymista, and are the subject of a separate review. The three complete study reports comprise the Applicant's response to the Written Request and Pediatric Research Equity Act requirements.

On October 22, 2014 the Division granted priority review to this application because it was submitted in response to a Pediatric Written Request.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission included a complete study report for the safety study, proposed labeling, appropriate case report forms, and the relevant data sets. The study report was appropriately indexed and organized to allow review.

Review of the application does not raise any data integrity concerns. Azelastine is a known drug substance with extensive post-marketing experience. Because of these reasons, no DSI review is recommended at this time.

3.2 Compliance with Good Clinical Practices

The Applicant includes a statement of Good Clinical Practice (GCP), indicating that all clinical trials were conducted under the supervision of an IRB. Pediatric assent forms were not deemed necessary by the IRB because of the subjects' ages. Informed consent from the caregiver was obtained prior to initiation of any study-related procedure.

3.3 Financial Disclosures

Please see Appendix 9.4 for the Clinical Investigator Financial Disclosure Review Template.

One investigator in MP442 (Study Site (b) (6)) reported financial interests. (b) (6) enrolled (b) (6) of 181 patients.

Reviewer's comment: as MP442 was primarily a safety study and the study site enrolled a small number of patients, the results from this single site are unlikely to have a significant impact on the overall assessment of risk-benefit.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no proposed change or new formulation in this supplement. The indication is an extension for the currently approved (b) (4) – Astepro 0.1% (b) (4) On November 14, 2014, a Filing Communication was sent from the Agency to the Applicant requesting the submission of an Environmental Assessment Claim for a

Categorical Exclusion. The Applicant did so on November 19, estimating that the total amount of azelastine hydrochloride drug substance for the US Market would be (b) (4), which is (b) (4) orders of magnitude below the threshold established in 21CFR §25.31(b).

The final CMC review is pending at the time of this review.

4.2 Clinical Microbiology

Azelastine hydrochloride contains benzalkonium chloride (b) (4). There is no new clinical microbiology data in this supplement.

4.3 Preclinical Pharmacology/Toxicology

The Preclinical Pharmacology/Toxicology program was reviewed by Dr. Luqi Pei under NDA 22371. There is no new pharmacology/toxicology information in this supplement.

4.4 Clinical Pharmacology

The Clinical Pharmacology program was reviewed under NDA 22371. There is no new clinical pharmacology information in this supplement

4.4.1 Mechanism of Action

Azelastine is a selective H1-receptor blocker.

4.4.2 Pharmacodynamics

No new pharmacodynamic data are included in this application. The proposed label includes pharmacodynamic data for azelastine hydrochloride, including data from a study that found no effect of intranasal azelastine on cardiac repolarization.

4.4.3 Pharmacokinetics

No new pharmacokinetic data are included in this application. These data were reviewed under NDAs 22203 and 22371.

5 Sources of Clinical Data

The primary source of clinical data in this supplement is one clinical trial, MP442, as shown in the table below. Overall, the conduct of study MP442 was consistent with the Agency's written request and guidance: "Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products." The study is adequately designed to evaluate the safety of Astepro in children age 6 months to 5 years, and also includes some measures of efficacy.

5.1 Tables of Studies/Clinical Trials

Table 2. Study Design

Study	Design	Dose	Population	N	Duration
MP442	Randomized, open label, active controlled, parallel group, multicenter trial of safety	Astepro 0.1% or 0.15%, one spray per nostril twice daily	6 months to 5 years, with allergic rhinitis	Randomized: 191 Astepro 0.1%: 96 Age 6 mos. to < 2 yrs.: 23 Age ≥ 2 to 5 yrs.: 73 Astepro 0.15%: 93 Age 6 mos. to < 2 yrs.: 22 Age ≥ 2 to 5 yrs.: 71	4 weeks

5.2 Review Strategy

The clinical review focused on the Phase 3 safety study for seasonal and perennial allergic rhinitis in children ages 6 months to 5 years (MP442). Review of the study was based primarily on this reviewer's independent analysis of the data sets provided by the Applicant, and secondarily on the Applicant's study report. The tables and analyses presented in this report reflect the independent analysis of the reviewer except where otherwise noted. Case report forms of patients with Serious Adverse Events were reviewed. The Applicant's bibliography was reviewed when relevant for this review. Postmarketing safety data based on annual reports submitted for Astelin (NDA 20-114) and Astepro (NDA 22371) were briefly reviewed. A literature review was performed to identify any new safety signals with azelastine.

The design and conduct of study MP442 will be described in Section 5.3, efficacy results in Section 6 and safety results in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

Study MP442 was a US multi-center, randomized, open label, active controlled, parallel group study of the safety and efficacy of Astepro 0.1% compared to Astepro 0.15% in patients age 6 months to 5 years with seasonal or perennial allergic rhinitis.

Reviewer's comment: An open label, active controlled study design is acceptable as the primary endpoint for this study was safety.

The study timeline consisted of a washout period for prohibited concomitant medications, a lead-in period to assess eligibility criteria, and a 4 week randomized treatment period. A schedule of study assessments is presented in **Table 3**.

Prohibited concomitant medications included antihistamines, anticholinergic agents, other intranasal therapies, antibiotics for respiratory tract infections, ocular medications, decongestants, corticosteroids, tricyclic antidepressants, monoamine oxidase inhibitors,

leukotriene modifiers, eye drops, cromolyn, immunosuppresants or immunomodulators, Xolair, initiation of immunotherapy, other investigational therapies.

To participate in the trial, patients had to meet all study inclusion criteria and none of the exclusion criteria at both Visit 1 and again at Visit 2, prior to randomization and first treatment dose.

Pertinent inclusion criteria

- Male and female subjects 6 months to 5 years
- A history of allergic rhinitis
- Maintenance immunotherapy injections (antigen desensitization) were acceptable as a concomitant medication so long as the dose was stable for at least 30 days before the first study visit. Adjustments to the regimen following a brief period of missed injections were acceptable.

Pertinent exclusion criteria

- Nasal mucosal erosion, ulceration or perforation (Grade 1B– 4)
- 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
- Respiratory tract infections within two weeks prior to Visit 1
- Subjects with significant pulmonary disease including asthma. Subjects with intermittent asthma who only required short-acting inhaled bronchodilators (not more often than twice per week) and who did not have nocturnal awakening as a result of asthma were eligible for enrollment
- Chronic obstructive sleep apnea syndrome (clinical diagnosis)

Astepro Nasal Spray 0.1% and 0.15% were approved by the FDA for the treatment of the symptoms of seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. A previous study (Protocol MP441) assessed these formulations (1 spray per nostril twice daily), in children 6 to 11 years with symptomatic perennial allergic rhinitis. The same formulation and doses were selected for evaluation in children 6 months to 5 years.

Investigators randomized participants 1:1 to Astepro 0.1% or 0.15% via a block randomization scheme stratified by age.

The active treatment in Astepro Nasal Spray is an approved product, commercially available in either a 0.1% or 0.15% formulation. Astepro was packaged in 30-mL high-density polyethylene bottles with a metered-dose nasal spray pump closure. After priming, each metered spray delivered a 0.137 mL mean volume of nasal spray

containing either 137 µg of azelastine hydrochloride (0.1%, lot 03-33-07c) or 205.5 µg of azelastine hydrochloride (0.15%, lot 0000009436). Open label study medications were prepared, packaged, and labeled in accordance with the treatment randomization schedule.

To assess adherence, bottles were weighed prior to dispensing and again at return visits. Where there was a significant discrepancy between actual bottle weights versus anticipated bottle weights or the Subject Diary, the subject/caregiver was re-trained.

Table 3. MP442 Evaluation Schedule

	Lead-in Period	Treatment Period		
Procedure	Visit 1[a]	Visit 2 Day 1 (Baseline)	Visit 3 Day 15 (±2 days)[c]	Visit 4 Day 29 (±3 days)[c]
Written informed consent	X[b]			
Inclusion/Exclusion criteria	X	X		
Physical examination, direct visual	X	X	X	X
Vital signs	X	X	X	X
Height and weight	X			X
Blood and urine samples for safety laboratory analysis	X	X	X	X
Assess concomitant medications	X	X	X	X
Randomization		X		
Instruct Subject's caregivers on proper completion of Subject Diary	X	X	X	
Dispense Subject Diary	X	X	X	
Instruct Subject's caregivers on proper use of study medications		X	X	
Weigh and dispense study medication		X		
Collect and weigh used study medication			X	X
Collect Subject Diary		X	X	X
Adverse events assessment		X	X	X
Contact Interactive voice/web response system IXRS	X	X		X

Source: Applicant Table 2 from Section 5.3.5.1 Study Report Body Section 9.1 p. 19
[a] Appropriate washout from prohibited concomitant medications after Informed Consent
[b] Prior to Visit 1 if washout of concomitant medications was needed
[c] Visit 3 and Visit 4 windows calculated from Visit 2

MP442 was designed primarily as a safety study with plan for description of the safety findings. MP442 was not designed as an efficacy study, but overall allergy symptom data were collected for participants. Participants' caregivers recorded allergy symptoms in a daily journal prior to the morning dose of study medication. Allergy symptoms were defined as runny nose, sneezing, itchy nose, and nasal stuffiness/congestion. Participants and their caregivers were asked "How are your allergy symptoms over the past 24 hours?" and to rate the severity according to the following scale:

- 0= None/Absent – no symptoms present
- 1= Mild – symptoms clearly present, but minimal awareness; easily tolerated
- 2= Moderate – definite awareness of symptoms that were bothersome but tolerable
- 3= Severe – hard to tolerate; caused interference with activities of daily living and/or sleeping.

Secondary efficacy endpoints included the percentage of days with allergy symptoms, the percentage of subjects with allergy symptoms by maximum severity, and change from baseline in symptom severity. The efficacy assessments and results are reviewed in Section 6.

Safety assessments consisted of subject/caregiver-reported adverse experiences, nasal examinations, vital signs, blood chemistry, hematology and urinalysis. The safety assessments and results are reviewed in Section 7.

A total of 191 participants were enrolled in MP442. All 191 were included in the safety and intention to treat populations. A total of 13 participants did not complete the study, 5 due to adverse events, 1 lost to follow-up, 2 to protocol violation, and 5 who elected to withdraw. Of those who elected to withdraw, two cited reasons related to the device, including “difficulty dosing subject” and “forcefulness of spray.” Overall, the reasons for discontinuations did not vary appreciably between treatment arms or by age stratum (**Table 4**).

Table 4. MP442 Subject Disposition, All Randomized Subjects and All Age Strata

	All Age Strata				6 Months to <2 Years of Age				2 to <6 Years of Age			
	Astepro 0.1% (n=96)		Astepro 0.15% (n=95)		Astepro 0.1% (n=23)		Astepro 0.15% (n=22)		Astepro 0.1% (n=73)		Astepro 0.15% (n=73)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
All Randomized Subjects	96	(100)	95	(100)	23	(100)	22	(100)	73	(100)	73	(100)
Safety Population	96	(100)	95	(100)	23	(100)	22	(100)	73	(100)	73	(100)
Subjects Discontinued	5	(5)	8	(8)	4	(17)	2	(9)	1	(1)	6	(8)
Subjects Completed	91	(95)	87	(92)	19	(83)	20	(91)	72	(99)	67	(92)
Primary Reason for Discontinuation From Study												
Adverse Event	2	(2)	3	(3)	2	(9)	0	0	0	0	3	(4)
Lost to Follow-Up	0	0	1	(1)	0	0	0	0	0	0	1	(1)
Protocol Violation	1	(1)	1	(1)	1	(4)	0	0	0	0	1	(1)
Withdrawal by Subject	2	(2)	3	(3)	1	(4)	2	(9)	1	(1)	1	(1)

Source: Astepro ADDS.XPT
Percentages are based on the number of subjects in each treatment group
Discontinuation is based on site-assigned pre-specified categories on the eCRF
Safety Population includes all randomized subjects who received at least 1 dose of study medication

Baseline characteristics and demographic information for patients in MP442 are presented in **Table 5**. Participants in the Astepro 0.1% arm were slightly more likely to be female and white, whereas participants in the Astepro 0.15% arm were slightly more likely to be male and Black or African American. Overall, a relatively high percentage of participants identified as Hispanic or Latino, and this was especially pronounced in the younger age stratum. Otherwise, the treatment arms and age strata appeared comparable in terms of demographic distribution.

Table 5. Subject Demographics and Baseline Characteristics, Safety Population, Study MP442

		All Age Strata		6 Months to <2 Years of Age		2 to <6 Years of Age	
		Astepro 0.1% (n=96)	Astepro 0.15% (n=95)	Astepro 0.1% (n=23)	Astepro 0.15% (n=22)	Astepro 0.1% (n=73)	Astepro 0.15% (n=73)
Age (Years)	Mean	3	3	1	1	4	4
	StdDev	(2)	(2)	(0)	(0)	(1)	(1)
Gender							
Female	N	45	36	10	9	35	27
	(%)	(47)	(38)	(43)	(41)	(48)	(37)
Male	N	51	59	13	13	38	46
	(%)	(53)	(62)	(57)	(59)	(52)	(63)
Ethnicity							
Hispanic or Latino	N	33	38	12	16	21	22
	(%)	(34)	(40)	(52)	(73)	(29)	(30)
Not Hispanic or Latino	N	63	57	11	6	52	51
	(%)	(66)	(60)	(48)	(27)	(71)	(70)
Race							
American Indian	N	0	2	0	0	0	2
	(%)	0	(2)	0	0	0	(3)
Asian	N	3	3	1	0	2	3
	(%)	(3)	(3)	(4)	0	(3)	(4)
Black or African American	N	27	34	4	5	23	29
	(%)	(28)	(36)	(17)	(23)	(32)	(40)
Native Hawaiian or Other Pacific Islander	N	0	2	0	0	0	2
	(%)	0	(2)	0	0	0	(3)
White	N	68	59	19	17	49	42
	(%)	(71)	(62)	(83)	(77)	(67)	(58)
Other	N	1	0	0	0	1	0
	(%)	(1)	0	0	0	(1)	0

Source: Astepro ADDM.XPT
Percentages are based on the number of subjects in each treatment group.
Summary statistics are based on the number of subjects with available data.
For race, more than one choice could be selected so percentages may total greater than 100%.

6. Review of Efficacy

Efficacy Summary

Evidence of efficacy comes from the Agency's prior findings for Astepro (NDA 22371) in seasonal and perennial allergic rhinitis in patients 6 years and older, and the supportive data contained in this submission for pediatric patients 6 months to 5 years. MP442 was an open-label, parallel-group, multicenter study that randomized 191 patients 1:1 to Astepro 0.1% or 0.15% and measured general allergy severity score, overall symptoms rated on 3-point scale from none to severe, over a 4-week period. A formal statistical comparison between the active treatments was not pre-specified because safety was the primary objective. (b) (4) The analyses from both this reviewer and the Applicant suggest a numerically greater improvement for the lower dose Astepro 0.1% (b) (4) in the youngest children age 6 months to 2 years.

6.1 Indication

The Applicant seeks an extension of the indication for Astepro 0.1% (b) (4) for seasonal allergic rhinitis down to age 2 years and for perennial allergic rhinitis down to age 6 months.

6.1.1 Methods

This supplement includes the results of one clinical trial, MP442. The design of MP442 is discussed in Section 5. As noted above, MP442 was designed primarily as a safety trial; however, efficacy endpoints were measured and are described in this section. Review of the study was based primarily on this reviewer's independent analysis of the data provided by the Applicant, and secondarily on the Applicant's study report. Except where otherwise noted, the tables and analyses presented in this report reflect the independent analysis of the reviewer.

6.1.2 Demographics

The demographics in MP442 were described in Section 5. See **Table 5**.

6.1.3 Subject Disposition

The subject disposition in MP442 was described in Section 5. See **Table 4**.

6.1.4 Analysis of Primary Endpoint(s)

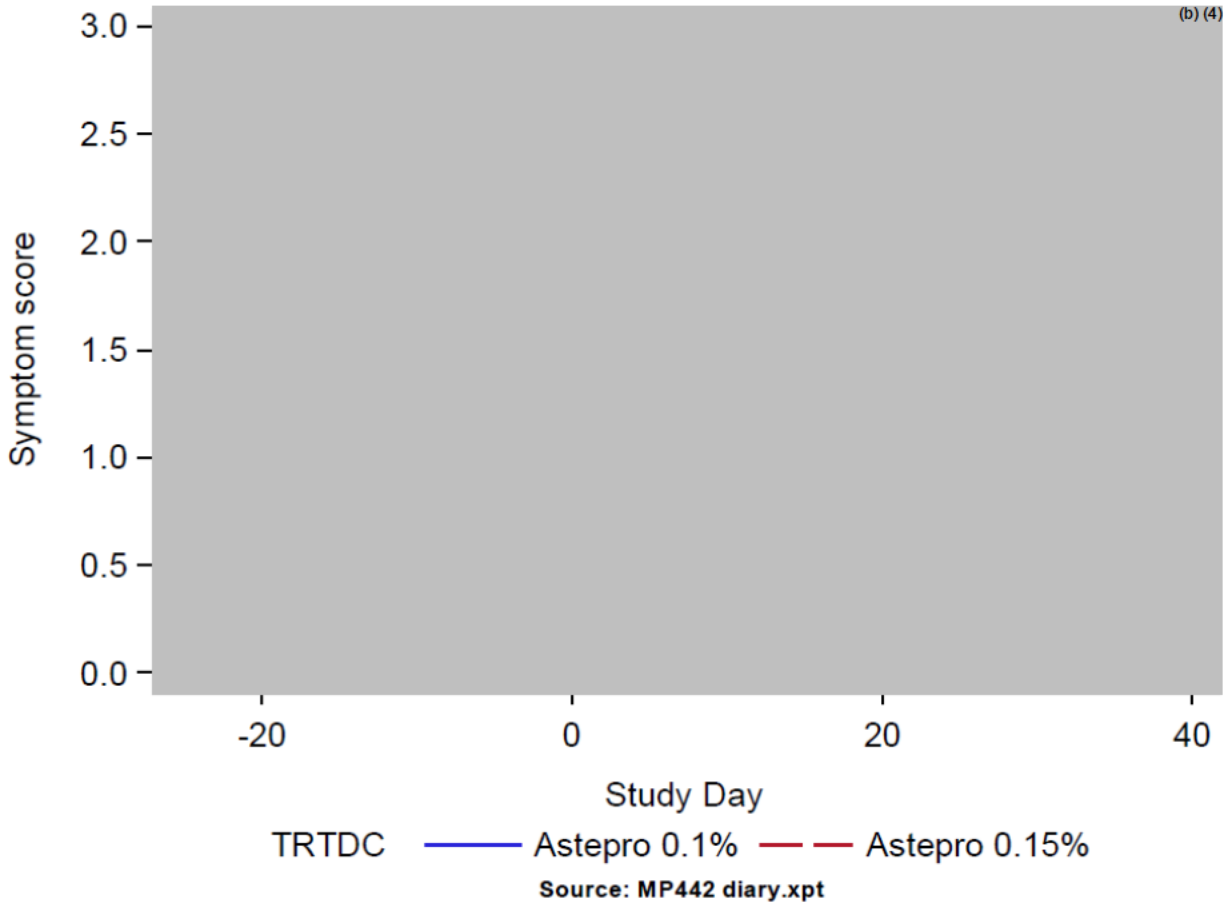
Caregivers recorded allergy symptoms in a daily journal prior to the morning dose of study medication. Exploration of the change in allergy symptoms over time is reasonable. Locally weighted (Loess) regression models were generated to explore the average trend over time for the allergy symptom score. Scores decreased by similar amounts and at similar rates over time for both treatment arms (**Figure 1**). The results of this reviewer's independent analysis were consistent with the Applicant's findings (**Table 6**).

Table 6. Daily average symptom severity

	All Age Strata				6 Months to <2 Years				2 to 5 Years			
	0.1%		0.15%		0.1%		0.15%		0.1%		0.15%	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	1.51	0.79	(b) (4)		1.60	0.73	(b) (4)		1.48	0.80	(b) (4)	
Change from baseline to Visit 3, Day 15	-0.31	0.69			-0.29	0.72			-0.31	0.67		
Change from baseline to visit 4, Day 29	-0.52	0.80			-0.68	0.78			-0.48	0.80		
Change from baseline overall	-0.41	0.71			-0.46	0.74			-0.40	0.70		

Source: Astepro.diary.xpt
Note(s): Based on a response to the daily diary question "How have your allergy symptoms been over the past 24hours?" where 0 = None/Absent, 1 = Mild, 2 = Moderate, 3 = Severe. Responses are averaged over the specific visit interval. Summary statistics are based on the total number subjects with available data. Baseline is defined as the average of the three days of assessments immediately prior to and including the day of randomization (maximum total of 4 assessments). The change from baseline is calculated as the average of all daily post-baseline scores.

Figure 1. Average allergy symptom score over time



Source: MP442 diary.xpt

6.1.5 Analysis of Secondary Endpoints(s)

None.

6.1.6 Other Endpoints

The Applicant analyzed the percentage of days participants reported symptoms with a score ≥ 1 (mild) during each visit interval. The mean percentage of days that subjects had allergy symptoms decreased over the study course in both treatment groups and across age strata. Overall mean percentage of days with allergy symptoms was (b) (4) and 73%, Astepro 0.15% and 0.1%, respectively, over the overall interval. The overall mean percentage of days with allergy symptoms was comparable among the 2 to 5 years age stratum (72% per group) and was (b) (4) and 77%, Astepro 0.15% and 0.1%, respectively, among the ≥6 months to <2 years age stratum.

The Applicant also analyzed the percentage of subjects with each category of symptom severity (none, mild, moderate or severe) by study interval. Over the course of the

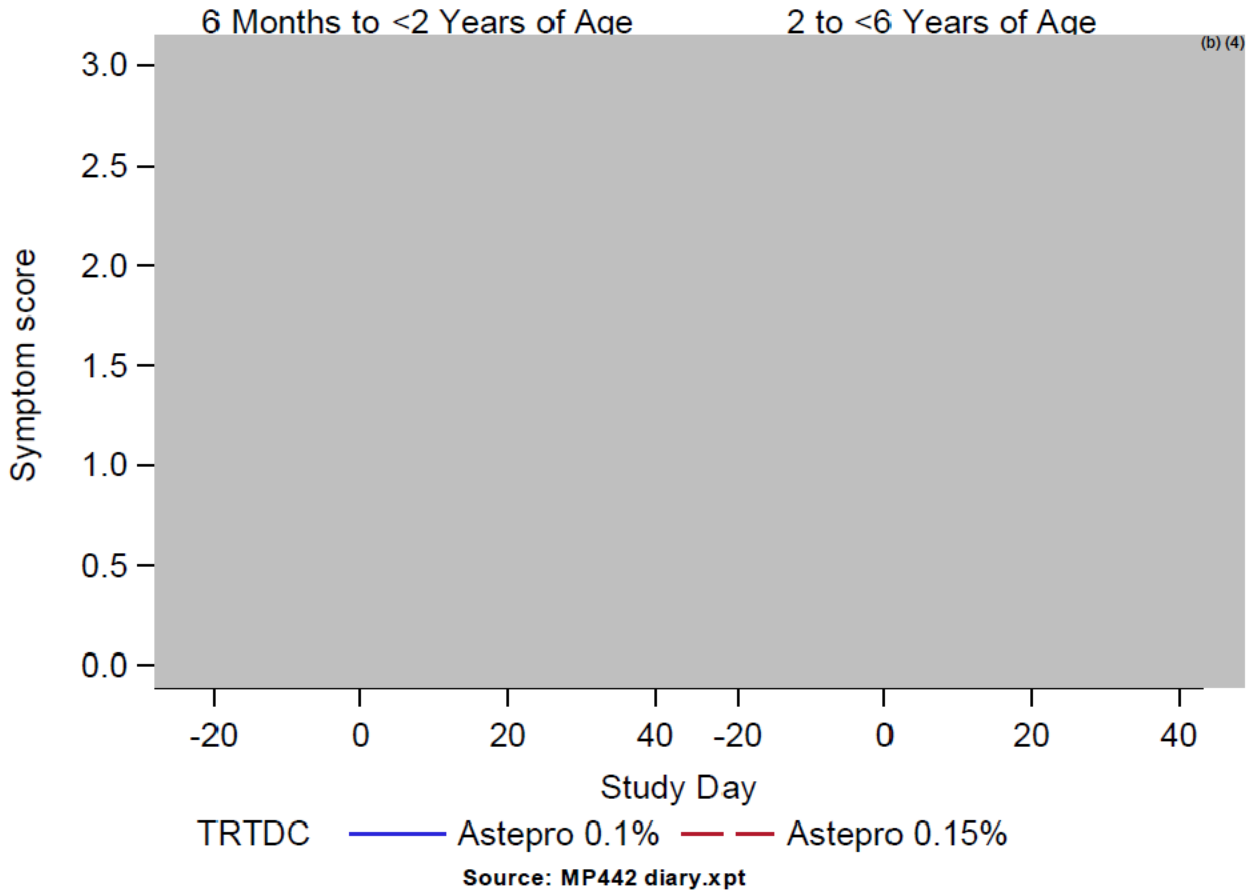
study, the percentage of subjects with none or mild symptoms increased as the percentage with moderate and severe symptoms decreased, in both treatment groups. In the Astepro 0.1% group, the percentage of subjects with allergy symptoms of none or mild increased from 34% at baseline to 44% at the last study visit. (b) (4), in the Astepro 0.15% group, the percentage of subjects with allergy symptoms of none or mild (b) (4) at the last study visit.

6.1.7 Subpopulations

Average allergy symptom scores decreased by similar amounts and at similar rates for both treatment arms in each age group, though there was slight numerical superiority for the lower dose Astepro 0.1% (b) (4) in the youngest children age 6 months to <2 years (

Figure 2). This was consistent with the Applicant's findings (**Table 6**).

Figure 2. Average allergy symptom score over time, stratified by age



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Review of the clinical development program for Astepro in participants ≥ 12 years of age (NDA 22371) found evidence that Astepro 0.15% was numerically superior to Astepro 0.1% and concluded that "some patients may benefit from a higher dosage strength of azelastine in the treatment of their seasonal allergic rhinitis symptoms." Similar to the studies included in NDA 22371, study MP442 in this NDA included an active comparator as a benchmark. A formal statistical comparison between the active treatments was not pre-specified. (b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No tolerance effects were noted in MP442, nor were they observed elsewhere in the development programs for azelastine.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The safety of Astepro in children age 6 months to 5 years was evaluated in MP442. There were no deaths in the clinical development program, and the rate of serious adverse events and adverse events leading to the discontinuation of treatment were low. There were no instances of nasal ulceration or perforation, and no reports of somnolence during MP442. The most commonly reported adverse events (≥2%) were pyrexia, cough, epistaxis, sneezing, dysgeusia, rhinalgia, upper respiratory infection, vomiting, otitis media, contact dermatitis, and oropharyngeal pain. Of note, a higher proportion of participants receiving the 0.15% formulation experienced at least one treatment emergent adverse event (28.4% vs. 20.8%) compared to those receiving the lower dose formulation (MP442 Study report p. 55).

7.1 Methods

Review of the study was based primarily on this reviewer's independent analysis of the data sets provided by the Applicant, and secondarily on the Applicant's study report. Except where otherwise noted, the tables and analyses presented in this report reflect the independent analysis of the reviewer.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Evidence of safety for Astepro in children is based primarily on the assessments performed in study MP442. These safety data are supplemented by the original safety data from the clinical development programs for Astelin and Astepro that were previously reviewed under NDAs 20-114, 22-203 and 22-371 as well as postmarketing data for Astelin and Astepro and published literature reports.

Safety Evaluations

MP442 assessed subject-reported adverse experiences, nasal examinations, vital signs, blood chemistry, hematology and urinalysis (**Table 3**).

Nasal exams were performed at each of the four study visits, and for two participants at unscheduled visits. The nasal exams consisted of three components. The first measured nasal irritation from grade 0 to 4: no abnormal findings (0), focal inflammation, erythema or hyperemia (1A), superficial erosion (1B), moderate erosion (2), ulceration (3), and perforation (4). The second component assessed epistaxis, which was graded as none, mild (self-limited), moderate (prevents daily activity), or severe (ER visit or hospitalization). The third component assessed mucosal edema, nasal discharge, mucosal erythema, mucosal bleeding, or crusting of the mucosa, and rated each as none, mild, moderate or severe. The presence and degree of findings on nasal examinations were at the Investigator's discretion. Participants with nasal irritation scores ≥ 1B at screening or randomization were ineligible to participate. Comments describing the lesions were required in the case report forms for participants who developed nasal irritation ≥ 1B during the study.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the version of the Medical Dictionary for Regulatory Activities current at the time of study conduct (MedDRA version 16.0).

The definitions used for adverse event reporting were appropriate.

Adverse Event – "any untoward medical occurrence in a subject … any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product was recorded as an AE."

Serious Adverse Event – "an AE (experience) or reaction that was an untoward medical occurrence at any dose that resulted in death, was life threatening (potential or immediate), required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event."

Treatment Emergent Adverse Event – "an AE with an onset date on or after the first dose of study drug, or an AE that worsened (increased in severity or frequency) after the initiation of treatment."

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

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

The study design, patient population, doses and drug exposures in the Phase 3 program were appropriate for the safety assessment of Astepro in patients age 6 months to 5 years. There were minor differences between this reviewer's analysis and the sponsor's report regarding duration of exposure and compliance, but they are not clinically important. The overall duration of exposure and number of doses administered were adequate to assess the safety of Astepro, and comparable between the two treatment arms and age strata (Table 7).

Table 7. Duration of exposure and compliance

		All Age Strata		6 Months to <2 Years of Age		2 to <6 Years of Age	
		Astepro 0.1% (n=96)	Astepro 0.15% (n=95)	Astepro 0.1% (n=23)	Astepro 0.15% (n=22)	Astepro 0.1% (n=73)	Astepro 0.15% (n=73)
Exposure duration (days)	Mean	29	29	27	29	29	29
	StdDev	(3)	(3)	(5)	(4)	(2)	(3)
Total sprays (n)	Mean	112	111	105	111	114	111
	StdDev	(12)	(15)	(19)	(17)	(9)	(14)
Compliance (%)	Mean	98	97	97	97	98	97
	StdDev	(5)	(6)	(4)	(5)	(5)	(7)

Source: Astepro.diary

7.2.2 Explorations for Dose Response

Formal exploration for dose response and drug toxicity was not performed, but the inclusion of two doses of Astepro allows for a qualitative assessment of safety.

7.2.3 Special Animal and/or In Vitro Testing

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

7.2.4 Routine Clinical Testing

The routine clinical testing in MP442 was adequate and included nasal examinations, vital signs, blood chemistry, hematology and urinalysis.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new in vitro or in vivo data on metabolism or clearance was submitted in this application. Clinical Pharmacology and drug-drug interaction studies were reviewed under NDA 20-114 and are described in the approved Astepro label.

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

The clinical program included focused nasal examinations to monitor for adverse events known to be associated with topical nasal antihistamines. Somnolence is a known potential class effect of antihistamines and can be evaluated through standard adverse event reporting.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the clinical development program.

7.3.2 Nonfatal Serious Adverse Events

One serious adverse event was reported. A three year old Black or African American male with a history of asthma was randomized to the 0.15% Astepro arm. On study day (b) (6) he developed an asthma exacerbation, was admitted to the hospital for treatment, and Astepro was discontinued. He was febrile and tachycardic, and subsequently tested positive for parainfluenza virus type 4. Two days later his symptoms had improved, he was discharged from the hospital, and discontinued from further study participation.

Reviewer comment: This adverse event likely was not attributable to Astepro.

7.3.3 Dropouts and/or Discontinuations

A total of 191 participants were enrolled in MP442. All 191 were included in the safety and intention to treat populations. A total of 13 participants did not complete the study, 5 due to adverse events, 1 lost to follow-up, 2 to protocol violations and 5 who elected to withdraw. The adverse events that triggered discontinuation included an asthma exacerbation, upper respiratory tract infection, laryngotracheitis, dysgeusia and sinusitis. Of those who elected to withdraw, two cited reasons related to the device, including “difficulty dosing subject” and “forcefulness of spray.” Overall, the reasons for discontinuations did not vary appreciably between treatment arms (**Table 4**).

7.3.4 Significant Adverse Events

One participant in the Astepro 0.15% arm had mild neutropenia (absolute neutrophil count of 1.2 x 10^3/µL, reference range 1.8-10 x 10^3/µL) noted on baseline labs. This decreased to 0.2 x 10^3/µL at visit 4, but increased to 1.8 x 10^3/µL by study day 60, which was within the normal range. No other hematologic parameters were affected and no treatment was given.

Two participants in the Astepro 0.1% arm had significant adverse events reported: one with self-limited non-cardiac chest pain and another with mild near syncope after phlebotomy.

7.3.5 Submission Specific Primary Safety Concerns

There were no instances of nasal ulceration or perforation, and no reports of somnolence during MP442.

The nasal exams consisted of three components. The first measured nasal irritation from grade 0 to 4: no abnormal findings (0), focal inflammation, erythema or hyperemia (1A), superficial erosion (1B), moderate erosion (2), ulceration (3), and perforation (4). The second component assessed epistaxis, which was graded as none, mild (self-limited), moderate (prevents daily activity), or severe (ER visit or hospitalization). The third component assessed mucosal edema, nasal discharge, mucosal erythema, mucosal bleeding, or crusting of the mucosa, and rated them as none, mild, moderate or severe. The presence and degree of findings on nasal examinations was at the Investigator’s discretion. Participants with nasal irritation scores ≥ 1B at screening or randomization were ineligible to participate. Comments describing the lesions were required in the case report forms for participants who developed nasal irritation ≥ 1B during the study.

The majority of participants had nasal mucosa with no abnormal findings (Grade 0). Approximately one quarter of participants had focal inflammation, erythema or hyperemia (Grade 1A). This proportion did not vary appreciably over time or by

treatment arm (**Table 8**). Of note, the younger age stratum (6 months to < 2 years) had a lower proportion of Grade 1A nasal exams when compared to the older age stratum (age 2 to 5 years).

Reviewer comment: As there is no a priori reason to suspect that allergic rhinitis would be milder in younger children, the observation of fewer Grade 1A nasal exams in younger participants suggests the possibility of measurement error. The exams may have been limited by participants' smaller anatomy and ability to cooperate with the exam.

Table 8. Astepro nasal mucosal grade over time

		6 Months to <2 Years of Age								2 to 5 Years of Age								
		Astepro 0.1%				Astepro 0.15%				Astepro 0.1%					Astepro 0.15%			
		Visit				Visit				Visit					Visit			
		1	2	3	4	1	2	3	4	1	2	3	4	U	1	2	3	4
Grade 0	N	20	21	19	22				(b) (4)	51	52	52	54	(b) (4)				(b) (4)
	(%)	(87)	(91)	(100)	(100)	(				(70)	(71)	(72)	(74)					
Grade 1A	N	3	2	0	0					22	21	20	19					
	(%)	(13)	(9)	0	0					(30)	(29)	(28)	(26)	(				

Source: ASTEPRO NASAL.XPT
U = Unscheduled

Table 9 is a shift table reporting the proportion of participants in each treatment arm whose nasal exams improved, worsened, or stayed the same compared to baseline across all visits. Overall the proportions were similar for both treatment arms.

Table 9. Nasal exam shift table from baseline for all visits

	Astepro 0.1%		Astepro 0.15%		(b) (4)
	N	(%)	N	(%)	
Mucosal Grade					
Worse	16	(4)	14		
Same	343	(90)	331		
Better	23	(6)	32		
Epistaxis					
Worse	9	(2)	.		
Same	368	(96)	367		
Better	5	(1)	10		
Mucosal Edema					
Worse	48	(13)	34		
Same	268	(70)	277		
Better	66	(17)	66		
Nasal Discharge					
Worse	51	(13)	67		
Same	246	(64)	243		
Better	85	(22)	67		
Mucosal Erythema					
Worse	38	(10)	27		
Same	291	(76)	295		
Better	53	(14)	55		
Mucosal Bleeding					
Worse	3	(1)	6		
Same	377	(99)	360		
Better	2	(1)	11		
Mucosal Crusting					
Worse	30	(8)	34		
Same	314	(82)	308		
Better	38	(10)	35		

Source: ASTEPRO NASAL.XPT

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported adverse events were pyrexia, cough, epistaxis, sneezing, dysgeusia, rhinalgia, upper respiratory infection, vomiting, otitis media, contact dermatitis, and oropharyngeal pain. The proportion of participants with at least one treatment emergent adverse event was larger in the group taking the higher dose of Astepro (28% for Astepro 0.15% compared to 21% for Astepro 0.1%).

Table 10. Common adverse events reported by ≥ 2% of subjects

	All Age Strata		6 months to < 2 years		2 to 5 years	
	Astepro 0.1% n=95	Astepro 0.15% n=96	Astepro 0.1% n=95	Astepro 0.15% n=96	Astepro 0.1% n=95	Astepro 0.15% n=96
Pyrexia, No. (%)	5 (5)	6 (6)	2 (9)	3 (14)	3 (4)	3 (4)
Cough	1 (1)	3 (3)	0	1 (5)	1 (1)	2 (3)
Epistaxis	0	3 (3)	0	0	0	3 (4)
Sneezing	0	3 (3)	0	0	0	3 (4)
Dysgeusia	0	2 (2)	0	0	0	2 (3)
Rhinalgia	0	2 (2)	0	0	0	2 (3)
Upper respiratory tract infection	1 (1)	2 (2)	1 (4)	2 (9)	0	0
Vomiting	1 (1)	1 (1)	0	1 (5)	1 (1)	1 (1)
Otitis media	3 (3)	3 (3)	1 (4)	0	2 (3)	0
Contact dermatitis	2 (2)	2 (2)	1 (4)	0	1 (1)	0
Oropharyngeal pain	2 (2)	2 (2)	1 (4)	0	2 (3)	0

Source: Adapted from Applicant's MP442 Study Report Listing 16.2.7.1 and Table 14.3.3
Percentages are based on the number of subjects in each treatment group. Treatment Emergent Adverse Events listed in order of most frequently reported in the 0.15% Astepro group, followed by most frequently reported in 0.1% group. Adverse Events (AEs) coded using the MedDRA dictionary Version 16.0. A subject with multiple AEs is counted only once in any row. Treatment-emergent adverse event (TEAE) is an adverse event with an onset date on or after the date of first dose of study drug.

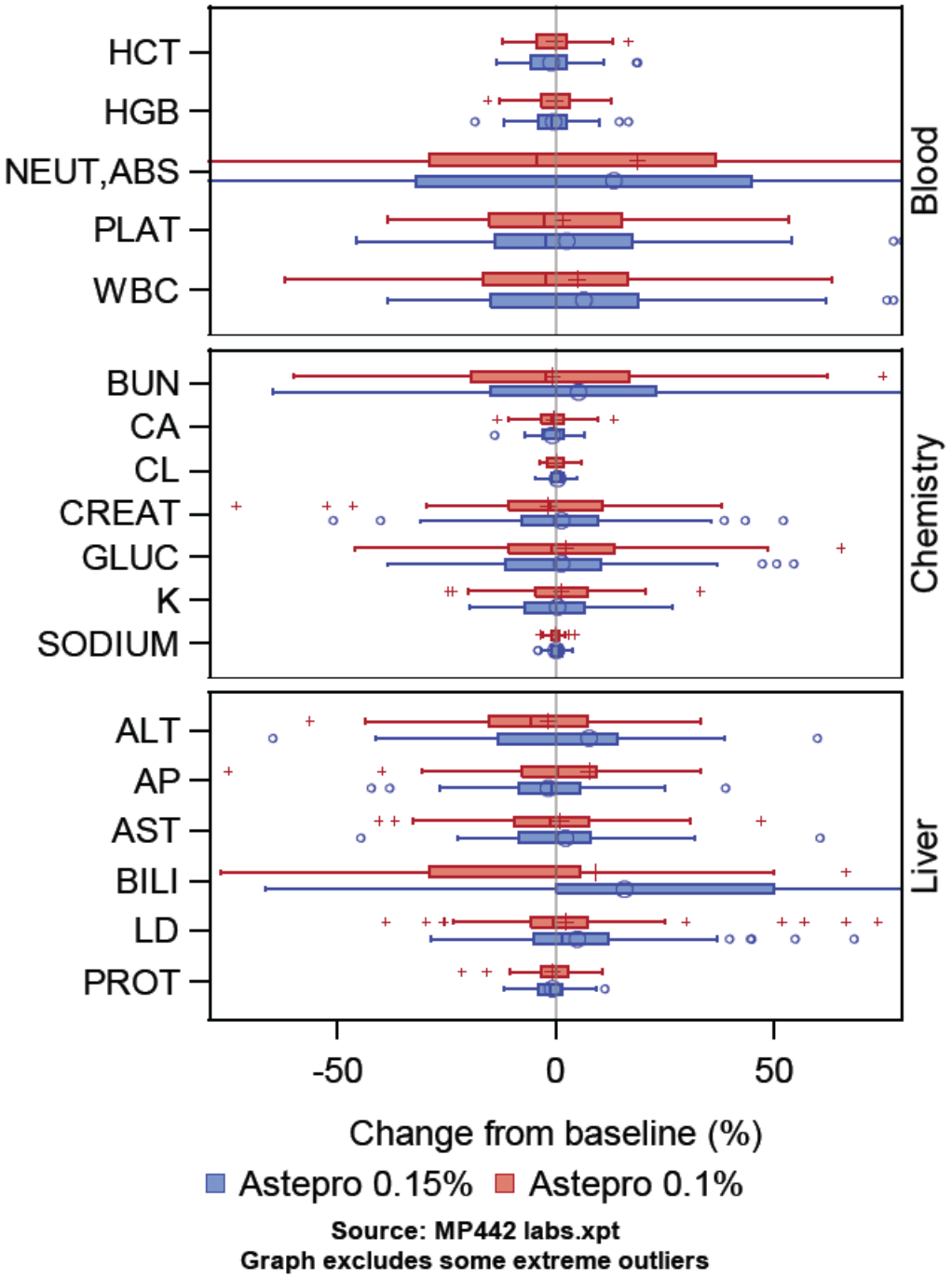
7.4.2 Laboratory Findings

Routine clinical chemistry, hematology and urinalysis testing were conducted at baseline and again at the end of the study. Generally, mean baseline and mean changes were similar across treatment groups. One exception was that participants taking Astepro 0.15% had a slight numerical increase in bilirubin levels from baseline that was not seen in those taking Astepro 0.1%. Similar changes were not seen in other

liver enzymes that would suggest a pattern of injury, and thus this difference is not likely to be clinically meaningful.

Figure 3 shows the percent change from baseline to end of study by treatment group. For clarity, the figure omits some extreme outliers. These extreme outliers were reviewed individually (data not shown). **Table 11** presents lab shifts.

Figure 3. Percent change from baseline lab value by treatment arm



Source: MP442 labs.xpt
Graph excludes some extreme outliers

Small numbers of participants had shifts in laboratory values of greater than twenty percent from normal at baseline to abnormal at the final study visit. The proportions were similar across treatment arms. No clinically important differences were noted.

Table 11. Astepro abnormal laboratory shifts

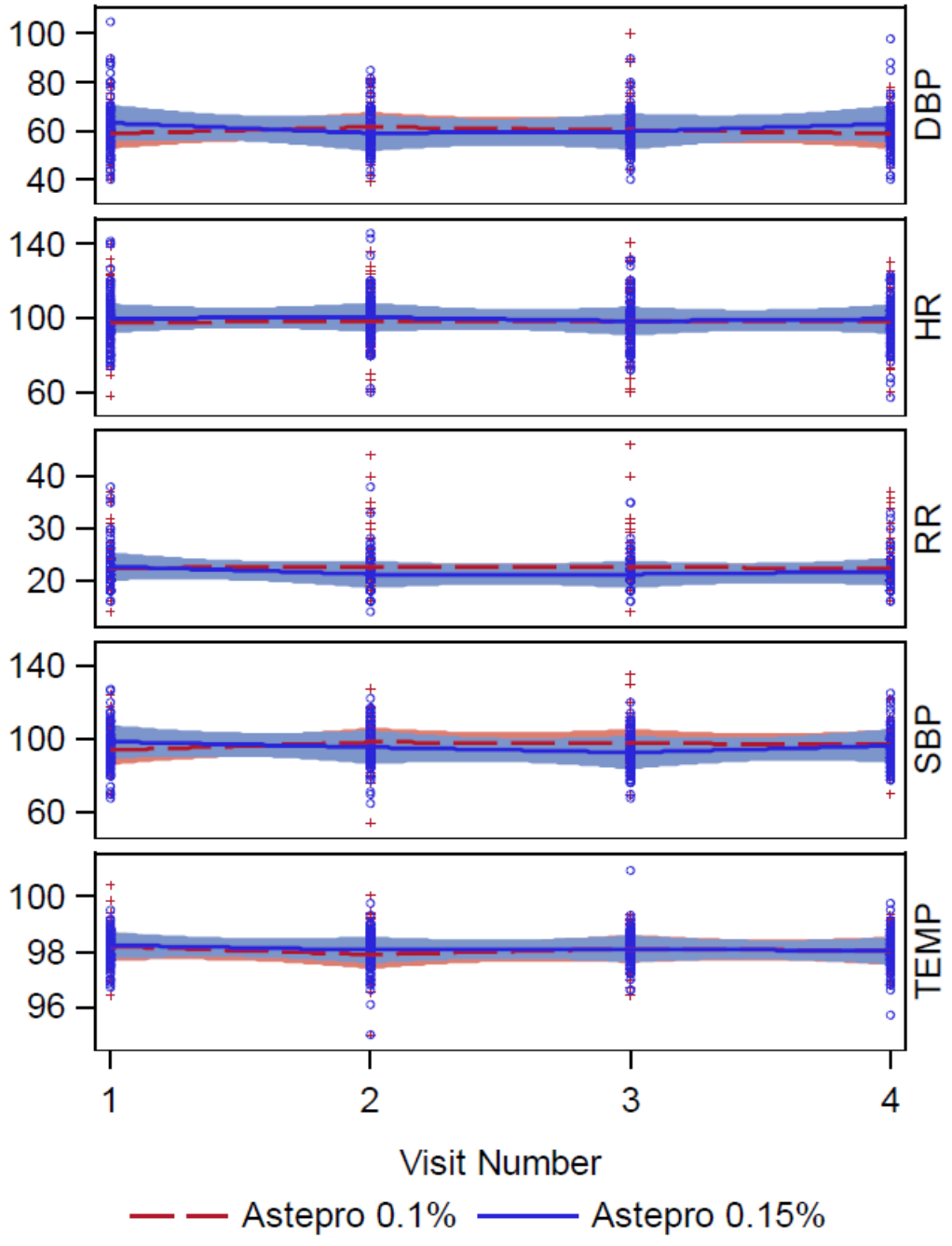
		Astepro 0.1%		Astepro 0.15%	
		Normal -> Low	Normal -> High	Normal -> Low	Normal -> High
		N (%)	N (%)	N (%)	N (%)
CHEMISTRY	ALT (U/L)	. .	1 (0)	. .	2 (1)
	AP (Alk Phos) (U/L)	2 (1)	2 (1)	1 (0)	. .
	AST (U/L)	. .	1 (0)	. .	1 (0)
	BUN (Urea) (mg/dL)	. .	5 (2)	. .	9 (3)
	Bilirubin (Total) (mg/dL)	4 (1)	. .	. .	. .
	Calcium (mg/dL)	. .	3 (1)	1 (0)	3 (1)
	Creatinine (mg/dL)	. .	2 (1)	. .	3 (1)
	Glucose (Random) (mg/dL)	8 (3)	2 (1)	6 (2)	1 (0)
	LD (U/L)	. .	2 (1)	. .	1 (0)
	Potassium (mEq/L)	. .	2 (1)	. .	1 (0)
	Protein (Total) (g/dL)	. .	. .	1 (0)	. .
HEMATOLOGY	Basophils (%)	1 (0)	3 (1)	. .	1 (0)
	Basophils (Abs) (x10E3/uL)	1 (0)	4 (1)	. .	1 (0)
	Eosinophils (%)	. .	11 (4)	. .	9 (3)
	Eosinophils (Abs) (x10E3/uL)	. .	3 (1)	. .	2 (1)
	Hematocrit (%)	3 (1)	12 (4)	. .	10 (3)
	Hemoglobin (g/dL)	2 (1)	. .	2 (1)	2 (1)
	MCV (fL)	1 (0)	6 (2)	. .	5 (2)
	Monocytes (%)	3 (1)	5 (2)	5 (2)	4 (1)
	Monocytes (Abs) (x10E3/uL)	8 (3)	. .	9 (3)	. .
	Neutrophils (%)	12 (4)	1 (0)	14 (5)	. .
	Neutrophils (Abs) (x10E3/uL)	11 (4)	. .	16 (5)	1 (0)
	Platelets (x10E3/uL)	. .	4 (1)	. .	4 (1)
	Red Cell Count (x10E6/uL)	4 (1)	2 (1)	1 (0)	1 (0)
	Total Lymphs (%)	2 (1)	7 (2)	. .	11 (4)
	Total Lymphs (Abs) (x10E3/uL)	. .	4 (1)	1 (0)	6 (2)
	White Cell Count (x10E3/uL)	8 (3)	3 (1)	4 (1)	5 (2)
URINALYSIS	Sp. Gravity	. .	7 (2)	1 (0)	4 (1)

Source: ASTEPRO LABS.XPT

7.4.3 Vital Signs

No clinically significant changes in mean values for blood pressure, pulse, respiratory rate, or body temperature were observed between treatment groups over the course of the study.

Figure 4. MP442 Mean vital signs by treatment group



Source: MP442 ADVS.xpt

Small numbers of participants had abnormal vital signs, but the proportions were similar across treatment arms.

Table 12. Shift table for abnormal vital signs across all visits

	Astepro 0.1%						Astepro 0.15%					
	High		Low		Normal		High		Low		Normal	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Body Temperature (F)	0	0	0	0	385	(100)	0	0	0	0	372	(100)
Diastolic Blood Pressure (mmHg)	37	(10)	6	(2)	342	(89)	30	(8)	2	(1)	340	(91)
Heart Rate (beats/min)	66	(17)	8	(2)	311	(81)	66	(18)	4	(1)	302	(81)
Respiratory Rate (breaths/min)	11	(3)	122	(32)	252	(65)	8	(2)	139	(37)	225	(60)
Systolic Blood Pressure (mmHg)	22	(6)	37	(10)	326	(85)	24	(6)	59	(16)	289	(78)

Source: MP442 ADVS.XPT
Percent within each treatment arm with abnormal vital sign measurement

7.4.4 Electrocardiograms (ECGs)

No ECGs were included in this submission.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were included in this submission.

7.4.6 Immunogenicity

As azelastine is a small molecule, immunogenicity was not anticipated and was not assessed in this submission. The adverse event profile for Astepro does not suggest an immunogenic effect.

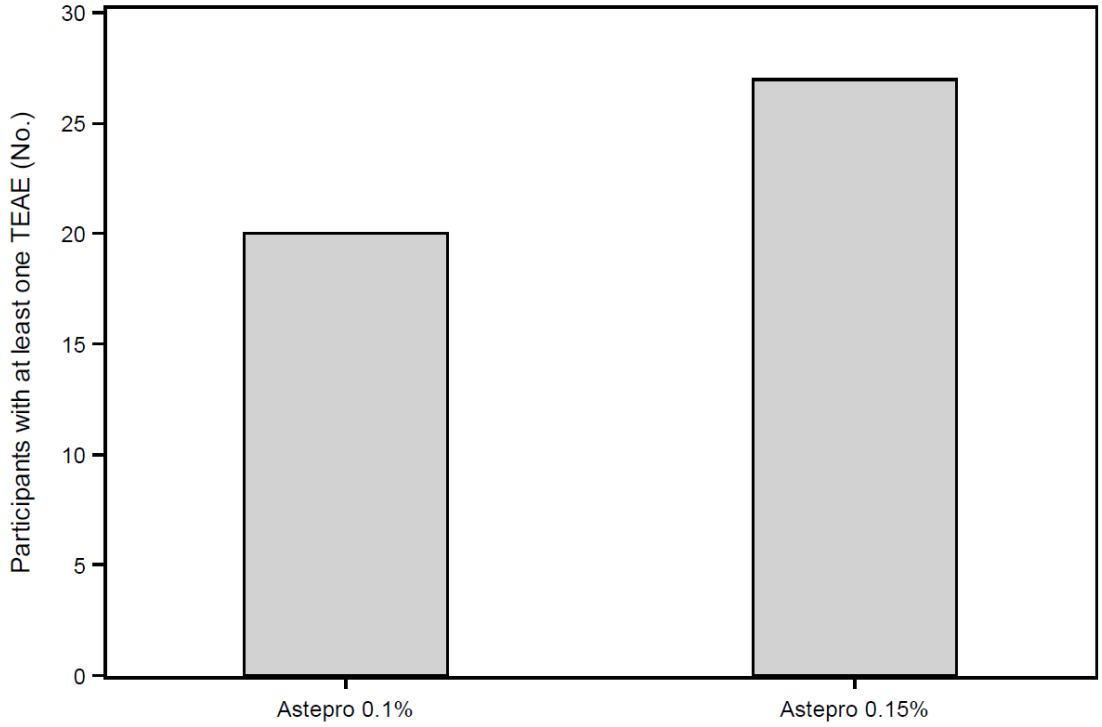
7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A higher rate of common adverse events was observed for participants in the 0.15% treatment arm, compared to those in the 0.1% treatment arm. Participants taking Astepro 0.15% had higher rates of treatment emergent adverse events, treatment-

related adverse events, and adverse events leading to discontinuation. The proportion of participants with at least one treatment emergent adverse event was larger in the group taking the higher dose of Astepro (28% for Astepro 0.15% compared to 21% for Astepro 0.1%). The proportion of participants with at least one treatment-related, treatment emergent adverse event was numerically higher in the group taking the higher dose of Astepro (13% for Astepro 0.15% compared to 2% for Astepro 0.1%). And, the percentage of subjects with treatment emergent adverse events leading to discontinuation also was higher in the group taking the higher dose of Astepro (3% for Astepro 0.15% vs. 2% for Astepro 0.1%).

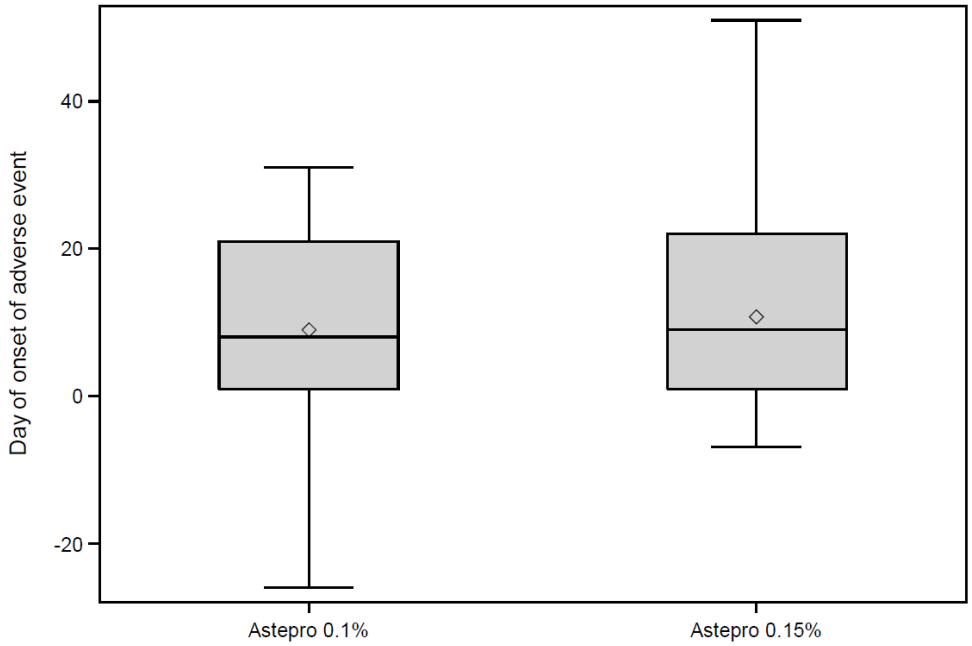
Figure 5. Higher rate of adverse events for Astepro 0.15%



7.5.2 Time Dependency for Adverse Events

There is no evidence of a clinically meaningful difference in time of onset of adverse events between the two treatment arms. Despite some differences in outliers, the mean, median and inter-quartile range for day of onset of adverse event were similar for both groups (**Figure 6**).

Figure 6. Time dependency for adverse events in MP442



7.5.3 Drug-Demographic Interactions

The Applicant reports no clinically noteworthy differences by sex or race in the incidence of treatment emergent adverse events between treatment groups (MP442 Study Report p. 61).

7.5.4 Drug-Disease Interactions

None reported.

7.5.5 Drug-Drug Interactions

None reported.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

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

7.6.2 Human Reproduction and Pregnancy Data

No formal data on azelastine and human pregnancy are available. Information in the current product labels for Astelin and Astepro note that azelastine is rated as Pregnancy Category C. In mice, rats and rabbits, no fetal or maternal effects were observed at doses less than three times the maximum recommended human daily intranasal dose.

7.6.3 Pediatrics and Assessment of Effects on Growth

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose, abuse, withdrawal or rebound symptoms were reported in the current submission. In the original development program reviewed under NDA 22371, one patient reported accidental overdose that led to early discontinuation. No further clinical sequelae were reported. Due to the route of administration, overdosage is unlikely to result in clinically significant adverse events, with the exception of potential increase in somnolence. Azelastine is not expected to have drug abuse potential, or cause withdrawal of rebound effects.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

The product label was reviewed for post-approval experience with Astepro. The label includes the following adverse reactions reported during the post-approval period: abdominal pain, nasal burning, nausea, sweet taste, and throat irritation. Additionally, the label reports adverse reactions observed with the post-approval use of the Astelin brand of azelastine hydrochloride 0.1% nasal spray, which include anaphylactoid reaction, application site irritation, atrial fibrillation, blurred vision, chest pain, confusion, dizziness, dyspnea, facial edema, hypertension, involuntary muscle contractions, nervousness, palpitations, paresthesia, parosmia, paroxysmal sneezing, pruritus, rash, disturbance or loss of sense of smell and/or taste, tachycardia, tolerance, urinary retention, and xerophthalmia.

The Applicant performed a cumulative review of all cases received from October 15, 2008 through July 31, 2014 during the marketing of Astepro Nasal Spray for inclusion in this supplement. There were 27 reports of insomnia. Based on this review, the Applicant is now recommending that insomnia be added to the Postmarketing section of the Astepro label. The Applicant also is proposing to relocate the following adverse

reactions from the Astelin list to the Astepro Postmarketing Experience section, including: atrial fibrillation, blurred vision, chest pain, confusion, dizziness, disturbance or loss of sense of smell and/or taste, dyspnea, facial swelling, hypertension, involuntary muscle contractions, nervousness, palpitations, paresthesia, parosmia, pruritus, rash, sneezing and tachycardia.

Review of a periodic adverse drug event report for the period of October 15, 2013 to October 14, 2014 was notable for one case of irregular heart rate necessitating hospitalization within days of initiating Astepro therapy.

Review of a periodic adverse drug event report for Astelin for the period of November 1, 2013 to October 31, 2014 was unremarkable.

Reviewer's comment: the Applicant's proposed labeling changes to section 6.2 are acceptable.

9 Appendices

9.1 Literature Review/References

A PubMed search conducted by this Reviewer on December 23, 2014, [search term: azelastine hydrochloride nasal NOT fluticasone; limits: human, clinical trial, meta-analysis, randomized clinical trial, English language, published in the last five years], yielded seven references.[1-7] Brief review did not indicate any new safety signals.

No literature review from the sponsor was noted.

9.2 Labeling Recommendations

At the time of this review, labeling discussions are ongoing. The submission includes a draft package insert proposing the expansion of the approved age range from 12 years and older to 6 months and older. The following list highlights the Applicant's major proposed changes:

- New indication down to 6 months for perennial allergic rhinitis and 2 years for seasonal allergic rhinitis at a dose of 0.1% (b) (4) 1 spray per nostril twice daily
- Inclusion of pediatric safety results in section 6.1
- Postmarketing experience updated in section 6.2
- Update age range in section 8.4
- No proposed labeling changes to section 14

One area of potential disagreement between the Applicant and the Agency for the labeling is with regard to the (b) (4)

9.3 Advisory Committee Meeting

Azelastine hydrochloride is a well-characterized pharmaceutical entity. Astepro Nasal Spray already is approved in patients 6 years and older and this application is to extend the indication to a younger age group. An advisory committee meeting was not necessary for this application.

9.4 Clinical Investigator Financial Disclosure Review Template

Date of Review: January 22, 2015

Covered Clinical Study (Name and/or Number): MP442

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: n=15		
Number of investigators who are Applicant employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): n=1 (b) (6)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Meda certified the absence of financial arrangements for all of the primary investigators, with the exception of (b) (6) works as a consultant, advisor, and advisory board member of Meda Pharmaceuticals. Meda and its representatives regularly monitored the study to verify study data, medical records and eCRFs in accordance with GCP regulations and guidelines.

Reference List

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3. Han D, Chen L, Cheng L et al. A multicenter randomized double-blind 2-week comparison study of azelastine nasal spray 0.1% versus levocabastine nasal spray 0.05% in patients with moderate-to-severe allergic rhinitis. ORL J Otorhinolaryngol Relat Spec 2011;73(5):260-265.

4. Howland WC, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in patients with allergy to Texas mountain cedar pollen. Int Forum Allergy Rhinol 2011;1(4):275-279.

5. Kalpaklioglu AF, Kavut AB. Comparison of azelastine versus triamcinolone nasal spray in allergic and nonallergic rhinitis. Am J Rhinol Allergy 2010;24(1):29-33.

6. Lieberman P, Meltzer EO, LaForce CF, Darter AL, Tort MJ. Two-week comparison study of olopatadine hydrochloride nasal spray 0.6% versus azelastine hydrochloride nasal spray 0.1% in patients with vasomotor rhinitis. Allergy Asthma Proc 2011;32(2):151-158.

7. Salapatek AM, Lee J, Patel D et al. Solubilized nasal steroid (CDX-947) when combined in the same solution nasal spray with an antihistamine (CDX-313) provides improved, fast-acting symptom relief in patients with allergic rhinitis. Allergy Asthma Proc 2011;32(3):221-229.

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/s/

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01/28/2015

SALLY M SEYMOUR
01/29/2015