CLINICAL REVIEW

Application Type	NDA Supplement
Application Number(s)	202236-S-008
Priority or Standard	Priority
Submit Date(s)	August 22, 2014
Received Date(s)	August 22, 2014
PDUFA Goal Date	February 22, 2015
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 / fluticasone propionate
(Proposed) Trade Name	Dymista
Therapeutic Class	antihistamine/corticosteroid
Applicant	Meda Pharmaceuticals
Formulation(s)	azelastine hydrochloride 0.1%/ fluticasone propionate 0.037% nasal spray
Dosing Regimen	1 spray per nostril twice daily
Indication(s)	Seasonal allergic rhinitis
Intended Population(s)	Patients ≥ 6 years of age

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The available data are adequate to support the approval of Dymista Nasal Spray for the proposed indication of "the relief of symptoms of seasonal allergic rhinitis in patients 6 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief." Dymista is a fixed-dose combination nasal spray of azelastine hydrochloride and fluticasone propionate, originally approved for use in patients 12 years of age and older on May 1, 2012. The safety profile is acceptable for the proposed use in children age six and older. Evidence of efficacy in this population is based upon the Agency's prior findings of efficacy for Dymista, for the two monocomponents (azelastine hydrochloride and fluticasone propionate) in this age group, and data from this submission that are supportive.

Meda Pharmaceuticals submitted a pediatric supplemental NDA application for Dymista. Dymista is comprised of 0.1% azelastine hydrochloride, an H_1-receptor antagonist, and 0.037% fluticasone propionate, a corticosteroid. Each actuation of the product contains 137 µg of azelastine hydrochloride and 50 µg of fluticasone propionate. The dosing regimen is one spray per nostril twice daily, for a total daily dose of 548 µg of azelastine hydrochloride and 200 µg of fluticasone propionate. Both azelastine hydrochloride and fluticasone propionate are available in the United States as active ingredients in multiple products including Astelin (azelastine hydrochloride 0.1% unsweetened), which received initial U.S. approval on November 1, 1996, and Flonase (fluticasone propionate), which received initial U.S. approval on October 19, 1994.

This application encompasses pediatric supplement No. 008 submitted on August 22, 2014 to NDA 202236. It includes the final study reports for studies MP4007 and MP4008, submitted to fulfill the Pediatric Research Equity Act requirement for NDA 202236. This supplement also is intended to fulfill some of the requirements outlined in the Written Request issued September 6, 2013. On the basis of these studies, the Applicant has proposed new labeling for Dymista, expanding the seasonal allergic rhinitis indication down to 6 years of age, 1 spray per nostril twice daily.

Evidence of efficacy comes from the Agency's prior findings of efficacy for Dymista, for the two monocomponents in this age group, as well as the supportive data from two studies contained in this submission for pediatric patients age 4 to 11 years. MP4008 was a double blind placebo controlled study that randomized 348 patients 1:1 to Dymista or placebo for two weeks and measured change from baseline in AM+PM 12-

hour reflective Total Nasal Symptom Score (rTNSS). The change in rTNSS was numerically supportive, but not statistically significant, for the 6 to 11 year age group.

The safety of Dymista in children age 4 to 11 years was evaluated in MP4008 and MP4007, an open label, active control, parallel group safety study that randomized 405 patients 3:1 to Dymista or fluticasone propionate nasal spray for three months. There were no deaths in the pediatric development program, and the rate of serious adverse events and adverse events leading to the discontinuation of treatment were low. There were fourteen instances of superficial nasal erosion and one instance of moderate erosion, but no instances of nasal ulceration or perforation. There were two reports of somnolence, one severe. Common adverse events included epistaxis, headache, cough, pyrexia, oropharyngeal pain, otitis media, vomiting, upper abdominal pain and upper respiratory tract infection.

In summary, the clinical recommendation for Dymista is approval, based on the acceptable safety profile in children age 6 years and older, the supportive efficacy data contained in this application, and the prior evidence of efficacy for this product and its monocomponents.

1.2 Risk Benefit Assessment

The risk/benefit assessment for expanding the indication for Dymista to children age 6 to 11 years is favorable given the improvement in nasal symptom scores and an acceptable safety profile. Though the improvement in nasal symptom scores did not achieve statistical significance, the data were numerically supportive in this supplement. Additional evidence of efficacy is based upon the known efficacy of the product's monocomponents for use for SAR in this age group. Astelin (azelastine hydrochloride) nasal spray is approved for use for SAR in children age 5 years and older, and Flonase (fluticasone propionate) nasal spray in children 4 years of age and older.

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

There are no recommendations for new postmarket requirements and commitments. Studies MP4007 and MP4008 fulfill post-marketing requirements 1888-1 and 1888-2, which were the remaining Pediatric Research Equity Act requirements for Dymista Nasal Spray. Meda has now fulfilled all of the Pediatric Research Equity Act requirements for Dymista Nasal Spray.

2 Introduction and Regulatory Background

2.1 Product Information

Dymista Nasal Spray is a fixed-dose combination nasal spray containing 0.1% azelastine and 0.037% fluticasone propionate. Both active pharmaceutical ingredients have been approved as prescription nasal sprays. Original prescription information for the commercially available fluticasone propionate and azelastine hydrochloride monotherapies also is provided below. Of note, fluticasone propionate recently was approved as an over-the-counter product for consumers down to the age of 4 years for the treatment of allergic rhinitis.

- Dymista Nasal Spray (azelastine/fluticasone propionate, 137/50 µg/spray); approved 2012
  - Adults and children 12 years and older
    - 1 spray per nostril twice daily (548 µg azelastine and 200 µg fluticasone propionate per day) for seasonal allergic rhinitis
- Flonase Nasal Spray (fluticasone propionate, 50 µg/spray); approved 1994 for (b) (4) allergic and nonallergic rhinitis
  - Adults and children 12 years and older
    - 2 sprays per nostril daily (200 µg/day)
    - 1 spray per nostril twice daily (200 µg/day)
    - Dose may be decreased to 1 spray per nostril daily (100 µg/day)
  - Children 4 to 11 years
    - 1 spray per nostril once daily (100 µg/day)
    - Some pediatric patients may require 200 µg/day, delivered as 1 spray per nostril twice daily or 2 sprays per nostril daily
- Astelin Nasal Spray (azelastine hydrochloride, 137 µg/spray); approved 1996
  - Children 5 to 11 years
    - 1 spray per nostril twice daily for seasonal allergic rhinitis
  - Adults and adolescents 12 years of age
    - 1 or 2 sprays per nostril twice daily for seasonal allergic rhinitis
    - 2 sprays per nostril twice daily for vasomotor rhinitis
- Astepro Nasal Spray 0.1% or 0.15% (azelastine hydrochloride, 137 or 205.5 µg/spray, respectively); approved 1996
  - Children 6 to 11 years
    - 1 spray per nostril twice daily for seasonal or perennial allergic rhinitis
  - Adults and adolescents 12 years of age and older
    - 1 or 2 sprays per nostril twice daily for seasonal allergic rhinitis
    - Astepro 0.15% 2 sprays per nostril once daily for seasonal allergic rhinitis

- Astepro 0.15% 2 sprays per nostril twice daily for perennial allergic rhinitis

2.2 Tables of Currently Available Treatments for Proposed Indications

The following table lists the available intranasal treatments for allergic rhinitis. It does not include oral treatments for allergic rhinitis.

Table 1. Available intranasal treatments for allergic rhinitis

Active Ingredient	Trade Name	Age Range
	H_1-receptor antagonists	
Azelastine hydrochloride	Astelin and generic	≥ 5 years
	Astepro	≥ 12 years
Olopatadine	Patanase	≥ 6 years
	Combination H_1-receptor antagonist and corticosteroid	
Azelastine and fluticasone	Dymista	≥ 12 years
	Corticosteroids	
Beclomethasone	Beconase AQ	≥ 6 years
Beclomethasone dipropionate	QNASL	≥ 12 years
Budesonide	Rhinocort Aqua	≥ 6 years
Ciclesonide	Omnaris	≥ 6 years
Ciclesonide	Zetonna	≥ 12 years
Fluticasone furoate	Veramyst	≥ 2 years
Fluticasone propionate	Flonase and generics	≥ 4 years
Flunisolide	Generics	≥ 6 years
Mometasone	Nasonex	≥ 2 years
Triamcinolone	Nasacort AQ and generic	≥ 2 years

2.3 Availability of Proposed Active Ingredient in the United States

Both azelastine hydrochloride and fluticasone propionate are available in the United States as active ingredients in multiple products.

Azelastine hydrochloride 0.1% (unsweetened) is available both as a branded product (Astelin) and generic. Azelastine hydrochloride is also available as 0.1% and 0.15% sweetened formulations under the trade name Astepro.

Fluticasone propionate is available both as a branded product (Flonase) and as multiple generic products.

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 unsweetened and sweetened azelastine nasal sprays. Section 5.1 of the current Astelin and Astepro labels contains 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.

Corticosteroids are known to be associated with a number of important systemic and local safety issues. Systemic adverse events include: immunosuppression, hypothalamic, pituitary and adrenal axis effects, and reduction in growth velocity, although with nasal corticosteroids systemic exposure is generally limited. Local adverse events with nasal corticosteroids are more common and include: epistaxis, nasal ulceration, and nasal septal perforation. This class of drugs is also known to carry an association with the development of cataracts and glaucoma. These events are described in the product label.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Agency approved Dymista on May 1, 2012 for the relief of symptoms of seasonal allergic rhinitis in patients 12 years and older who require treatment with both azelastine fluticasone and fluticasone propionate for symptomatic relief. The Approval Letter outlined the following required studies under the Pediatric Research Equity Act:

- 1888-1: Conduct a trial to evaluate the long-term safety of Dymista in children 4 to 11 years of age with seasonal allergic rhinitis or perennial allergic rhinitis.
    - Final Protocol Submission: October 2012
    - Study Completion: February 2014
    - Final Report Submission: June 2014
- 1888-2: Conduct a trial to evaluate the efficacy and safety of Dymista in children 4 to 11 years of age with seasonal allergic rhinitis.
    - Final Protocol Submission: February 2013
    - Study Completion: December 2013
    - Final Report Submission: June 2014

A waiver for patients younger than 2 years of age was granted given that the existence of seasonal allergic rhinitis in this age group is uncertain. Historically the Division has not asked that nasal corticosteroids be studied in children younger than 2 years given the consensus that seasonal allergic rhinitis occurs in children 2 years of age and older

and perennial allergic rhinitis occurs in children 6 months of age and older (J Allergy Clin Immunol 2000, 106:832). A waiver for patients 2 to 4 years was granted given that Dymista does not provide a meaningful benefit over existing therapies and is unlikely to be used in a large number of patients in this age group.

A Written Request was issued on September 6, 2013, requesting studies to investigate the potential use of a fixed-dose combination nasal spray of azelastine and fluticasone propionate for the treatment of seasonal allergic rhinitis in children 4 to 11 years of age. The Written Request outlined the following clinical studies to be completed and submitted by September 30, 2014:

- *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.

On March 20, 2014, Meda requested an extension of final report submission due to unexpected weather conditions impacting the duration of the allergy season. The deferral extension was discussed with the Pediatric Review Committee and was granted on April 29, 2014. The new date for final report submission was September 2014 for both studies.

A pre-SNDA meeting was held January 13, 2014. It was agreed that safety data from the two studies would not be pooled given the differences in trial design. (b) (4) but the division did not agree, stating that (b) (4)

Study 1 refers to MP442 for Astepro (azelastine hydrochloride), under NDA 22-203. Studies 2 and 3 correspond to PMR's 1888-1 and 1888-2 (MP007 and MP008) outlined above for Dymista under NDA 202-236. The three complete study reports comprise the Applicant's response to the Written Request and Pediatric Research Equity Act requirements.

The Division granted priority review to the application on September 19, 2014 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 and fluticasone are known drug substances with extensive post-marketing experience. Dymista is an approved product for patients 12 years and older and the Applicant requests (b) (4). For these reasons, no DSI review is recommended.

3.2 Compliance with Good Clinical Practices

The Applicant includes a statement of good clinical practice, indicating that all clinical trials were conducted under the supervision of an institutional review board. Informed consent from the caregiver and pediatric informed assent from subjects 7 years of age and older were 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. A list of clinical investigators was provided by the Applicant, 41 investigators for MP4007 and 35 for MP4008. None were employees. Meda and its representatives regularly monitored the study to verify study data, medical records and case report forms in accordance with good clinical practice regulations and guidelines. Meda certified the absence of financial arrangements for all of the primary investigators, with the exception of (b) (4). (b) (4) works as a consultant, advisor, and advisory board member of Meda Pharmaceuticals.

(b) (4) recruited sixteen participants to MP4007, the safety study. Fourteen were randomized to the Dymista treatment arm. He reported three adverse events

(headache, ear pain, nasal septum disorder), all for participants randomized to Dymista. In the study as a whole, 41% in the Dymista arm and 37% in the Fluticasone arm reported at least one treatment emergent adverse event. Of (b) (4) participants, adverse events were reported by 21% in the Dymista arm (3/14) and 0 in the Fluticasone arm (0/2). No Division of Scientific Investigations audit is recommended at this time.

Reviewer's comment: The imbalance in adverse event reporting rates from (b) (4) *participants vs. the study as a whole is noted, but it is unlikely to have biased the safety study as a whole given the relatively small number of participants that he recruited (16/404).*

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 formulation.

The final Chemistry Manufacturing and Controls review is pending at the time of this review.

4.2 Clinical Microbiology

Dymista is a (b) (4) There is no new clinical microbiology data in this supplement.

4.3 Preclinical Pharmacology/Toxicology

The Preclinical Pharmacology/Toxicology program was reviewed with the original NDA 202236 submission. There is no new pharmacology/toxicology information in this supplement.

4.4 Clinical Pharmacology

The Clinical Pharmacology program was reviewed with the original NDA 202236 submission. There is no new clinical pharmacology information in this supplement

4.4.1 Mechanism of Action

Azelastine hydrochloride is a H_1-receptor antagonist. Fluticasone propionate is a corticosteroid. While corticosteroids have been demonstrated to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, etc.), and mediators (e.g., histamine, eicosanoids, etc.) the exact mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known.

4.4.2 Pharmacodynamics

No new pharmacodynamic data is included in this application.

4.4.3 Pharmacokinetics

No new pharmacokinetic data is included in this application.

5 Sources of Clinical Data

The primary sources of clinical data in this supplement are two clinical trials, as shown in the table below. Overall, the conduct of the studies was consistent with the Agency's written request and guidance: "Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products." The studies are adequately designed to evaluate the safety and efficacy of Dymista in children age 4 to 11 years.

5.1 Tables of Studies/Clinical Trials

Table 2. Study design

Study	Population	N	Design	Treatment Arms	Duration	Endpoint
MP4007	Age 4 to 11 years with allergic rhinitis	405 (354)*	Randomized, open label, active control, parallel group	1 spray per nostril twice daily • Dymista • fluticasone propionate	3 months	Safety
MP4008	Age 4 to 11 years moderate to severe seasonal allergic rhinitis	348 (304)*	Randomized, double blind, placebo controlled	1 spray per nostril twice daily • Dymista • Placebo	2 weeks	Efficacy, Safety

*N age 6 to 11 years

5.2 Review Strategy

The clinical review focused on the safety study for allergic rhinitis (MP4007), and the safety and efficacy study of moderate to severe seasonal allergic rhinitis (MP4008), both performed in children age 4 to 11 years. Review of the studies 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. Postmarketing safety data based on annual reports submitted for Dymista were reviewed. A literature review was performed to identify any new safety signals with azelastine and fluticasone.

The design of studies MP4007 and MP4008 will be described in Section 5.3, the efficacy results in Section 6, and safety results in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

MP4007

Study MP4007 was a phase three, US, multi-center, randomized, open label, active control, parallel group study of the safety of Dymista compared to fluticasone in participants ages 4 to 11 years with allergic rhinitis.

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

Dymista nasal spray consists of a fixed-dose combination of azelastine hydrochloride and fluticasone propionate. Each actuation of the Dymista nasal spray pump delivers 137 µg of azelastine hydrochloride and 50 µg of fluticasone propionate such that 1 spray per nostril twice daily delivers a total daily dose of 548 µg of azelastine hydrochloride and 200 µg of fluticasone propionate. The approved adult dose for Dymista nasal spray was used for the pediatric population, 4 to 11 years of age. The approved dosage of azelastine hydrochloride in pediatric patients ages 5 to 11 years of age (Astelin Package Insert) is 1 spray per nostril twice daily of a 137 µg per spray formulation. This equates to 548 µg per day of azelastine hydrochloride, which is the same dosing used in the formulation of Dymista nasal spray. The approved dosage of fluticasone propionate (Flonase Package Insert) is 200 µg per day. In pediatric patients ages 4 years and older, the recommended dosing of fluticasone propionate is 100 µg per day (1 spray per nostril once daily); however, treatment with 200 µg per day is approved in children who do not adequately respond to the lower dose of 100 µg per day. Dymista nasal spray is formulated with a dose of fluticasone propionate of 200 µg/day.

Reviewer's comment: The rationale for dose selection in this population is acceptable.

Pertinent inclusion criteria

- Male and female participants 4 to 11 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)

- Pregnancy, lactation or of childbearing potential without abstinence or use of a medically acceptable method of contraception

A lead-in period for eligibility assessment of inclusion and exclusion criteria (2 to 30 days) was followed by randomization. A stratified block randomization scheme assigned subjects in a 3:1 ratio to the two treatments, Dymista and Fluticasone. The scheme was stratified by age (4 to < 6, 6 to < 9, and 9 to 11 years). Participants were then followed for a three-month active study period. A schedule of study evaluations is presented in Table 3.

Table 3. MP4007 Study evaluation schedule

	Lead-in Period	Treatment Period			
Procedure	Visit 1[a] Day -30 to -2	Visit 2 Day 1 (Baseline)	Visit 3 Day 15 (±3 days)[c]	Visits 4 & 5 Days 30 & 60 (±5 days)	Visit 4 Day 29 (±3 days)[c]
Written informed consent and pediatric assent	X[b]				
Inclusion/Exclusion criteria	X	X			
Physical examination, direct visual	X	X	X		X
Medical history	X				
Nasal examination	X	X	X	X	X
Vital signs	X	X	X	X	X
Height and weight	X				X
Blood and urine samples for safety laboratory analysis	X				X
Review results of safety laboratory analysis		X			
Urine pregnancy test[d]	X	X	X	X	X
Assess concomitant medications	X	X	X		X
Randomization		X			
PRQLQ[e]		X	X	X	X
EQ-FD-Y[e]		X	X	X	X
Instruct Subject's caregivers on proper completion of Subject Diary	X	X	X	X	
Dispense Subject Diary	X	X	X	X	
Instruct Subject's caregivers on proper use of study medications		X	X	X	
Weigh and dispense study medication		X	X[f]	X	
Collect and weigh used study medication				X	X
Collect Subject Diary		X	X	X	X
Adverse events assessment		X	X	X	X
Contact Interactive voice/web response system IXRS	X	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 -6 windows calculated from Visit 2
[d] In females ≥ 9 years
[e] In children ≥ 6 years
[f] At Visit 3 study medication dispensed at Visit 2 was weighed and returned to subject

The study treatment, Dymista Nasal Spray, is an approved product that contains azelastine hydrochloride and fluticasone propionate. The treatment was supplied in amber glass bottles with a metered-dose nasal spray pump closure containing 23 g of study medication. After priming, each metered spray delivered approximately 137 µg of azelastine hydrochloride and 50 µg of fluticasone; one spray per nostril twice daily delivered 548 µg of azelastine hydrochloride and 200 µg of fluticasone.

The control treatment was a commercial Fluticasone Nasal Spray (Roxanne Laboratories, Columbus OH generic equivalent to Flonase® Nasal Spray [Fluticasone Propionate 50µg]). This was supplied in amber glass bottles with a metered-dose nasal spray pump closure containing 16g of medication. After priming, each metered spray delivered approximately 50µg of fluticasone propionate. Instructions for use and storage information were according to the manufacturer's package insert.

Both the study treatment and Fluticasone Nasal Spray were provided to the subject/caregiver in the commercial bottle, open label. Each bottle provided 120 sprays, i.e., 30 days of medication.

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.

Prohibited medications included antihistamines, anticholinergic agents, other intranasal therapies, decongestants, corticosteroids, tricyclic antidepressants, monoamine oxidase inhibitors, leukotriene modifiers, eye drops, cromolyn, immunosuppresants or immunomodulators, Xolair, initiation of immunotherapy, other investigational therapies.

MP4007 was not designed as an efficacy study, but efficacy was explored. The proportion of days that overall allergy symptoms were reported and proportions by severity were provided by treatment group and are reviewed in Section 6.

The primary endpoint for MP4007 was a safety analysis, which consisted of subject/caregiver-reported adverse events, nasal examinations, vital signs, and laboratory assessments. These are reviewed in Section 7.

A total of 405 participants enrolled in MP4007. All but one were included in the safety population: she had epistaxis at randomization, prior to the first dose of treatment, and was withdrawn from participation by the investigator. A total of 28 participants did not complete the study: 10 due to adverse events, 5 due to lost-to-follow-up, 2 to non-compliance, 3 to other, 2 to protocol violations, 1 to treatment failure, and 5 participants elected to withdraw. Overall, the reasons for discontinuations did not vary appreciably between treatment arms or by age stratum (Table 4).

Table 4. MP4007 Subject disposition, all randomized subjects and all age strata

	All Age Strata				4 to < 6 years				6 to < 9 years				9 to 11 years			
	Dymista		Fluticasone		Dymista		Fluticasone		Dymista		Fluticasone		Dymista		Fluticasone	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Randomized	304	(100)	101	(100)	39	(100)	12	(100)	129	(100)	44	(100)	136	(100)	45	(100)
Safety	304	(100)	100	(99)	39	(100)	12	(100)	129	(100)	43	(98)	136	(100)	45	(100)
Discontinued	19	(6)	9	(9)	4	(10)	1	(8)	7	(5)	5	(11)	8	(6)	3	(7)
Completed	285	(94)	92	(91)	35	(90)	11	(92)	122	(95)	39	(89)	128	(94)	42	(93)
Primary Reason for Discontinuation From Study																
AE	6	(2)	4	(4)	2	(5)	1	(8)	0	0	1	(2)	4	(3)	2	(4)
Lost to Follow-Up	3	(1)	2	(2)	1	(3)	0	0	2	(2)	1	(2)	0	0	1	(2)
Non-Compliance	2	(1)	0	0	0	0	0	0	1	(1)	0	0	1	(1)	0	0
Other	2	(1)	1	(1)	0	0	0	0	1	(1)	1	(2)	1	(1)	0	0
Protocol Violation	1	(0)	1	(1)	0	0	0	0	1	(1)	1	(2)	0	0	0	0
Treatment Failure	1	(0)	0	0	0	0	0	0	1	(1)	0	0	0	0	0	0
Withdrawal	4	(1)	1	(1)	1	(3)	0	0	1	(1)	1	(2)	2	(1)	0	0

Source: MP4007 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 MP4007 are presented in Table 5. Participants in the Dymista arm were slightly more likely to be male. Overall, a relatively high percentage of participants identified as Hispanic or Latino. Otherwise, the treatment arms and age strata appeared comparable in terms of demographic distribution.

Table 5. MP4007 Subject demographics and baseline characteristics

		All Age Strata		4 to < 6 years		6 to < 9 years		9 to 11 years	
		Dymista	Fluticasone	Dymista	Fluticasone	Dymista	Fluticasone	Dymista	Fluticasone
Age (Years)	Mean	8	8	5	5	7	7	10	10
	StdDev	(2)	(2)	(0)	(1)	(1)	(1)	(1)	(1)
	Min	4	4	4	4	6	6	9	9
	Max	11	11	5	5	8	8	11	11
Gender									
F	N	121	50	15	6	58	25	48	19
	(%)	(40)	(50)	(38)	(55)	(45)	(56)	(35)	(42)
M	N	183	51	25	5	70	20	88	26
	(%)	(60)	(50)	(63)	(45)	(55)	(44)	(65)	(58)
Ethnicity									
Hispanic or Latino	N	69	22	11	1	31	12	27	9
	(%)	(23)	(22)	(28)	(9)	(24)	(27)	(20)	(20)
Not Hispanic or Latino	N	225	76	27	10	92	32	106	34
	(%)	(74)	(75)	(68)	(91)	(72)	(71)	(78)	(76)
Not Reported	N	10	3	2	0	5	1	3	2
	(%)	(3)	(3)	(5)	0	(4)	(2)	(2)	(4)
Race									
American Indian or Alaska Native	N	4	1	1	0	2	1	1	0
	(%)	(1)	(1)	(3)	0	(2)	(2)	(1)	0
Asian	N	12	2	2	0	4	2	6	0
	(%)	(4)	(2)	(5)	0	(3)	(4)	(4)	0
Black or African American	N	62	21	12	3	24	11	26	7
	(%)	(20)	(21)	(30)	(27)	(19)	(24)	(19)	(16)
Native Hawaiian or Pacific Islander	N	2	1	0	0	2	1	0	0
	(%)	(1)	(1)	0	0	(2)	(2)	0	0
White	N	237	80	26	9	100	31	111	40
	(%)	(78)	(79)	(65)	(82)	(78)	(69)	(82)	(89)
Height (in)	Mean	52	52	44	44	50	49	57	57
	StdDev	(5)	(6)	(2)	(2)	(3)	(3)	(4)	(4)
	Min	40	39	40	39	44	41	46	49
	Max	66	64	47	47	58	54	66	64
Weight (lbs)	Mean	72	75	45	46	62	60	89	97
	StdDev	(25)	(29)	(6)	(7)	(18)	(13)	(22)	(29)
	Min	32	33	32	33	35	42	44	50
	Max	159	162	60	54	152	91	159	162

Source: MP4007 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%.

MP4008

Study MP4008 was a phase three, US, multi-center, randomized, double-blind, placebo-controlled, parallel group study that was designed to evaluate the efficacy and safety of Dymista Nasal Spray compared to placebo at a dosage of one spray per nostril twice daily, when given to subjects 4 to 11 years of age with seasonal allergic rhinitis.

Pertinent inclusion criteria

- Male and female subjects 4 to 11 years
- A history of seasonal allergic rhinitis to pollen in the prevailing allergy season
- Positive allergy skin prick test to a prevailing pollen
- 12-hour reflective Total Nasal Symptom Score (rTNSS) of ≥6 and a reflective (r) congestion score of ≥2 at Visit 1
- Adherence to at least 6 doses of placebo medication taken during the lead-in period between Visit 1 and Visit 2
- A total 12-hour rTNSS ≥42 and a total 12-hour reflective (r) congestion score of ≥14 over the lead-in period preceeding Visit 2

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)
- Pregnancy, lactation or of childbearing potential without abstinence or use of a medically acceptable method of contraception
- Planned travel outside of the pollen area during the study period

Prohibited medications included antihistamines, anticholinergic agents, other intranasal therapies, decongestants, corticosteroids, tricyclic antidepressants, monoamine oxidase inhibitors, leukotriene modifiers, eye drops, cromolyn, immunosuppresants or immunomodulators, Xolair, initiation of immunotherapy, other investigational therapies.

A lead-in period of up to seven days for eligibility assessment of inclusion and exclusion criteria was followed by randomization. A block randomization scheme was used to assign subjects 1:1 to Dymista or placebo, stratified by age (4 to < 6, 6 to < 9, and 9 to 11 years). Participants were then followed for a two week study period. A schedule of study evaluations is presented in Table 6.

Table 6. MP4008 Study evaluation schedule

	Lead-in Period	Treatment Period		
Procedure	Visit 1[a] Screening	Visit 2[c] Day 1 Randomization	Visit 3[†] Day 8 (±1 day)	Visit 4[†]/ET Day 15 (±3 days)
Written informed consent and pediatric assent[b]	X[b]			
Symptom qualification	X	X		
Inclusion/Exclusion criteria	X	X		
Skin test	X			
Physical examination	X			
Medical history	X			
Nasal examination	X	X	X	X
Vital signs	X	X	X	X
Height	X			
Weight	X			X
Blood and urine samples for safety laboratory analysis	X			
Review results of safety laboratory analysis		X		
Urine pregnancy test[d]	X	X	X	X
Assess concomitant medications	X	X	X	X
Randomization		X	X	X
PRQLQ[g]		X	X	X
EQ-FD-Y[g]		X	X	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	X
Weigh and dispense study medication		X		
Collect and weigh used study medication			X	X
Collect Subject Diary		X	X	X
Adverse events assessment[e]		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. 18
ET =Early Termination /end of treatment
a The Lead-in period was planned for up to 7 days.
b Informed consent/assent was given prior to Visit 1 if wash-out of concomitant medications was needed. A washout from prohibited concomitant medications took place on an as-needed basis, after Informed Consent/Assent occurred and prior to the Lead-in period.
c Visit 2 was to occur a minimum of 4 days after Visit 1, and prior to noon on the day of the visit.
d All females ≥9 years of age
e Any adverse event that occurred subsequent to signing the informed consent was to be recorded.
f Visit windows calculated from Visit 2: Visit 3 (8±1day) and Visit 4 (minimum at Day 15; maximum at Day 18)
g PRQLQ=Pediatric Rhinoconjunctivitis Quality of Life Questionnaire and EQ-5D-Y™ =youth version of the standardized instrument for use as a measure of health outcome were administered at Visits 2, 3, and 4 to subjects ≥6 years of age.

Dymista Nasal Spray or placebo was provided to the subject/caregiver in amber glass bottles containing either study medications or vehicle with a metered-dose nasal spray pump closure. Each bottle provided 120 sprays, i.e., 30 days of medication. The study treatment, Dymista Nasal Spray, is an approved product that contains azelastine

hydrochloride and fluticasone propionate. After priming, each metered spray delivered approximately 137µg of azelastine hydrochloride and 50µg of fluticasone propionate; one spray per nostril twice daily delivered 548µg of azelastine hydrochloride and 200µg of fluticasone propionate. The placebo nasal spray contains the same components as Dymista Nasal Spray with the exception of the active ingredients and was supplied and delivered in the same manner.

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.

MP4008 was designed as the primary pediatric efficacy study, and the primary endpoint was defined as change from baseline in AM+PM 12-hour reflective Total Nasal Symptom Score (rTNSS) for the entire double-blind period (i.e. Day 2 AM to Day 14 PM).The primary efficacy analysis was prespecified for the 6 to 11 year age group, with exploratory analyses planned for the 4 to 5 year age group.

Reviewer's comment: This statistical analysis plan is acceptable.

Other relevant efficacy measures included the Total Ocular Symptom Score (TOSS), Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ), and Total Symptom Score (rTSS). More details about the efficacy assessments and results are reviewed in Section 6. Safety assessments consisted of subject/caregiver-reported adverse experiences, nasal examinations, and vital signs. The safety assessments and results are reviewed in Section 7.

A total of 348 participants were enrolled in MP4008. All 348 were included in the safety and intention to treat populations. A total of 4 participants did not complete the study, two due to adverse events (asthma and acid reflux), one to treatment failure, and one to time away from the study site, ie time away from exposure to the relevant pollens. Overall, the reasons for discontinuations did not vary appreciably between treatment arms or by age stratum (Table 7).

Table 7. MP4008 Subject disposition, all randomized subjects and all age strata

	All Age Strata				4 to < 6 years				6 to < 9 years				9 to 11 years			
	Dymista		Placebo		Dymista		Placebo		Dymista		Placebo		Dymista		Placebo	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Randomized	173	(100)	175	(100)	21	(100)	23	(100)	59	(100)	60	(100)	93	(100)	92	(100)
Safety	173	(100)	175	(100)	21	(100)	23	(100)	59	(100)	60	(100)	93	(100)	92	(100)
Intention to Treat	173	(100)	175	(100)	21	(100)	23	(100)	59	(100)	60	(100)	93	(100)	92	(100)
Per Protocol	147	(85)	154	(88)	19	(90)	17	(74)	51	(86)	55	(92)	77	(83)	82	(89)
Discontinued	2	(1)	2	(1)	0	0	0	0	0	0	2	(3)	2	(2)	0	0
Completed	171	(99)	173	(99)	21	(100)	23	(100)	59	(100)	58	(97)	91	(98)	92	(100)
Reason for Discontinuation																
AE	1	(1)	1	(1)	0	0	0	0	0	0	1	(2)	1	(1)	0	0
Other	0	0	1	(1)	0	0	0	0	0	0	1	(2)	0	0	0	0
Treatment Failure	1	(1)	0	0	0	0	0	0	0	0	0	0	1	(1)	0	0

Source: MP4008 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 MP4008 are presented in Table 8. Overall, the treatment arms and age strata appeared comparable in terms of demographic distribution.

Table 8. MP4008 Subject demographics and baseline characteristics

		All Age Strata		4 to < 6 years		6 to < 9 years		9 to 11 years	
		Dymista	Placebo	Dymista	Placebo	Dymista	Placebo	Dymista	Placebo
Age (Years)	Mean	8	8	5	5	7	7	10	10
	StdDev	(2)	(2)	(1)	(0)	(1)	(1)	(1)	(1)
	Min	4	4	4	4	6	6	9	9
	Max	11	11	5	5	8	8	11	11
Gender									
Female	N	77	85	11	13	24	34	42	38
	(%)	(45)	(49)	(52)	(57)	(41)	(57)	(45)	(41)
Male	N	96	90	10	10	35	26	51	54
	(%)	(55)	(51)	(48)	(43)	(59)	(43)	(55)	(59)
Ethnicity									
Hispanic or Latino	N	21	32	3	5	9	12	9	15
	(%)	(12)	(18)	(14)	(22)	(15)	(20)	(10)	(16)
Not Hispanic or Latino	N	151	143	18	18	50	48	83	77
	(%)	(87)	(82)	(86)	(78)	(85)	(80)	(89)	(84)
Not Reported	N	1	0	0	0	0	0	1	0
	(%)	(1)	0	0	0	0	0	(1)	0
Race									
American Indian or Alaska Native	N	3	1	1	0	1	1	1	0
	(%)	(2)	(1)	(5)	0	(2)	(2)	(1)	0
Asian	N	4	0	1	0	3	0	0	0
	(%)	(2)	0	(5)	0	(5)	0	0	0
Black or African American	N	53	49	6	5	20	23	27	21
	(%)	(31)	(28)	(29)	(22)	(34)	(38)	(29)	(23)
Native Hawaiian or Other Pacific Islander	N	1	0	0	0	1	0	0	0
	(%)	(1)	0	0	0	(2)	0	0	0
White	N	119	130	14	18	36	39	69	73
	(%)	(69)	(74)	(67)	(78)	(61)	(65)	(74)	(79)
Height (in)	Mean	135	135	109	115	128	127	146	144
	StdDev	(15)	(15)	(7)	(10)	(7)	(8)	(10)	(11)
	Min	97	104	97	104	110	104	127	115
	Max	169	167	123	152	143	141	169	167
Weight (lbs)	Mean	35	35	19	24	30	28	41	43
	StdDev	(13)	(14)	(3)	(9)	(8)	(7)	(12)	(15)
	Min	15	15	15	16	17	15	23	21
	Max	82	102	25	52	59	60	82	102

Source: MP4008 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

The results from MP4008 did not show a statistically significant difference between Dymista and placebo for the primary efficacy endpoint. The following should be considered when interpreting the efficacy data. MP4008 was designed with approximately 80% power, thus, there is a twenty percent chance that the study would fail to detect a clinically meaningful outcome when one was in fact present. In addition, there are challenges to the assessment of efficacy in children as symptoms are reported by a caregiver. This could introduce measurement error, which would also increase the chance of failing to detect a clinically meaningful difference. Despite the lack of statistical significance, there was a numerical trend favoring Dymista over placebo, which is supportive.

A second consideration in support of the efficacy of Dymista is that both active pharmaceutical ingredients are approved for the treatment of seasonal allergic rhinitis in children. Evidence of efficacy for Astepro (azelastine hydrochloride) 0.15% and 0.1% was observed in a study of 489 children age 6 to 11 years, reviewed under supplement No. 8 to NDA 22203. The study found that the rTNSS mean change from baseline was -3.4 for both Astepro 0.15% and Astepro 0.1%, vs. -2.5 for placebo (p=0.005 and 0.02, respectively). Fluticasone nasal spray was approved for use in children down to age 4 years for the treatment of seasonal and perennial allergic rhinitis and nonallergic rhinitis based on evidence from studies of 650 patients age 4 to 11.

Third, Dymista is approved for seasonal allergic rhinitis in patients 12 years and older and there is no evidence to suggest that the pathophysiology of allergic rhinitis is fundamentally different in younger children; thus, extrapolation of efficacy can be considered.

Based upon the totality of available data, it is reasonable to conclude sufficient support for the efficacy of Dymista for children 6 years and older with seasonal allergic rhinitis.

6.1 Indication

The Applicant proposes that Dymista is indicated for the treatment of seasonal allergic rhinitis in patients six years of age and older.

6.1.1 Methods

Refer to Section 5.3 for a discussion of the protocols and planned analyses for study MP4008. The design of the trial generally was consistent with the principles laid out in the Agency's Draft Guidance on this topic, as well as with the programs conducted for other products approved for seasonal allergic rhinitis.

Since MP4008 was the designated efficacy trial, the efficacy results of MP4008 will be discussed in the following sections. Efficacy was explored in MP4007 and the exploratory results will be briefly mentioned.

6.1.2 Demographics

The Dymista and placebo groups were reviewed in Section 5 and were comparable with regard to demographic and baseline characteristics overall and for each age stratum (Table 8). The subjects ranged in age from 4 years to 11 years with a mean age of 8 years in both the Dymista and placebo groups. Approximately half of the subjects were male (55% and 51%, respectively) and the majority was white (69% and 74%, respectively).

6.1.3 Subject Disposition

A total of 348 participants were enrolled in MP4008. All 348 were included in the safety and intention to treat populations. A total of 4 participants did not complete the study, two due to adverse events (asthma and acid reflux), one to treatment failure, and one to time away from pollen area. Overall, the reasons for discontinuations did not vary appreciably between treatment arms or by age stratum (Table 7).

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for MP4008 was the change in reflective total nasal symptom score (rTNSS) from baseline in participants age 6 to 11. The primary endpoint was the change from baseline in AM+PM 12-hour reflective Total Nasal Symptom Score (rTNSS) over the double-blind treatment period (morning of day 2 to evening of day 14) in children age 6 to 11 years. The TNSS was defined as the sum of the nasal symptom scores of itchy nose, nasal congestion, runny nose, and sneezing, rated twice daily in an eDiary by participants or their caregivers, using a scale from 0 to 3 (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; and 3 = severe symptoms). Reflective values represented the severity of the symptoms over the previous 12 hours.

Baseline was defined as the average of all non-missing AM and PM scores over the 3.5-day placebo lead-in period up to and including the AM assessment of the day of randomization (Day 1).

The results are shown in the table below. The results were numerically but not statistically supportive for the 6 to 11 year age group. The data were not numerically supportive for the age 4 to 5 stratum, though this group included only 44 participants.

Table 9. MP4008 rTNSS

	Treatment	Overall change from baseline LS Mean[a]	Difference (95%CI)	p-value
6 to 11 years	Placebo (n=152)	-2.77	-0.80 (-1.75, 0.15)	0.099
	Dymista (n=152)	-3.83		
4 to 5 years	Dymista (n=21)	-2.44	+5.26 (+2.99,+7.53)	<.0001
	Placebo (n=23)	-7.71		

Source: Integrated Summary of Efficacy Table 2
[a] LS mean, difference, confidence intervals, and P values are from repeated measures ANCOVA model with treatment group and treatment day (Days 2 through 14) as fixed effects and baseline as a covariate. The model was fit with a first-order antedependent covariance structure specified. Overall LS mean includes Day 2 through Day 14. P value is for treatment effect.

The Applicant also performed five sensitivity analyses of the primary endpoint in the per protocol population, the intention to treat population with a compound symmetric covariance structure, an analysis excluding immunotherapy subjects, an analysis including a treatment-by-age stratum interaction, and an analysis imputing missing data of the primary endpoint. All were numerically supportive, but only the per protocol analysis was statistically supportive (MP4008 study report p. 57).

An additional consideration in support of the efficacy of Dymista is that both active pharmaceutical ingredients are approved for the treatment of seasonal allergic rhinitis in children. Evidence of efficacy for Astepro (azelastine hydrochloride) 0.15% and 0.1% was observed in a study of 489 children age 6 to 11 years, reviewed under supplement No. 8 to NDA 22203. This study, MP441, was a randomized, double-blind, placebo-controlled, parallel-group study that measured morning and evening reflective total nasal symptom scores (rTNSS), which measured the sum of runny nose, sneezing, itchy nose, and nasal congestion as scored on a 0-3 scale, collected daily, and averaged over 4 weeks of treatment. The study found that the rTNSS mean change from baseline was -3.4 for both Astepro 0.15% and Astepro 0.1%, vs. -2.5 for placebo (p=0.005 and 0.02, respectively), as reported in the package insert. Fluticasone propionate nasal spray is approved for use in children down to age 4 years for the treatment of seasonal and perennial allergic rhinitis and nonallergic rhinitis. Evidence of efficacy for intranasal fluticasone propionate was observed in studies of 650 patients age 4 to 11, as reported in the package insert.

Data to support evidence of efficacy for Dymista in the 4 to 5 year age group are lacking. The results from MP4008 showed numerical and strong statistical superiority for

placebo over Dymista in this group. This should be interpreted with caution as the number of participants was small (n=44), and these paradoxical results may be due to measurement error from relying on caregivers to report symptoms in young children. However, data also are lacking for the Astepro monocomponent in this age group. Thus, there is insufficient evidence of efficacy for Dymista in the 4 to 5 year age group.

6.1.5 Analysis of Secondary Endpoints(s)

Study MP4008 evaluated six secondary endpoints. Results were numerically supportive for all six measures, but achieved statistical significance only for one measure, the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ).

1) The changes from baseline for the entire double-blind period in AM+PM reflective Total Ocular Symptom Score (rTOSS)
2) Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) change from baseline to Visit 4
3) The changes from baseline for the entire double-blind period in the AM+PM instantaneous Total Nasal Symptom Score (iTNSS)
4) Instantaneous Total Ocular Symptom Score (iTOSS)
5) Reflective Total Symptom Score (rTSS)
6) Instantaneous TSS (iTSS)

The TNSS was defined as the sum of the nasal symptom scores of itchy nose, nasal congestion, runny nose, and sneezing, rated twice daily in an eDiary, using a scale from 0 to 3 (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; and 3 = severe symptoms). The TOSS was defined as the sum of the ocular symptom scores of itchy eyes, watery eyes, and eye redness, rated twice daily on the same 4-point scale. The TSS was calculated as the sum of the TNSS and TOSS. Reflective values represented the severity of the symptoms over the previous 12 hours, and instantaneous values represented the severity at the moment of evaluation. Baseline was defined as the average of all non-missing AM and PM scores over the 3.5-day placebo lead-in period up to and including the AM assessment of the day of randomization (Day 1).

Participants randomized to Dymista achieved larger average reductions from baseline in allergy symptom scores compared to those randomized to placebo for all six secondary endpoints (**Table 10)**. The difference was statistically significant only for the PRQLQ, though this should be interpreted with caution given that the primary endpoint failed to achieve statistical significance.

Table 10. Secondary endpoints: difference in mean change from baseline score for Dymista vs. placebo

Endpoint	Difference (95%CI)	p-value
rTOSS	-0.53 (-1.23, 0.18)	0.1
PRQLQ	-0.29 (-0.55, -0.03)	0.03*
iTNSS	-0.43 (-1.38, 0.51)	0.4
iTOSS	-0.43 (-1.12, 0.27)	0.2
rTSS	-1.34 (-2.91, 0.23)	0.09
iTSS	-0.92 (-2.49, 0.64)	0.2

For participants age 6 to 11 years
An analysis of covariance was performed to measure the difference between Dymista and placebo in least square mean change from baseline. CI = confidence interval, i = instantaneous, ITT = intention-to-treat, PRQLQ = Pediatric Rhinoconjunctivitis Quality of Life Questionnaire r = reflective, TNSS = total nasal symptom score, TOSS = total ocular symptom score, TSS = total symptom score

Study MP4007 was designed primarily as a safety study, however, secondary efficacy endpoints included a daily assessment of overall allergy symptom severity rated on a scale from 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms), percentage of days with allergy symptoms, percentage of subjects with allergy symptoms by maximum severity, and PRQLQ assessments over the 90 day treatment period.

Average symptom scores decreased for both groups with a change from baseline of -0.88 and -0.82, for Dymista and Fluticasone, respectively. The two groups had similar decreases in the percentage of days with allergy symptoms for each study interval (91% and 92% at the baseline visit and 61% and 63% at the final visit for Dymista and Fluticasone, respectively). The percentage of subjects with severe allergy symptoms decreased for both groups over the course of the study, from 34% for both Dymista and Fluticasone at baseline to 16% and 25%, respectively, at the final study visit. Mean scores for the PRQLQ for each domain (nose symptoms, eye symptoms, practical problems, activity limitations, and other symptoms) also decreased from baseline to the end of treatment for both treatment groups. The change from baseline to final study visit in the PRQLQ was -0.78 and -0.79 for Dymista and Fluticasone, respectively.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

A differential treatment response was observed among the youngest participants, age 4 to 5 years old. The results for this group favored placebo over Dymista. Among those age 4 to 5 years, participants randomized to Dymista had a worsening in their reflective total nasal symptom score of 5.26 points greater than those randomized to placebo, and

though the treatment groups were small, this difference was highly statistically significant ($p < 0.0001$).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dose of this fixed combination product was evaluated, so there was no exploration of dose response with regards to efficacy. The total daily doses of azelastine hydrochloride and fluticasone propionate provided by the combination (548 µg and 200 µg, respectively) are consistent with the dosing recommendations for the approved monotherapy products, with the caveat that the fixed combination does not provide the dosing flexibility available with the individual monotherapies.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No tolerance effects were noted in MP4007 or MP4008, nor were they observed elsewhere in the development program for Dymista.

6.1.10 Additional Efficacy Issues/Analyses

The Applicant analyzed the primary endpoint stratified by whether the symptom diary was reported by the participant or the caregiver in the age 6 to 11 years stratum. When the caregiver reported the symptoms, the mean difference between Dymista and placebo in the rTNSS was modest (-0.41 (-1.66,+0.84); p=0.5). When the participant reported his or her own symptoms, the mean difference between Dymista and placebo in the rTNSS was more pronounced (-1.54 (-2.72,-0.36); p=0.01). Of those age 9 to 11 years, 52% reported their own symptoms, vs. 19% of those age 6 to < 9 years.

Reviewer comment: The rTNSS remains the gold standard for a primary endpoint in allergic rhinitis trials, but the challenges of caregiver reported assessment in children are noted. The Applicant's analysis suggests that in this study, caregiver reported rTNSS may have been confounded by measurement error, which could bias the study toward the null.

7 Review of Safety

Safety Summary

The safety of Dymista in children age 4 to 11 years was evaluated in MP4008 and MP4007, an open label, active control, parallel group safety study that randomized 405 patients 3:1 to Dymista or fluticasone propionate nasal spray for three months. There were no deaths in the pediatric development program, and the rate of serious adverse events and adverse events leading to the discontinuation of treatment were low. There were fourteen instances of superficial nasal erosion and one instance of moderate erosion, but no instances of nasal ulceration or perforation. There were two reports of

somnolence, one severe. Common adverse events included epistaxis, headache, cough, pyrexia, oropharyngeal pain, otitis media, vomiting, upper abdominal pain and upper respiratory tract infection.

7.1 Methods

Review of the safety data is 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 Dymista in children is based primarily on the assessments performed in studies MP4007 and MP4008. These safety data are supplemented by postmarketing data for Dymista and published literature reports, as well as the original safety data from the clinical development program for Dymista.

Safety Evaluations

Both studies assessed subject-reported adverse events, nasal examinations, and vital signs. MP4007 additionally measured blood chemistry, hematology and urinalysis.

Nasal exams were performed at each of the study 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 (Section 2.7.4 Summary of Clinical Safety p. 6).

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

By mutual agreement between the Agency and the Applicant, safety data were not pooled between the two studies given the differences in study design (Pre-sNDA meeting, January 13, 2014).

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 Dymista in patients 4 to 11 years of age. There were minor differences between this reviewer's analysis and the Applicant'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 Dymista, and comparable between the two treatment arms for both studies.

Table 11. Safety population exposure and compliance

MP4007	Dymista Nasal Spray				Fluticasone Nasal Spray			
	Mean	StdDev	Min	Max	Mean	StdDev	Min	Max
Exposure duration (days)	88	9	1	101	88	9	5	109
Total sprays (n)	342	36	2	396	345	37	12	430
Compliance (%)	97	4	52	100	98	3	67	100

MP4008	Dymista Nasal Spray				Placebo Nasal Spray			
	Mean	StdDev	Min	Max	Mean	StdDev	Min	Max
Exposure duration (days)	16	2	6	22	16	2	8	22
Total doses (n)	37	14	4	74	37	14	8	84
Compliance (%)	91	10	29	100	92	9	44	100

Sources: MP4007 and MP4008 diary.xpt

7.2.2 Explorations for Dose Response

Only one dose of this fixed combination product was evaluated, so there was no exploration of dose response with regards to 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 both studies was adequate and included nasal examinations and vital signs. MP4007 additionally measured 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. The Applicant's proposed label relies on information available for Astelin, Astepro, and Flonase regarding metabolism, clearance, and drug-drug interactions.

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 combination products. 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

Two serious adverse events were reported for one participant in the Dymista arm of MP4007. A nine year old white male participant experienced gastroenteritis with elevated liver enzymes on study day 69. He was hospitalized and treated with normal saline and odansetron. On the next day, his symptoms improved, he was discharged home, and study medication was discontinued. On day 78 liver enzymes were repeated and had returned to normal levels.

Reviewer comment: These adverse events likely were not attributable to Dymista.

No serious adverse events were reported for MP4008.

7.3.3 Dropouts and/or Discontinuations

A total of 405 participants were enrolled in MP4007. Of those, 1 did not meet inclusion or exclusion criteria. All 405 were included in the intention to treat population. One participant was excluded from the safety population due to an adverse event prior to dosing, for a total of 404. A total of 28 participants did not complete the study, 10 due to adverse events, 5 lost to follow-up, 2 to noncompliance, 3 “other,” 2 for protocol violations, 1 for treatment failure, and 5 participants who elected to withdraw. Adverse events leading to discontinuation in the Dymista arm included asthma, reflux, otitis media, moderate nasal mucosal erosion, throat irritation and nasal discomfort, severe inflammation of nasal mucosa, gastroenteritis with elevated liver enzymes. Adverse events leading to discontinuation in the fluticasone arm included asthma and epistaxis. Overall, the reasons for discontinuations did not vary appreciably between treatment arms (Table 12).

Table 12. MP4007 discontinuation by treatment arm

	Dymista Nasal Spray		Fluticasone Nasal Spray	
	N	(%)	N	(%)
AE	6	(21)	4	(14)
Lost to Follow-Up	3	(11)	2	(7)
Non-Compliance	2	(7)	.	.
Other	2	(7)	1	(4)
Protocol Violation	1	(4)	1	(4)
Treatment Failure	1	(4)	.	.
Withdrawal by Subject	4	(14)	1	(4)

Source: MP4007 ADDS.XPT

A total of 348 participants were enrolled in MP4008. Of those, 1 did not meet inclusion or exclusion criteria. All 348 participants were included in the intention to treat and safety populations. A total of 4 participants did not complete the study, 2 due to adverse events including asthma and acid reflux, 1 for treatment failure, and 1 who traveled away from the study area, and thus the relevant pollen exposure. Overall, the reasons for discontinuations did not vary appreciably between treatment arms (Table 4).

7.3.4 Significant Adverse Events

Two participants in MP4007 experienced significant adverse events leading to discontinuation that were thought to be related to Dymista, including one case of moderate nasal mucosal erosion, and another of throat irritation and nasal discomfort.

Two participants in MP4008 experienced adverse events leading to discontinuation, including asthma and acid reflux. These were thought to be unrelated to study drug administration.

7.3.5 Submission Specific Primary Safety Concerns

In MP4007 there were two reports of somnolence, one severe. There were no reports of somnolence in MP4008.

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.

There were no instances of nasal ulceration or perforation. By this reviewer's analysis, in MP4007 there were 9 instances of Grade 1B superficial nasal erosion, and one instance of Grade 2 moderate erosion. In MP4008 there were five instances of grade 1B superficial nasal erosion.

Reviewer's comment: nasal erosions, ulcerations and perforations are known complications of intranasal medication use. Overall, the safety profile of Dymista is acceptable for this submission-specific safety concern.

Table 13. Nasal mucosal grade over time

MP4007		Dymista Nasal Spray Visit							Fluticasone Nasal Spray Visit						
		1	2	3	4	5	6	UNS	1	2	3	4	5	6	UNS
Grade 0	N	210	212	208	213	199	233	3	71	68	63	66	69	75	3
	(%)	(69)	(70)	(70)	(72)	(69)	(78)	(75)	(70)	(67)	(66)	(71)	(74)	(77)	(100)
Grade 1A	N	94	92	88	82	85	64	1	30	33	30	26	24	22	.
	(%)	(31)	(30)	(30)	(28)	(30)	(21)	(25)	(30)	(33)	(32)	(28)	(26)	(22)	.
Grade 1B	N	.	.	1	.	3	1	.	.	.	2	1	.	1	.
	(%)	.	.	(0)	.	(1)	(0)	.	.	.	(2)	(1)	.	(1)	.
Grade 2	N	.	.	.	.	.	1	.	.	.	.	.	.	.	.
	(%)	.	.	.	.	.	(0)	.	.	.	.	.	.	.	.

MP4008		Placebo Nasal Spray Visit					Dymista Nasal Spray Visit				
		1	2	3	4	UNS	1	2	3	4	UNS
Grade 1A	N	39	41	37	36	.	46	36	29	30	1
	(%)	(22)	(23)	(21)	(21)	.	(27)	(21)	(17)	(17)	(50)
Grade 0	N	136	134	137	139	2	127	137	141	139	1
	(%)	(78)	(77)	(79)	(79)	(100)	(73)	(79)	(82)	(80)	(50)
Grade 1B	N	.	.	.	.	.	.	.	1	4	.
	(%)	.	.	.	.	.	.	.	(1)	(2)	.

Source: MP4007 and MP4008 NASAL.XPT
UNS = unscheduled visit

Table 14 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 in both MP4007 and MP4008.

Table 14. Nasal exam shift tables from baseline for all visits

MP4007	Dymista		Fluticasone	
	N	(%)	N	(%)
Mucosal Grade				
Worse	132	(7)	37	(6)
Same	1489	(83)	489	(83)
Better	181	(10)	65	(11)
Epistaxis				
Worse	20	(1)	13	(2)
Same	1746	(97)	564	(95)
Better	36	(2)	14	(2)
Mucosal Edema				
Worse	208	(12)	46	(8)
Same	1103	(61)	379	(64)
Better	491	(27)	166	(28)
Nasal Discharge				
Worse	230	(13)	58	(10)
Same	1024	(57)	354	(60)
Better	548	(30)	179	(30)
Mucosal Erythema				
Worse	165	(9)	49	(8)
Same	1343	(75)	459	(78)
Better	294	(16)	83	(14)
Mucosal Bleeding				
Worse	24	(1)	8	(1)
Same	1726	(96)	549	(93)
Better	52	(3)	34	(6)
Mucosal Crusting				
Worse	115	(6)	19	(3)
Same	1517	(84)	504	(85)
Better	170	(9)	68	(12)

MP4008	Dymista		Placebo	
	N	(%)	N	(%)
Mucosal Grade				
Worse	39	(6)	24	(3)
Same	621	(90)	642	(91)
Better	33	(5)	36	(5)
Epistaxis				
Worse	6	(1)	2	(0)
Same	681	(98)	696	(99)
Better	6	(1)	4	(1)
Mucosal Edema				
Worse	80	(12)	68	(10)
Same	460	(66)	494	(70)
Better	153	(22)	140	(20)
Nasal Discharge				
Worse	82	(12)	85	(12)
Same	436	(63)	476	(68)
Better	175	(25)	141	(20)
Mucosal Erythema				
Worse	56	(8)	42	(6)
Same	560	(81)	567	(81)
Better	77	(11)	93	(13)
Mucosal Bleeding				
Worse	14	(2)	10	(1)
Same	674	(97)	676	(96)
Better	5	(1)	16	(2)
Mucosal Crusting				
Worse	37	(5)	30	(4)
Same	618	(89)	625	(89)
Better	38	(5)	47	(7)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events in MP4007 included epistaxis, headache, cough, pyrexia, oropharyngeal pain, otitis media, vomiting, upper abdominal pain and upper respiratory tract infection. The proportion of participants experiencing any treatment emergent adverse event was similar in both the Dymista and fluticasone treatment arms, and across age strata (**Table 15**). Common adverse events in MP4008 included dysgeusia and epistaxis, which were more common in the Dymista arm for the 6 to 11 age group.

Table 15. Treatment-emergent adverse events reported in ≥ 3% of subjects in the Dymista group by decreasing order of frequency, safety population

MP4007

	4 to 5 years		6 to 11 years	
	Dymista (N = 40)	Fluticasone (N = 11)	Dymista (N = 264)	Fluticasone (N = 89)
Any TEAE n (%)	18 (45)	5 (45)	106 (40)	32 (36)
Epistaxis	4 (10)	1 (9)	26 (10)	8 (9)
Headache	2 (5)	0 (0)	18 (7)	3 (3)
Cough	3 (8)	0 (0)	8 (3)	3 (3)
Pyrexia	2 (5)	0 (0)	8 (3)	2 (2)
Oropharyngeal pain	0 (0)	0 (0)	9 (3)	0 (0)
Otitis Media	3 (8)	0 (0)	6 (2)	3 (3)
Vomiting	0 (0)	1 (9)	9 (3)	1 (1)
Abdominal pain	0 (0)	1 (9)	8 (3)	1 (1)
Upper respiratory tract infection	2 (5)	1 (9)	6 (2)	0 (0)

MP4008

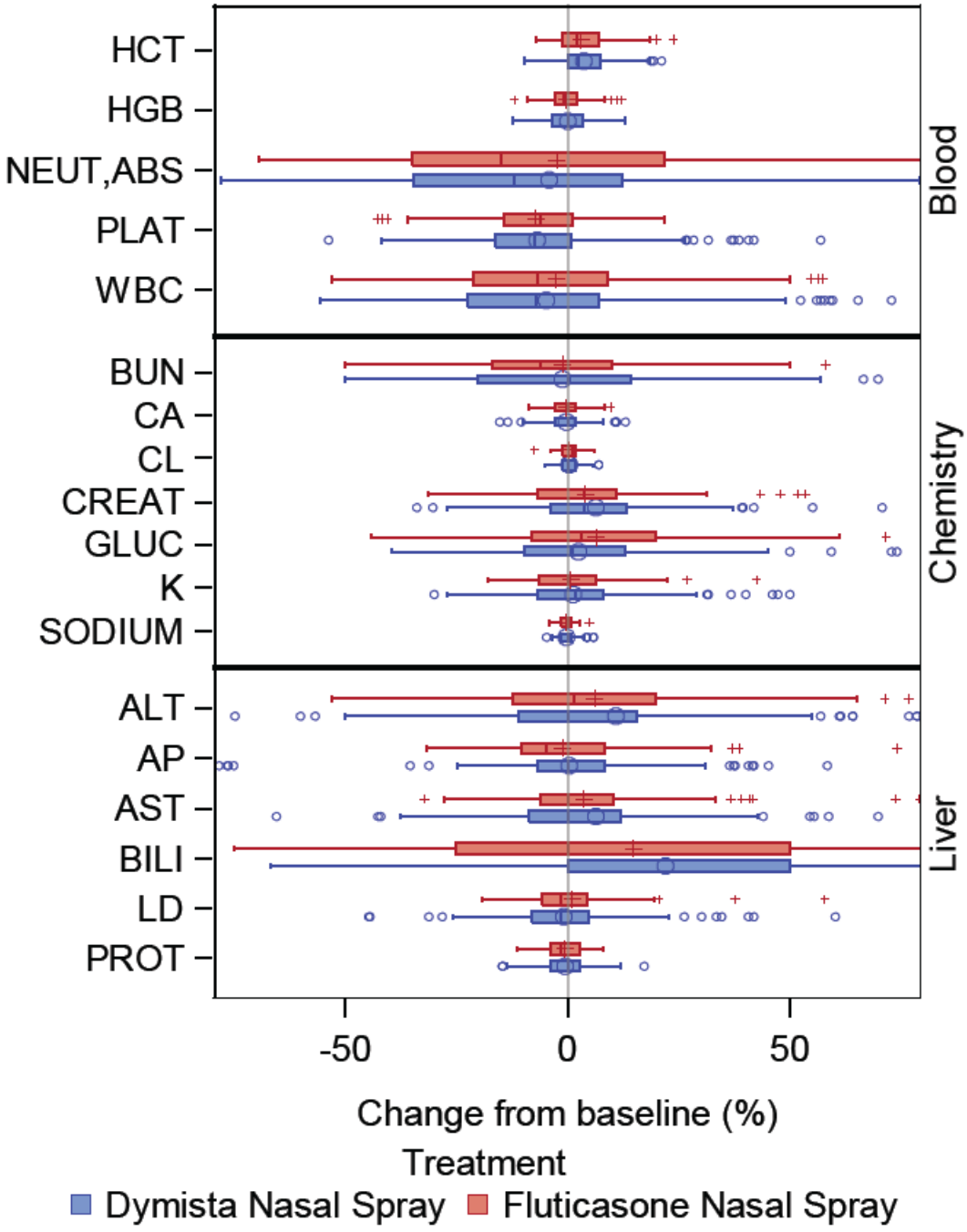
	4 to 5 years		6 to 11 years	
	Dymista (N = 21)	Placebo (N = 23)	Dymista (N = 152)	Placebo (N = 152)
Any TEAE n (%)	4 (19)	5 (22)	14 (9)	4 (3)
Dysgeusia	1 (5)	0 (0)	6 (4)	0 (0)
Epistaxis	0 (0)	2 (9)	6 (4)	3 (3)

Source: Adapted from MP4007 and MP4008 Tables 14.3.2
Preferred terms are listed by decreasing order of frequency in the Dymista group
Treatment-emergent adverse event (TEAE) is an AE with an onset date on or after the first dose of study drug.
Note: Percentages are based on the number of subjects in each treatment group. AEs coded using the MedDRA dictionary Version 16. A subject with multiple AEs is counted only once in any row.

7.4.2 Laboratory Findings

Routine clinical chemistry, hematology and urinalysis testing were conducted at baseline and at the end of the study. Overall, mean baseline and mean changes were not clinically significant and were similar across treatment groups. Figure 1 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 16 presents lab shifts. No clinically important differences were observed between treatment arms.

Figure 1. Percent change from baseline lab value by treatment arm



Source: MP4007 labs.xpt
Graph excludes some extreme outliers

Small numbers of participants had abnormal laboratory values, but the proportions were similar across treatment arms in both studies. No clinically important differences were noted.

Table 16. MP4007 Abnormal laboratory shifts

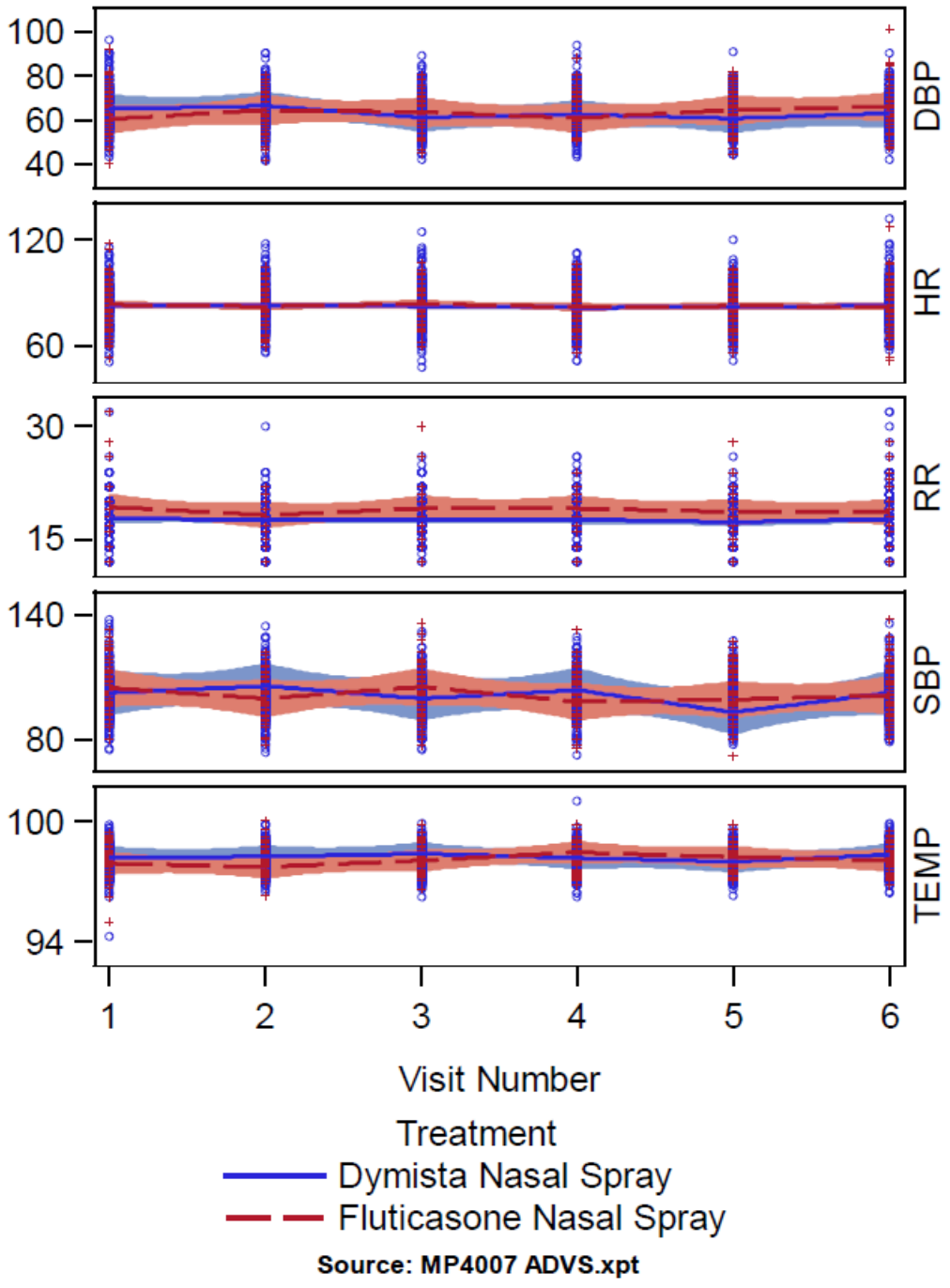
		Dymista Nasal Spray				Fluticasone Nasal Spray			
		Normal -> Low		Normal -> High		Normal -> Low		Normal -> High	
		N	(%)	N	(%)	N	(%)	N	(%)
CHEMISTRY	ALT (U/L)	.	.	16	(3)	.	.	9	(2)
	AP (Alk Phos) (U/L)	9	(2)	.	.	2	(0)	.	.
	AST (U/L)	.	.	7	(1)	.	.	1	(0)
	BUN (Urea) (mg/dL)	.	.	20	(4)	.	.	10	(2)
	Bilirubin (Total) (mg/dL)	1	(0)	1	(0)	.	.	.	.
	Calcium (mg/dL)	1	(0)	6	(1)	.	.	.	.
	Chloride (mEq/L)	.	.	1	(0)	.	.	.	.
	Creatinine (mg/dL)	.	.	6	(1)	.	.	1	(0)
	Glucose (Random) (mg/dL)	13	(3)	.	.	1	(0)	2	(0)
	LD (U/L)	2	(0)	7	(1)	1	(0)	2	(0)
	Potassium (mEq/L)	1	(0)	6	(1)	.	.	3	(1)
HEMATOLOGY	Basophils (%)	.	.	6	(1)	.	.	3	(1)
	Basophils (Abs) (x10E3/uL)	.	.	1	(0)	.	.	.	.
	Eosinophils (%)	.	.	10	(2)	.	.	1	(0)
	Eosinophils (Abs) (x10E3/uL)	.	.	9	(2)	.	.	.	.
	Hematocrit (%)	.	.	10	(2)	.	.	4	(1)
	Hemoglobin (g/dL)	4	(1)	3	(1)	1	(0)	2	(0)
	MCV (fL)	.	.	27	(5)	.	.	12	(2)
	Monocytes (%)	8	(2)	13	(3)	.	.	2	(0)
	Monocytes (Abs) (x10E3/uL)	41	(8)	.	.	11	(2)	.	.
	Neutrophils (%)	29	(6)	1	(0)	12	(2)	.	.
	Neutrophils (Abs) (x10E3/uL)	41	(8)	3	(1)	11	(2)	.	.
	Platelets (x10E3/uL)	2	(0)	6	(1)	1	(0)	2	(0)
	Red Cell Count (x10E6/uL)	1	(0)	2	(0)	.	.	.	.
	Total Lymphs (%)	.	.	37	(7)	.	.	15	(3)
	Total Lymphs (Abs) (x10E3/uL)	.	.	6	(1)	.	.	1	(0)
	White Cell Count (x10E3/uL)	9	(2)	4	(1)	1	(0)	1	(0)
URINALYSIS	Sp. Gravity	.	.	24	(5)	.	.	6	(1)

Source: MP4007 LABS.XPT

7.4.3 Vital Signs

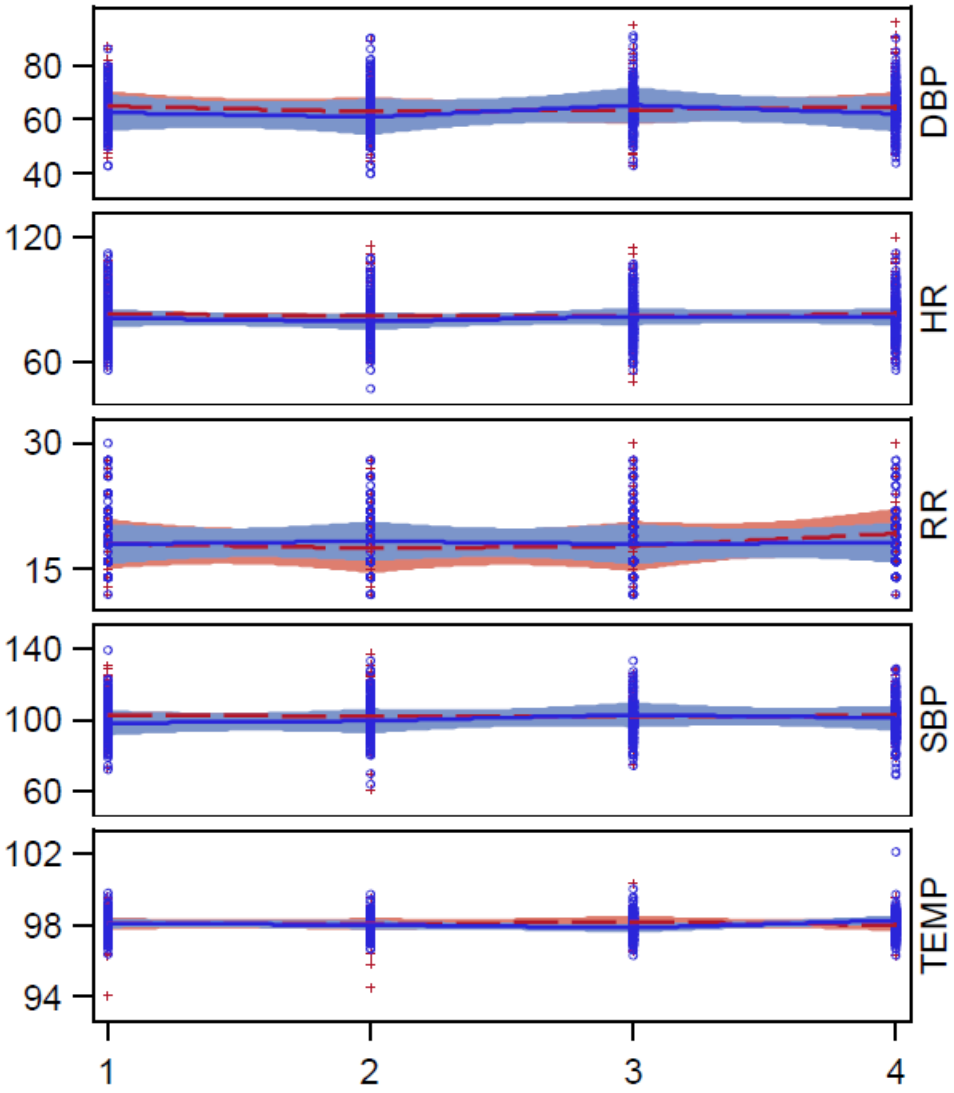
No clinically significant changes in mean values for blood pressure, pulse, respiratory rate, or body temperature were observed between treatment groups over the course of the two studies (Figure 2 and Figure 3).

Figure 2. MP4007 Mean vital signs by treatment group



Source: MP4007 ADVS.xpt

Figure 3. MP4008 Mean vital signs by treatment group



Source: MP4008 ADVS.xpt

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

Table 17. Shift tables for abnormal vital signs across all visits

MP4007	Dymista Nasal Spray						Fluticasone Nasal Spray					
	High		Low		Normal		High		Low		Normal	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Body Temperature (F)	0	0	0	0	1789	(100)	0	0	0	0	584	(100)
Diastolic Blood Pressure (mmHg)	22	(1)	0	0	1767	(99)	3	(1)	0	0	581	(99)
Heart Rate (beats/min)	0	0	0	0	1790	(100)	0	0	0	0	584	(100)
Respiratory Rate (breaths/min)	0	0	34	(2)	1755	(98)	0	0	6	(1)	578	(99)
Systolic Blood Pressure (mmHg)	63	(4)	88	(5)	1638	(92)	25	(4)	23	(4)	536	(92)

MP4008	Dymista Nasal Spray						Placebo Nasal Spray					
	High		Low		Normal		High		Low		Normal	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Body Temperature (F)	0	0	0	0	691	(100)	0	0	0	0	701	(100)
Diastolic Blood Pressure (mmHg)	9	(1)	0	0	681	(99)	4	(1)	0	0	697	(99)
Heart Rate (beats/min)	0	0	0	0	691	(100)	0	0	1	(0)	700	(100)
Respiratory Rate (breaths/min)	0	0	20	(3)	671	(97)	0	0	10	(1)	691	(99)
Systolic Blood Pressure (mmHg)	36	(5)	27	(4)	627	(91)	19	(3)	42	(6)	640	(91)

Sources: MP4007 and MP4008 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 each monocomponent of the combination product is a small molecule, immunogenicity was not anticipated and was not assessed in this submission. The adverse event profile for Dymista does not suggest an immunogenic effect.

7.5 Other Safety Explorations

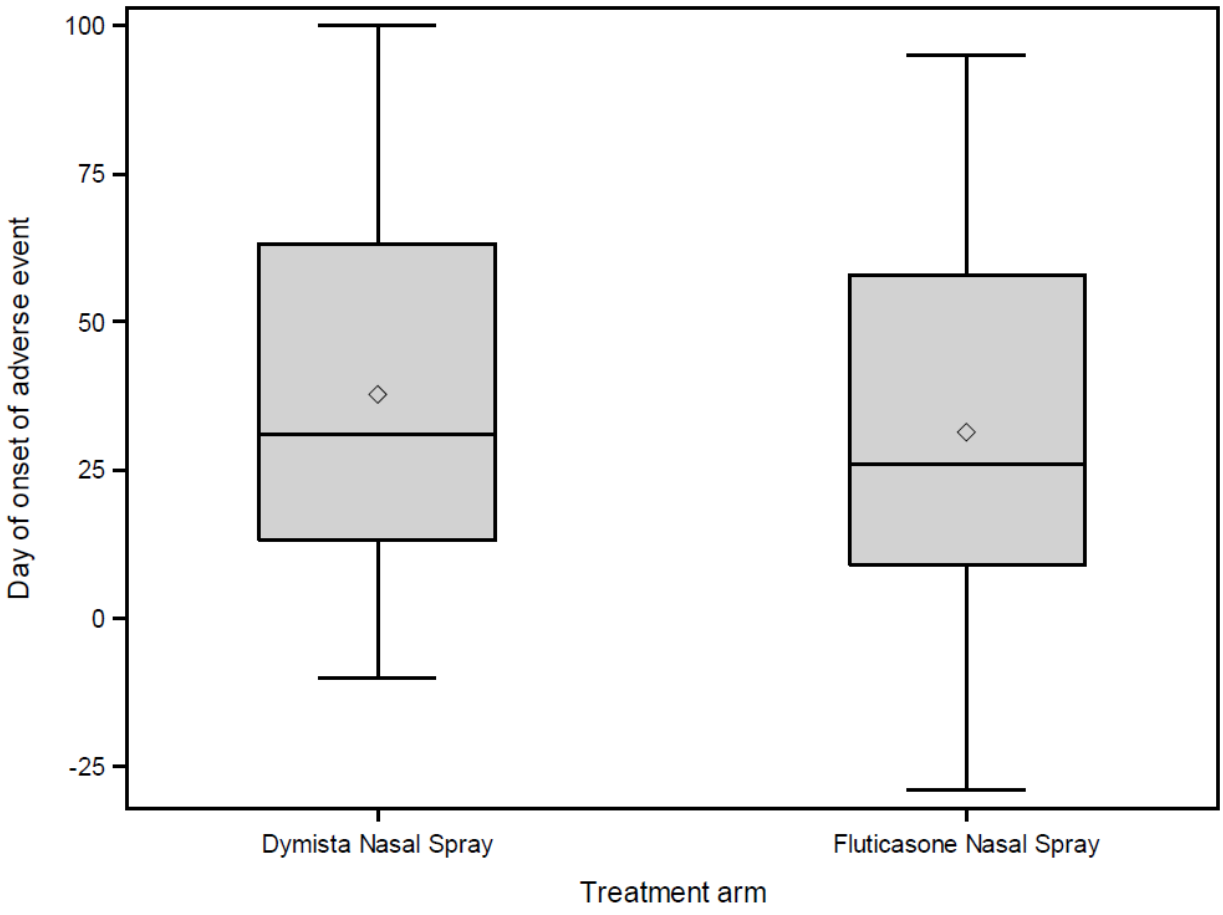
7.5.1 Dose Dependency for Adverse Events

Only one dose of this fixed combination product was evaluated, so there was no exploration of dose dependency for adverse events.

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. The mean, median and inter-quartile range for day-of-onset of adverse event were similar for both groups (Figure 4).

Figure 4. Time dependency for adverse events in MP4007



7.5.3 Drug-Demographic Interactions

In MP4008 in the Dymista group, more females than males reported a TEAE (22.1% vs 11.5%), and TEAEs were reported by 17.6% among Caucasians/Whites and by 13.0% by Non-Caucasians. In the Placebo group, the incidences of TEAEs were similar among males and females and among race/ethnic groups.

7.5.4 Drug-Disease Interactions

No specific evaluations were done for Dymista in patients with either renal or hepatic impairment. The proposed label includes information regarding the impact of renal impairment on azelastine hydrochloride pharmacokinetics: 70-75% higher Cmax and AUC in patients with a creatinine clearance < 50 mL/min compared to subjects with normal renal function. The proposed label also notes that the pharmacokinetics of azelastine hydrochloride are not influenced by hepatic impairment.

7.5.5 Drug-Drug Interactions

The Dymista clinical development program did not include a specific evaluation for interactions between Dymista and other drugs. The proposed label includes (b) (4)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Nonclinical carcinogenicity studies were not conducted for Dymista, given reassuring results from past evaluations of azelastine and fluticasone. The adverse event profile for Dymista does not suggest a carcinogenic effect.

7.6.2 Human Reproduction and Pregnancy Data

Dymista is rated as Pregnancy Category C. Animal reproductive studies of azelastine hydrochloride and fluticasone propionate in mice, rats, and/or rabbits revealed evidence of teratogenicity as well as other developmental toxic effects.
It is not known whether azelastine hydrochloride and fluticasone propionate are excreted in human breast milk. Corticosteroids other than fluticasone propionate have been reported to be excreted in human milk. In a study of rats, tritiated fluticasone propionate was detected in the mothers' milk. Thus, (b) (4) nursing woman.

7.6.3 Pediatrics and Assessment of Effects on Growth

No formal growth effect studies in children were included in this submission. Cases of growth suppression have been reported for intranasal corticosteroids, including fluticasone propionate. The approved label includes class labeling describing the association between intranasal corticosteroids and the reduction of growth velocity in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose, abuse, withdrawal or rebound are unlikely for a nasal product. Oral ingestion of antihistamines does have the potential to cause serious adverse effects in young children. Oral doses of azelastine hydrochloride of 120 mg/kg and greater (approximately 460 times the maximum recommended daily inhalation dose in adults and children on a mg/m2 basis) were lethal in mice; responses seen prior to death were tremor, convulsions, decreased muscle tome, and salivation. In dogs, single oral doses of azelastine hydrochloride as high as 10 mg/kg (approximately 260 times the maximum recommended daily inhalation dose in adults and children on a mg/m2 basis) were well tolerated, but single oral doses of azelastine hydrochloride of 20 mg/kg were lethal. Single oral doses in adults of up to 16 mg of azelastine hydrochloride or fluticasone propionate have not resulted in an increased incidence of adverse events.

There have been no reports of dependence, withdrawal or rebound in more than 15 years of clinical use of Dymista and its components in the US and Europe.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

The current product label was reviewed for post approval experience with Dymista. The label includes the following adverse reactions reported during the post approval period for azelastine hydrochloride: anaphylactoid reaction, application site irritation, atrial fibrillation, chest pain, confusion, dyspnea, facial edema, involuntary muscle contractions, nasal sores, palpitations, paresthesia, parosmia, pruritus, rash, disturbance or loss of sense of smell and/or taste, tolerance, urinary retention, vision abnormal and xerophthalmia.

The following events have been identified during post-approval use of fluticasone propionate nasal spray and also are included in the current label: hypersensitivity reactions, including angioedema, skin rash, edema of the face and tongue, pruritus, urticaria, bronchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid reactions,

which in rare instances were severe, alteration or loss of sense of taste and/or smell and, rarely, nasal septal perforation, nasal ulcer, sore throat, throat irritation and dryness, cough, hoarseness, and voice changes, ocular dryness and irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts. Cases of growth suppression have been reported for intranasal corticosteroids, including fluticasone propionate.

The Applicant reported the following serious unlisted events in the periodic safety report included in the supplement for the period spanning May 1, 2012 to June 15, 2014:

- Convulsions and tremors
- Migraines and paraesthesia
- Chest discomfort, eye pain, thirst and dry mouth
- Asthma hospitalization
- Hypertension, nasal discomfort, burning sensation, eye pain, toothache and oral pain
- Lip pain and sinus headache
- Dyspnea, nervousness, discomfort, dysphagia, restlessness, dizziness, paraesthesia oral, paraesthesia, swollen tongue, chest discomfort, nasal congestion and headache
- VIIth nerve paralysis, nervous system disorder, dyspepsia, erythema, respiratory rate decreased, muscle fatigue, heart rate irregular, asthenia, and cardiac disorder

In addition, the Applicant noted fifteen reports of nasal discomfort, thirteen reports of dizziness, seven reports each of erythema, eye swelling, nasal dryness, and anxiety, six reports of hypertension, five reports of nervousness, and four reports of increased heart rate.

Review of the periodic safety report for the period of June 16, 2014 to October 21, 2014 was notable for three patients who experienced the following serious unlisted adverse events:

- Aphonia, tinnitus and pharyngeal erythema
- Muscle pain, joint pain and palatal skin loss
- Deafness, middle ear effusion

In addition, there were three cases of nasal discomfort, two cases of dizziness, and two cases of nervousness.

In response to this post marketing experience, the Applicant proposes the following addition to section 6.2 of the label:

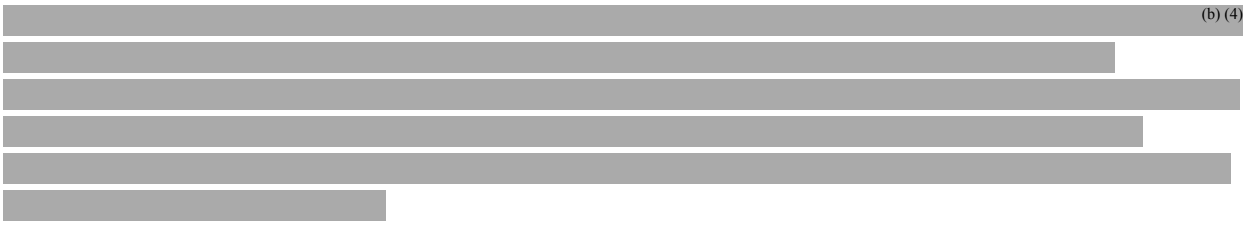


Table 18. Sources of postmarketing data for proposed adverse event labeling changes

	PSUR 5/1/202-6/15/2014	PSUR 6/16/2014-10/21/2014	Fluticasone propionate label	Azelastine hydrochloride label	Unknown
nasal discomfort	✓	✓			
dizziness	✓	✓			
blurred vision			✓		
dyspnea			✓	✓	
loss of smell and/or taste			✓	✓	
nausea					✘
fatigue	✓				
erythema	✓	✓			
eye swelling	✓				
anxiety	✓				
nasal dryness	✓				
aches and pain		✓			
hypertension	✓				
nervousness	✓	✓			
nasal septal perforation			✓		
vomiting					✘
face swelling					✘
increased heart rate	✓				
dysphonia		✓			

9 Appendices

9.1 Literature Review/References

A PubMed search conducted by this Reviewer on December 19, 2014, [search term: azelastine and fluticasone; limits: human, clinical trial, meta-analysis, randomized clinical trial, English language, published in the last five years], yielded nine references.[1-9] Brief review did not indicate any new safety signals.

The Applicant's literature review included a Pubmed search, the published abstracts from 2010 to 2014 for the American College of Allergy, Asthma & Immunology and the American Academy of Allergy, Asthma and Immunology, and clinicaltrials.gov. There were no publications or abstracts reporting the use of combination azelastine and fluticasone propionate or any combination antihistamine and nasal steroid in children. One study (NCT00845195) was listed at clinicaltrials.gov that compared olopatadine nasal spray 0.6% and azelastine HCl nasal spray 0.1% in combination with fluticasone nasal spray in patients 12 years and older with seasonal allergic rhinitis but no results were published. No new safety signals were identified.

9.2 Labeling Recommendations

At the time of this review, labeling discussions are ongoing. The submission includes a revised package insert. Labeling recommendations include:

(b) (4)

Reviewer's comment: These general labeling concepts are acceptable and supported by the submitted data.

A line-by-line labeling review raises concern about the following:

(b) (4)

9.3 Advisory Committee Meeting

Azelastine hydrochloride and fluticasone propionate are well-characterized pharmaceutical entities. Dymista Nasal Spray is already approved in patients 12 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 21, 2015

Covered Clinical Study (Name and/or Number): MP4007 and MP4008

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: n=41 for MP4007 and n=35 for MP4008		
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) (4)		
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) (4). (b) (4) 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

1. Berger WE, Shah S, Lieberman P et al. Long-term, randomized safety study of MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in an advanced delivery system) in subjects with chronic rhinitis. J Allergy Clin Immunol Pract 2014;2(2):179-185.

2. Carr W, Bernstein J, Lieberman P et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol 2012;129(5):1282-1289.

3. Carr WW, Ratner P, Munzel U et al. Comparison of intranasal azelastine to intranasal fluticasone propionate for symptom control in moderate-to-severe seasonal allergic rhinitis. Allergy Asthma Proc 2012;33(6):450-458.

4. Derendorf H, Munzel U, Petzold U et al. Bioavailability and disposition of azelastine and fluticasone propionate when delivered by MP29-02, a novel aqueous nasal spray. Br J Clin Pharmacol 2012;74(1):125-133.

5. Hampel FC, Ratner PH, Van BJ et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol 2010;105(2):168-173.

6. LaForce CF, Carr W, Tilles SA et al. Evaluation of olopatadine hydrochloride nasal spray, 0.6%, used in combination with an intranasal corticosteroid in seasonal allergic rhinitis. Allergy Asthma Proc 2010;31(2):132-140.

7. Meltzer E, Ratner P, Bachert C et al. Clinically relevant effect of a new intranasal therapy (MP29-02) in allergic rhinitis assessed by responder analysis. Int Arch Allergy Immunol 2013;161(4):369-377.

8. Meltzer EO, LaForce C, Ratner P, Price D, Ginsberg D, Carr W. MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial of efficacy and safety. Allergy Asthma Proc 2012;33(4):324-332.

9. Price D, Shah S, Bhatia S et al. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. J Investig Allergol Clin Immunol 2013;23(7):495-503.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHLEEN M DONOHUE
01/28/2015

SALLY M SEYMOUR
01/29/2015