CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-236
Priority or Standard	Standard
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Division / Office	DPARP/ODE II
Reviewer Name(s)	Jennifer Rodriguez Pippins, MD, MPH
Review Completion Date	March 27, 2012
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 (Total Daily Dose: 548 µg azelastine, 200 µg fluticasone)
Indication(s)	Seasonal allergic rhinitis
Intended Population(s)	Patients 12 years of age and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is New Drug Application (NDA) is Approval. The Application contains adequate evidence of efficacy to support the indication, "the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief," and provides an acceptable safety profile for the proposed product.

Meda Pharmaceuticals has submitted a 505(b)(2) application for a fixed-dose combination nasal spray of 0.1% azelastine hydrochloride, a H_1-receptor antagonist, and 0.037% fluticasone propionate, a corticosteroid. The proposed tradename is Dymista® (code name: MP29-02). Each actuation of the product contains 137 µg of azelastine hydrochloride and 50 µg of fluticasone propionate. The proposed 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. In addition to relying on the Agency's prior findings of efficacy and safety for the reference products, the Applicant completed an extensive clinical development program for MP29-02, which includes four 2-week phase 3 efficacy and safety clinical trials (MP-4001, MP-4002, MP-4004, and MP-4006) and a year-long safety trial (MP-4000). In addition, two pharmacokinetic (PK) trials were conducted (X-03065-3282 and X-03065-3283).

Evidence of efficacy comes primarily from Trials MP-4002, MP-4004, and MP-4006, which were randomized, double-blind, placebo- and active-controlled, with a 2-week treatment period. These trials employed a factorial design, evaluating the proposed product, MP29-02, along with placebo, as well as two investigational monotherapy comparators, azelastine hydrochloride and fluticasone propionate, each formulated (separately) in the MP29-02 vehicle. This factorial design allows for the evaluation of the contribution of each component to the efficacy of the novel combination product. In each of the three pivotal 2-week efficacy and safety trials, results for the analysis of the primary endpoint, the change from baseline in the reflective Total Nasal Symptom Score (rTNSS) AM and PM combined over the 14-Day treatment period, were statistically significant for the comparisons between MP29-02 and placebo, as well as the comparisons of MP29-02 to each of the monotherapy comparators. These results provide replicate evidence of efficacy for the proposed combination product; the factorial

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design also provides replicate evidence of the contribution of each component. Results for the secondary endpoints were generally supportive of the primary analysis. Based on these results, the clinical review concludes that the Application provides sufficient evidence to support the seasonal allergic rhinitis indication. The Application does not, however, provide adequate support for a claim (b) (4) being sought by the Applicant. (b) (4)

The safety of MP29-02 is primarily supported by the results of the three 2-week efficacy and safety trials (MP-4002, MP-4004, and MP-4006) and the year-long safety trial (MP-4000). 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 occurrences of nasal septal perforation, and only one instance of nasal ulceration which was reported for a patient receiving placebo. The incidence of epistaxis associated with MP29-02 was 1-2%, which is comparable to that reported in the Astelin product label, and lower than that reported for Flonase. Other common adverse events associated with MP29-02 in clinical trials were: dysgesuia, headache, pyrexia, cough, nasal congestion, rhinitis, viral infection, upper respiratory tract infection, pharyngitis, pain, and diarrhea. The rate of somnolence was low. Ophthalmic examinations did not reveal any signals for either glaucoma or posterior subcapsular cataract formation, and results from an HPA-Axis substudy indicate that the effect of MP29-02 is comparable to that of commercially available generic fluticasone propionate.

In summary, the clinical recommendation is Approval, based on the assessment that the Application has provided adequate evidence to support efficacy of MP29-02 in the treatment of the symptoms of SAR for adults and adolescents 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate, and has also demonstrated an acceptable safety profile. It is notable that MP29-02, if approved, would be the first combination intranasal product for the treatment of allergic rhinitis.

1.2 Risk Benefit Assessment

The clinical review's risk-benefit assessment is favorable for the proposed product. This is based on the overall results for the primary endpoint from the 2-week efficacy and safety trials, which were both statistically significant and of reasonable magnitude. The clinical development program therefore provides sufficient evidence of the likelihood that patients requiring treatment with both azelastine hydrochloride and fluticasone propionate will benefit from the combination treatment offered by MP29-02. This,

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coupled with a relatively benign adverse event profile as described above, supports a favorable risk-benefit assessment for MP29-02.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket Risk Evaluation and Mitigation Strategies (REMS) are recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

A pediatric program for ages 4-11 years will be required under the Pediatric Research Equity Act (PREA); see Section 7.6.3.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed product, Dymista Nasal Spray (code name: MP29-02), is a fixed-dose combination nasal spray of 0.1% azelastine hydrochloride, a H_1-receptor antagonist, and 0.037% fluticasone propionate, a corticosteroid. Each actuation of MP29-02 contains 137 µg of azelastine hydrochloride and 50 µg of fluticasone propionate. The proposed product will be supplied in a glass bottle fitted with a metered-dose spray pump unit, consisting of a nasal spray pump and a plastic dust cap. Each bottle contains 23 mg (1 mg/g) of azelastine hydrochloride and 8.5 mg (0.37 mg/g) of fluticasone propionate as active ingredients. The 23 g trade package is designed to deliver 120 metered sprays.

The proposed indication is (b) (4) [redacted] [redacted]" The proposed 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.

[1] As discussed in Section 6.1, the clinical review recommends a modification of the indication to: "the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief."

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2.2 Tables of Currently Available Treatments for Proposed Indications

Both of the active ingredients comprising the proposed fixed-dose combination product, azelastine hydrochloride and fluticasone propionate, are FDA-approved treatments for allergic rhinitis (see Section 2.3). In addition, there are numerous other nasal sprays available for the treatment of allergic rhinitis, as summarized in Table 1.

Table 1. FDA-Approved Nasal Sprays for Seasonal Allergic Rhinitis

Active Ingredient	Trade Name	Age Range
	H_1-receptor antagonists	
Azelastine hydrochloride	Astelin and generic Astepro	≥ 5 years ≥ 12 years
Olopatadine	Patanase	≥ 6 years
	Corticosteroids	
Beclomethasone	Beconase AQ	≥ 6 years
Budesonide	Rhinocort Aqua	≥ 6 years
Ciclesonide	Omnaris	≥ 6 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. Astelin received initial U.S. approval on November 1, 1996. Azelastine hydrochloride 0.1% (unsweetened) 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.

Dosage and administration for Astelin are as follows:

- Adults and adolescents (12 years of age and older):
  - SAR: 1-2 sprays (137 mcg/spray) in each nostril BID (MDD=1096 mcg)
  - VMR: 2 sprays (137 mcg/spray) in each nostril BID (TDD=1096 mcg)
- Children (5-11 years)
  - SAR: 1 spray (137 mcg/spray) in each nostril BID (TDD=548 mcg)

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Azelastine hydrochloride is also available as 0.1% and 0.15% sweetened formulations under the tradename Astepro. Both the 0.1% and 0.15% sweetened formulations are indicated for seasonal allergic rhinitis in adults and adolescents 12 years of age and older; the 0.15% sweetened formulation is also indicated for perennial allergic rhinitis in adults and adolescents 12 years of age and older.

Dosage and administration for Astepro are as follows:

- Adults and adolescents (12 years of age and older):
  - SAR:
    - 0.1%: 1-2 sprays (137 mcg/spray) in each nostril BID (MDD=1096 mcg)
    - 0.15%:
      - 1-2 sprays (205.5 mcg/spray) in each nostril BID (MDD=1644 mcg) – OR –
      - 2 sprays in each nostril QD (TDD=822)
  - PAR:
    - 0.15%: 2 sprays in each nostril BID (TDD=1644 mcg)

Fluticasone propionate is available both as a branded product (Flonase) and as multiple generic products. Flonase received initial U.S. approval on October 19, 1994. Fluticasone propionate nasal spray is indicated for seasonal allergic rhinitis, perennial allergic rhinitis, and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

Dosage and administration for fluticasone propionate nasal spray are as follows:

- Adults
  - 2 sprays (50 mcg/spray) in each nostril QD (TDD=200 mcg)
  - May be divided into 100 mcg BID
  - May be able to reduce to 1 spray (50 mcg/each) in each nostril QD (TDD=100 mcg) for maintenance therapy
  - May be able to use 200 mcg QD prn
- Adolescents and Children (4 years of age and older)
  - 1 spray (50 mcg/spray) in each nostril QD (TDD=100 mcg)
  - May increase to 2 sprays (50 mcg/spray) in each nostril QD (TDD=200 mcg)
  - Once control achieved, should decrease to 1 spray (50 mcg/spray) in each nostril QD (TDD=100 mcg)

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2.4 Important Safety Issues With Consideration to Related Drugs

Antihistamines
Antihistamines are known to be associated with somnolence. This is true for Astelin, which carries a Precautions statement in its product label. There is also a history of an association between Terfenadine, an early second-generation antihistamine, and QT interval prolongation as well as cardiac arrhythmias, which led to the removal of Terfenadine from the market. The Astelin product label states that a study evaluating the impact of Astelin on cardiac repolarization did not demonstrate an effect on corrected QT interval (QTc).

Corticosteroids
Corticosteroids are known to be associated with a number of important systemic and local safety issues. Systemic adverse events include: immunosuppression, HPA Axis effects, and reduction in growth velocity. Local adverse events 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 all described in the Flonase product label.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following timeline summarizes the presubmission regulatory activity related to the clinical development program for the proposed product and this NDA submission.

- IND 77,363 submitted by MedPointe Pharmaceuticals on April 2, 2007
  - IND allowed to proceed
  - Comments provided on May 21, 2007 included:
    - Reminder that the program needs to establish the contribution of each component
    - Statement that Astelin® and Flonase were not appropriate comparators because of pharmaceutical differences between the combination and marketed products
- Type A meeting held on September 10, 2007
  - MedPointe agreed to evaluate the individual monotherapies in the same vehicle and device as the combination product in clinical studies
  - Division commented that the proposed product should be evaluated in a population that required concurrent therapy with both azelastine and fluticasone; identifying such a population would be challenging

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- Special Protocol Assessment (SPA) submitted for Trial MP4002 on December 21, 2007
    - Division provided a No-Agreement Letter on January 31, 2008, which noted concerns about:
        - The identified patient population
        - The lack of a titration option with the fixed dose combination
        - The need for characterization of the *in vitro* performance of the investigational monotherapy comparators
    - Type A meeting held to discuss the SPA on April 29, 2008
        - Division stated its position that there is no clear regulatory pathway for the development of the proposed combination
- Meda contacted the ODE II Office Director about the interpretation and application of 21 CFR 300.50 ("Combination Rule"), early 2009
    - Regulatory Briefing held spring 2009 to discuss application of the Combination Rule in this instance
    - Subsequent to the Regulatory Briefing, teleconference held between the Division and Meda on April 23, 2009. The Sponsor was informed that:
        - Division could now envision a regulatory pathway forward for the combination product
        - Evaluation of TNSS as the primary endpoint would be acceptable for both the combination product and the monotherapy comparators
        - The contribution of each monotherapy component must still be demonstrated
        - There should be no pharmaceutical differences between the monotherapy components and the combination product
        - The data should demonstrate a clinically meaningful benefit for the combination product (with a reasonable study size)
        - An appropriate patient population requiring the combination therapy should be identified
- Pre-NDA meeting held on August 17, 2010
    - The Division reiterated its concern about the lack of flexibility of dosage titration with the fixed dose combination, however, it agreed that a lower dose of MP29-02 was not required for NDA filing.
    - The Division stated that the proposed pharmacokinetic (PK) program appeared reasonable, and that if the systemic exposure from MP29-02 were equal or less than the systemic exposures for fluticasone and

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azelastine, respectively, from the corresponding commercially marketed monotherapies, then the PK assessments would facilitate bridging to the systemic safety profiles established for the commercial monotherapies. To that extent, a separate HPA axis effect trial for MP29-02 would not be required if the PK data were robust. However, the Division also noted that PK data would not be able to account for formulation differences that may alter the efficacy and local safety of locally acting products, and given this limitation, the results from MP4001 would likely be viewed as secondary support.

- The Division communicated concern regarding the proposed indication for the treatment of nasal (b) (4) symptoms associated with SA (b) (4)
- The Applicant was asked to include in the NDA submission a rationale for the large sample size in trial MP-4006.
- The Division stated that the appropriate selection of a patient population would be a review issue, and that this concern should be addressed in the NDA submission.
- The Division recommended that the Applicant address in the NDA submission the rationale for including an additional trial in the clinical program, when typically two trials would be sufficient for establishing efficacy.

2.6 Other Relevant Background Information

This Reviewer notes that Dymista (Azelastine Hydrochloride and Fluticasone Propionate) Nasal Spray, if approved, would be the first combination intranasal product for the treatment of allergic rhinitis.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

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Review of the application did not raise any data integrity concerns. On initial review it did not appear that the results from any of the individual centers were driving the overall conclusions of the trials. Moreover, the application states that none of the clinical investigators disclose a proprietary interest in the proposed product or significant equity related to the Applicant. Because of these reasons, no DSI review was recommended.

3.2 Compliance with Good Clinical Practices

The Application includes a statement of Good Clinical Practice (GCP), indicating that all clinical trials were conducted under the supervision of an IRB (ethics committees for trials outside of the United States) and with adequate informed consent procedures.

3.3 Financial Disclosures

The application states that none of the clinical investigators disclosed a proprietary interest in the proposed product or significant equity related to the Applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The preliminary recommendation from the Chemistry, Manufacturing, and Controls (CMC) team review is Approval. The final CMC review remains pending at this time.

Deficiencies in the CMC section of the Application were noted by the Division at the time of filing, including the incomplete nature of the information provided for the comparator and placebo drug products used in the pivotal clinical studies. A clear description of the monotherapy comparators is a prerequisite for the interpretation of data from the pivotal efficacy trials, which rely on a factorial design as the method by which the contribution of each component to the combination product is established. This CMC data, therefore, was assessed as being critical to the interpretation of the efficacy data.

In addition to the lack of complete information describing the monotherapy comparators, a number of additional CMC issues have been raised during the review process. In written and telephone communications dated August 31, 2011, October 11, 2011,

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November 17, 2011, and November 22, 2011, the Division requested the following additional CMC information:

- Data describing particle size distribution for the clinical and registration batches, for both release and stability testing, including that which would address the comparability of the combination drug products used in clinical trials to the corresponding monocomparator drug products
- Data addressing concerns regarding device ruggedness, in response to observations by the review team that removal of the dust cap at times resulted in detachment of the nozzle from the actuator
- Specifications for the excipient (b) (4)
- Revised regulatory specifications for the release and stability testing of the drug product intended for marketing
- Revised stability data for the representative to-be-marketed drug product batches
- Revision of the proposal for drug product expiry
- Revision of the microbiological controls of drug product and inclusion of microbial limits in the commercial product stability testing protocol

The Applicant provided their responses to the issues outlined above on December 7, 2011. This submission was deemed to constitute a major amendment to the Application. As this major amendment was submitted within three months of the user fee goal date, it resulted in an extension of that date by three months to May 1, 2012.

The CMC review of the December 7, 2011, submission concludes that the comparability of the monotherapies and the combination drug product evaluated in the pivotal clinical trials was acceptable. While the final CMC review is pending the resolution of several issues regarding specifications and methods, these issues are not anticipated to impact approvability.

4.2 Clinical Microbiology

The Product Quality Microbiology Review recommends Approval of the proposed product, which is a non-sterile nasal spray (b) (4).

4.3 Preclinical Pharmacology/Toxicology

The Preclinical Pharmacology/Toxicology Review recommends Approval.

The nonclinical safety program for the proposed product is based upon the complete toxicology programs conducted for both individual active drugs, which are described in the current package inserts for the individual monoproducts. In addition, the Applicant conducted 14-day intranasal toxicology studies in rats and dogs and a 3-month intranasal toxicology study in rats with the combination of azelastine hydrochloride and

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fluticasone propionate. Per the nonclinical review, findings from the 3-month study included decreased body weight and decreased body weight gain for both the azelastine/fluticasone and fluticasone groups, as well as increased mast cells in the mesenteric lymph nodes for both the combination and fluticasone groups. In addition, an increase in mast cells in the mandibular lymph nodes was noted for the azleastine/fluticasone group; the review states that this findings is of "uncertain toxicological relevance" (Marcie Wood, Ph.D., Pharmacology/Toxicology NDA Review and Evaluation, September 23, 2011).

4.4 Clinical Pharmacology

The Clinical Pharmacology Review recommends Approval.

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. The proposed label includes pharmacodynamic data for azelastine hydrochloride, including an evaluation of azelastine and cardiac repolarization, as described in Section 2.4.

4.4.3 Pharmacokinetics

The Applicant conducted two pharmacokinetic trials: Trials X-03065-3282 and X-03065-3283. These were randomized, open-label, three-period, cross-over trials, each evaluating three treatments in 30 healthy adults. Trial X-03065-3282 evaluated MP29-02, the investigational monocomparator azelastine hydrochloride, and Astelin. Trial X-03065-3282 evaluated MP29-02, the investigational monocomparator fluticasone propionate, and commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.). Each treatment was delivered as a single dose of 2 sprays per nostril. These trials allowed for an assessment of drug-drug interaction (by comparing the systemic blood levels of azelastine and fluticasone after administration of MP29-02 versus after the investigational monotherapy comparators), as well as of potential formulation effect (by comparing the systemic blood levels of azelastine and fluticasone after administration of the investigational monotherapy comparators versus after the commercial products).

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Results from Trials X-03065-3282 and X-03065-3283 are presented in Table 2. The ratios for the pharmacokinetic parameters reveal no indication of a drug-drug interaction between fluticasone propionate and azelastine hydrochloride when combined in MP29-02. Trial X-03065-3282 does demonstrate a higher fluticasone propionate systemic exposure associated with MP29-02 as compared to that for the commercially available generic fluticasone product (ranging from 44-61% higher, depending on the pharmacokinetic parameter examined).

Table 2. Point Estimates and 90%-Confidence Intervals for Pharmacokinetic Ratios

	C_{max}	$AUC_{0\text{-tlast}}$	$AUC_{0\text{-}\infty}$
Trial X-03065-3282			
MP29-02 vs. FP in MP29-02 vehicle	0.91 (0.83-1.00)	0.94 (0.84-1.05)	1.01 (0.85-1.20)
MP29-02 vs. generic FP	1.57 (1.32-1.87)	1.61 (1.37-1.89)	1.44 (1.15-1.80)
Trial X-03065-3283			
MP29-02 vs. AH in MP29-02 vehicle	1.03 (0.92-1.14)	0.99 (0.91-1.07)	0.98 (0.90-1.07)
MP29-02 vs. Astelin	1.07 (0.93-1.24)	1.06 (0.96-1.16)	1.05 (0.96-1.16)

Source: Section 5.3.3.1.1 (X-03065-3282), pg. 52-53 (Tables 14, 16, 18); Section 5.3.3.1.1 (X-03065-3283), pg. 46-48 (Tables 12, 14, 16)
Key: AH=azleastine hydrochloride; FP=fluticasone propionate

While the pharmacokinetic program allows for bridging between MP29-02 and the commercial products, the ability to apply the systemic safety profile of commercially available fluticasone propionate to MP29-02 is limited by the increase in systemic exposure to fluticasone demonstrated by Trial X-03065-3282. This increase in systemic exposure to fluticasone propionate for MP29-02 was identified as a potential review issue in the Agency's Filing Communication dated June 13, 2011, which stated:

> The clinical impact of the increased fluticasone systemic exposure including the effects on HPA-axis will be a review issue.

The clinical significance of this issue with regards to HPA-Axis effects is discussed in Section 7.4.5. This Reviewer's conclusion is that the totality of the data suggests that the systemic exposure to fluticasone associated with MP29-02 falls within the range of fluticasone exposures associated with other products for which no substantial effect on HPA axis has been identified. Moreover, the clinical program for MP29-02 supports the systemic safety of the proposed product.

A detailed review of Trials X-03065-3282 and X-03065-3283 will be provided in the Clinical Pharmacology team's review.

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5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3. Clinical development program for MP29-02

Trial / Locations	Population	Total n* (Pediatric n)#	Design	Treatment Arms@	Duration	Relevance
MP-4001 8 centers, United States	Adults and adolescents 12 years and older, SAR	610 (43)	R, DB, PC, AC	1 spray per nostril BID: • MP 29-02 • Astelin® • fluticasone propionate (commercial) • Placebo	2 weeks	Efficacy, Safety
MP-4002 44 centers, United States	Adults and adolescents 12 years and older, SAR	832 (98)	R, DB, PC, AC	1 spray per nostril BID: • MP 29-02 • azelastine hydrochloride • fluticasone propionate • Placebo	2 weeks	Efficacy, Safety
MP-4004 41 centers, United States	Adults and adolescents 12 years and older, SAR	779 (55)	R, DB, PC, AC	1 spray per nostril BID: • MP 29-02 • azelastine hydrochloride • fluticasone propionate • Placebo	2 weeks	Efficacy, Safety
MP-4006 49 centers, United States	Adults and adolescents 12 years and older, SAR	1801 (197)	R, DB, PC, AC	1 spray per nostril BID: • MP 29-02 • azelastine hydrochloride • fluticasone propionate • Placebo	2 weeks	Efficacy, Safety
MP-4000 37 centers, India	Adults and adolescents 12 to 80 years of age, PAR or VMR	612 (36)	R, OL, AC, PG	1 spray per nostril BID • MP 29-02 2 sprays per nostril QD • fluticasone propionate (commercial)	12 months	Long-term Safety
X-03065-3282 1 center,	Adults, Healthy	30 (0)	R, OL, CO	2 sprays per nostril • MP 29-02 • fluticasone propionate • fluticasone	Single dose	PK

Germany				propionate (commercial)		
X-03065-3283 1 center, Germany	Adults, Healthy	30 (0)	R, OL, CO	2 sprays per nostril • MP 29-02 • azelastine hydrochloride • Astelin®	Single dose	PK

Source: Section 2.5, pg. 9, 11, and 13-14 (Table 4)
*** Total n refers to the number of total number patients or subjects randomized.**
[#] Pediatric n refers to the number of number of patients 12 to < 18 years of age in the ITT population for Trials MP-4001, MP-4002, MP-4004, and MP-4006, and in the Safety Population for Trial MP-4000.
[@] The terms "azelastine hydrochloride" and "fluticasone propionate" refer to the investigational monotherapy comparators formulated in the MP 29-02 vehicle. The term "fluticasone propionate (commercial)" refers to commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.).
Key: AC=active-controlled; BID= twice daily; CO=crossover; DB=double-blind; OL= open label; PAR=perennial allergic rhinitis; PC=placebo-controlled; PG=parallel group; PK=pharmacokinetic; QD=once daily; R=randomized; SAR=seasonal allergic rhinitis; VMR=vasomotor rhinitis

5.2 Review Strategy

The clinical development program for MP29-02 is comprised of four 2-week phase 3 efficacy and safety clinical trials (MP-4001, MP-4002, MP-4004, and MP-4006) and a year-long safety trial (MP-4000). In addition, two pharmacokinetic (PK) trials were conducted (X-03065-3282 and X-03065-3283).

With regards to the organization of this review, Section 5.3 includes a discussion of the design employed by the four 2-week phase 3 efficacy and safety trials. The design of the year-long safety trial is discussed in Section 7.1.1. The efficacy results from the 2-week safety and efficacy trials are discussed in Section 6, which is followed in Section 7 by a review of the safety findings both the 2-week trials as well as the year-long safety trial. A high-level summary of the design and results of the two pharamacokinetic trials is provided in Section 4.4.

As described in Sections 5.3 and 7.1.1, the monotherapy comparators used in trial MP-4001, Astelin® and commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.), differ from those employed in the other three efficacy and safety trials, investigational azelastine hydrochloride and fluticasone propionate each formulated (separately) in the MP29-02 vehicle. The commercial monotherapies in Trial MP-4001 are not appropriate comparators for the purpose of satisfying the Combination Rule; therefore, while the results of Trial MP-4001 are clinically relevant, they are considered as secondary evidence in terms of supporting a regulatory action.

The review of efficacy focuses first on the analysis of the primary endpoint, the change from baseline in the reflective combined AM + PM Total Nasal Symptom Score (rTNSS) over the entire 14-day treatment period, using data from the three relevant 2-week efficacy and safety trials (MP-4002, MP-4004, and MP-4006). Relevant secondary endpoints such as the instantaneous Total Nasal Symptom Score (iTNSS), onset of

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action, and Rhinoconjunctivities Quality of Life Questionnaire (RQLQ) are discussed, as is the Applicant's analysis of the reflective Total Ocular Symptom score (rTOSS). A brief overview of efficacy results from Trial MP-4001 is provided separately in Section 6.1.10.

The review of safety is based primarily upon results from the three 2-week efficacy and safety trials (MP-4002, MP-4004, and MP-4006), as well as from the year-long safety trial (MP-4000). Pooling across trials MP-4002, MP-4004, and MP-4006 to examine the emergence of any safety signals was deemed acceptable as these trials were very similar in design.

5.3 Discussion of Individual Studies/Clinical Trials

The clinical development program for MP29-02 is comprised of four 2-week phase 3 efficacy and safety clinical trials and a year-long safety trial. A summary of the protocols for these phase 3 trials is provided here. In addition, two pharmacokinetic (PK) trials were conducted; these are summarized in Section 4.4.

2-week Phase 3 Efficacy and Safety Trials: MP-4001, MP-4002, MP-4004, MP-4006
The clinical development program includes four similarly designed 2-week randomized, double-blind, placebo- and active-controlled, parallel group phase 3 trials in patients with moderate-to-severe SAR. The objective of these trials was to compare the efficacy and safety of MP29-02 to placebo as well as to two monotherapy comparators. The overall design of these trials is consistent with the Agency's Draft Guidance for Industry on the clinical development of drug products for allergic rhinitis.[2]

A summary of these four trials is provided in Table 4.

Table 4. 2-week Phase 3 Efficacy and Safety Trials

Trial Number	Season Conducted	Number of Sites	Number Randomized	Monotherapy Comparators
MP-4001	2007-2008, Texas Mountain Cedar	8	610	Astelin® and commercially available generic fluticasone propionate
MP-4002	2008, spring	44	832	azelastine hydrochloride and fluticasone propionate, each formulated in the MP 29-02 vehicle
MP-4004	2008, fall	41	779	
MP-4006	2009	49	1801	

Source: 5.3.5.1.3 MP4001, 5.3.5.1.3 MP4002, 5.3.5.1.3 MP4004, 5.3.5.1.3 MP4006

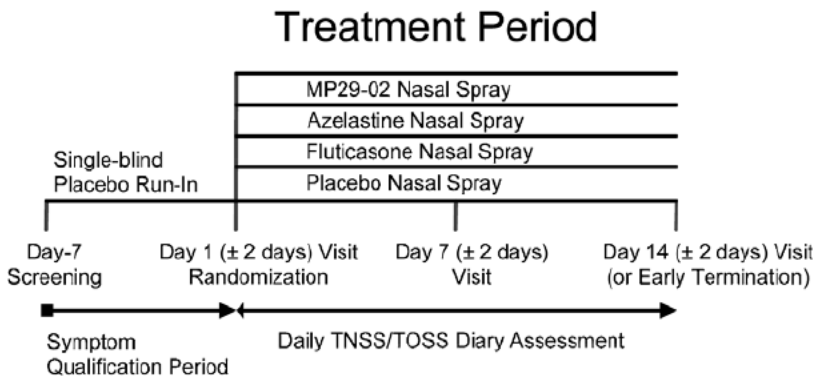
[2] Draft Guidance, "Allergic Rhinitis: Clinical Development Programs for Drug Products," April 2000. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071293.pdf. Accessed December 7, 2011.

As was discussed previously with the Applicant, it is notable that 1) an additional trial (MP-4006) was conducted when typically two trials would be sufficient for establishing efficacy, and 2) Trial MP-4006 employed a large (double) sample size compared to the other trials. This is of particular relevance given that there is no established minimal clinically important difference for the primary efficacy endpoint evaluated in the clinical development program (TNSS). The Division had concerns that the treatment difference may be statistically significant, driven by the large sample size, but be of questionable clinical relevance. During the pre-NDA interaction the Applicant was asked to provide a rationale for these decisions in the NDA submission. In the Summary of Clinical Efficacy (Section 2.7.3) the Applicant explains that 1) based on feedback from the (b) (4), a decision was made to conduct MP-4006 (b) (4) and 2) the large sample size of trial MP-4006 was chosen based on the observed results (treatment effect and standard deviations) of prior trials, with the goal of increasing power and precision. The Clinical Review's assessment of the large sample size employed in Trial MP-4006 is discussed in Section 6.1.4.

General Trial Design

Each of these trials was randomized, double-blind, placebo- and active-controlled, with a 2-week treatment period. A schematic of the general design of the four trials is presented in Figure 1.

Figure 1. General Trial Design: Trials MP-4001, MP-4002, MP-4004, MP-4006



Source: 5.3.5.3.27, pg. 15 (Figure 1)

Treatment arms

Each of the trials evaluated four treatments: MP29-02, two monotherapy comparators, and placebo, each administered as 1 spray per nostril BID.

(b) (4)

Notably, the monotherapy comparators used in trial MP-4001, Astelin® and commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.), differ from those employed in the other three efficacy and safety trials, investigational azelastine hydrochloride and fluticasone propionate each formulated (separately) in the MP29-02 vehicle. Therefore, MP-4001 is considered as secondary support for efficacy and safety.

Primary and Secondary or Additional Endpoints

The primary efficacy endpoint evaluated in each of the four 2-week efficacy and safety trials was the change from baseline[4] in the 12-hour reflective Total Nasal Symptom Score (rTNSS) over the entire 14-day treatment period. This choice of primary endpoint is consistent with Agency recommendations as outlined in the Draft Guidance on allergic rhinitis previously cited.

These four trials also evaluated the following secondary or additional endpoints:

- Change from baseline in instantaneous TNSS (iTNSS) for the entire 14-day treatment period
- Change from baseline in 12-hour reflective TOSS (rTOSS) and instantaneous TOSS (iTOSS) for the entire 14-day study period
- Change from baseline to Day 14 in the RQLQ in patients 18 years of age and older
- Onset of action (change from baseline in iTNSS over the 4-hour period following initial administration of trial drug)
    - Trials MP-4002, MP-4004, MP-4006
- Change from baseline in the 12-hour reflective individual symptom scores for the entire 14-day study period
- Daily scores – Daily change from baseline in 12-hour rTNSS and iTNSS
- Change from baseline in the individual symptom score for postnasal drip[5] for the entire 14-day study period

This review's analysis of efficacy focuses on an evaluation of the data for the primary endpoint, rTNSS, as well as for the following secondary endpoints: iTNSS, rTOSS, and RQLQ. Onset of action (based on an evaluation of iTNSS) is also discussed. The Applicant's evaluation of iTNSS and onset of action were both consistent with the recommendations outlined in the Draft Guidance on allergic rhinitis previously cited. While the RQLQ and rTOSS are not specifically mentioned in the Draft Guidance, there is some regulatory precedent for their use in allergic rhinitis programs (e.g., the fluticasone furoate clinical development program); (b) (4)

[4] Baseline TNSS is defined as the average of all TNSS scores over the entire 7-day placebo run-in period.
[5] Scored on the same scale as that used for the TNSS.

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(b) (4)

Details on the scoring system for the TNSS and TOSS are provided below, along with a description of the RQLQ.

TNSS
The TNSS grades each of four symptoms (runny nose, sneezing, itchy nose, and nasal congestion) on the following 0-3 point scale:

0=None – no symptoms present
1=Mild – mild symptoms which are noticeable and do not interfere with any activity
2=Moderate – symptoms which are slightly bothersome and slightly interfere with activity OR nighttime sleep
3=Severe – symptoms which are bothersome and interfere with activity OR nighttime sleep

The minimum and maximum possible scores are 0 and 12, respectively.

TOSS
The TOSS grades each of three symptoms (itchy eyes, watery eyes, eye redness) on 0-3 point scales. The grading scale for itchy eyes and watery eyes is the same as that for the TNSS. The grading scale for eye redness is as follows:

0=None – no redness present
1=Mild – slightly dilated blood vessels and pinkish color compared to subject's normal color
2=Moderate – more dilation of blood vessels and red color compared to subject's normal color
3=Severe – large, numerous dilated blood vessels and deep red color compared to subject's normal color

The minimum and maximum scores for the TOSS are 0 and 9, respectively.

RQLQ
The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is a tool that measures the subjective impact of seasonal allergic rhinitis on patients' health-related quality of life. It is comprised of 28 items in seven domains evaluated on a 7-point scale where 0=no impairment and 6=maximum impairment. A change from baseline ≥ 0.5 points is considered to represent a clinically meaningful improvement. The RQLQ was administered to patients 18 years of age and older in the 2-week efficacy and safety trials.

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Population
The four 2-week phase 3 efficacy and safety clinical trials evaluated adults and adolescents 12 years of age and older with seasonal allergic rhinitis.

As noted in Section 2.5, during pre-submission interactions with the Sponsor the Division recommended that the proposed product be evaluated in a population requiring concurrent therapy with both azelastine and fluticasone. It is therefore notable that the inclusion and exclusion criteria for the efficacy and safety trials did not exclude patients with a history of failed therapy with either Astelin® or commercially available fluticasone propionate. Nevertheless, the efficacy results from the clinical trials provide assurance of the contribution of each component to MP29-02, as discussed in Section 6.1.4.

A detailed summary of the inclusion and exclusion criteria for the four 2-week phase 3 efficacy and safety clinical trials (MP-4001, MP-4002, MP-4004, and MP-4006) follows below.

Summary of Inclusion Criteria:

- Males and females, 12 years of age and older
- Provides informed consent and, if applicable, pediatric assent
- Moderate-to-severe rhinitis, defined as rhinitis with one or more of the following being present: sleep disturbance; impairment of daily activities, leisure and/or sport; impairment of school or work; troublesome symptoms
    - Criterion for Trials MP-4002, MP-4004, MP-4006
- Screening Visit: A 12-hour reflective TNSS ≥ 8 out of a possible 12 and a congestion score of 2 or 3 on Visit 1
- Randomization Visit: A 12-hour reflective TNSS (AM or PM) ≥ 8 on 3 separate symptoms assessments (one of which was within 2 days of Day 1, and could include the morning of Day 1) during the Lead-in Period; an AM or PM 12-hour reflective nasal congestion score of 2 or 3 must have been recorded on 3 separate symptom assessments (one of which was within 2 days of Day 1, and could include the morning of Day 1)
    - Criterion for Trials MP-4001, MP-4002, MP-4004
- Randomization Visit: For the 3 days prior to Randomization and on the morning of Randomization, the sum of the 7 consecutive reflective AM and PM TNSS assessments was ≥ 56, with a nasal congestion score ≥ 14; with a congestion score ≥ 2 at time point zero, prior to beginning the onset of action assessment
    - Criterion for Trial MP-4006 only
- Randomization Visit: Had an instantaneous TNSS score of ≥ 8 just prior to beginning the onset of action assessment

  - Criterion for Trials MP-4002, MP-4004, and MP-4006
- Taken at least 10 doses of run-in placebo medication.
  - Criterion for Trials MP-4002, MP-4004, and MP-4006
- Willing and able to comply with trial requirements.
- At least a 2-year history of SAR during Texas Mountain Cedar season (Trial MP-4001), OR during spring allergy season (Trial MP-4002), OR during fall allergy season (Trial MP-4004) OR during the current allergy season (Trial MP-4006), AND had a positive response[6] to skin prick within the last year
- General good health and free of any disease or concomitant treatment that could interfere with the interpretation of trial results as determined by the investigator or Applicant's medical officer.
- If receiving immunotherapy injections, on a stable regimen for at least 30 days prior to the first trial visit
- A 6-month washout period was required following the last dose of sublingual immunotherapy

Summary of Exclusion Criteria:

- On focused nasal examination, the presence of any nasal mucosal erosion, nasal mucosal ulceration, or nasal septum perforation (Grade 1b-4) at Screening or Randomization
  - Criterion for Trials MP-4004 and MP-4006 specified any superficial and moderate nasal mucosal erosions
- Other nasal disease(s) likely to affect deposition of intranasal medication, such as sinusitis, rhinitis medicamentosa, clinically significant polyposis, or nasal structural abnormalities
- Nasal surgery or sinus surgery within the previous year
- Chronic sinusitis – more than 3 episodes per year
- Planned travel outside of the pollen area during the trial
- Use of any investigational drug within 30 days prior to Day -7.
- Presence of any hypersensitivity to drugs similar to azelastine hydrochloride or fluticasone propionate

[6] Positive response to skin prick is defined as a wheal diameter of at least 3 mm larger than the negative control for Trials MP-4001, MP-4002, and MP-4004. For Trial MP-4006, a positive response is defined as a wheal diameter of at least an average of 5x5 mm larger than the negative control and a positive wheal of at least an average of 5x5 mm to histamine.

- Women who were pregnant or nursing, or women of childbearing potential who were not abstinent or not practicing a medically acceptable method of contraception
- Respiratory tract infections within 14 days prior to Day -7
- Asthma (with the exception of intermittent asthma)
- Significant pulmonary disease including COPD
- Clinically significant arrhythmia or symptomatic cardiac conditions
- A known history of alcohol or drug abuse within the last 2 years
- Existence of any surgical or medical condition or physical or laboratory findings, which in the opinion of the Investigator or Sponsor's medical monitor, significantly altered the absorption, distribution, metabolism, or excretion of study drug, that might significantly affect the subject's ability to complete the trial, or safety in the trial
- History of glaucoma
    - Criterion for Trials MP-4002, MP-4004, and MP-4006
- Clinically relevant abnormally physical findings within 1 week of randomization which, in the opinion of the investigator, would have interfered with the objectives of the study or may have precluded compliance with study procedures
- Employee (or employee's family member) of the research center or private practice
- Participation in another of the previous 2-week efficacy and safety trials
    - For Trial MP-4006 the Sponsor attempted to ensure that no more than 50% of patients had participated in Trials MP-4001, MP-4002, or MP-4004

Use of prohibited medications or therapies within the given time period prior to Day -7, as described in Table 5.

Table 5. Prohibited medications and washout periods, Trials MP-4001, MP-4002, MP-4004, and MP-4006

Medication	Time Period Prior to Day -7
loratadine, desloratadine, cetirizine, levocitirizine, fexofenadine	5 days
antihistamines (including nasal spray, ophthalmic preparations, sleep and diet aids, and cold preparations)	5 days
Astelin® Nasal Spray	5 days

oral and intranasal anticholinergic agents	5 days
Ephedrine or pseudoephedrine containing products	5 days
Decongestants including cold preparations	5 days
Ocular corticosteroids	7 days
Cromolyn compounds	14 days
Oral antibiotics for respiratory infections	14 days
Leukotriene inhibitors	14 days
Ocular mast cell stabilizers	14 days
Monoamine oxidase inhibitors	14 days
Nasally inhaled corticosteroids	14 days
Orally inhaled corticosteroids	30 days
Systemic steroids	30 days
Tricyclic antidepressants	30 days
Immunosuppressives/immunomodulators[7]	30 days
IgE antagonist	130 days
Sublingual immunotherapy	6 months

Source: Section 5.3.5.1.4 MP4001, pg. 124-125; Section 5.3.5.1.4 MP4002, pg. 125; Section 5.3.5.1.4 MP4004, pg. 19; Section 5.3.5.1.4 MP4006, pg. 129

Also prohibited throughout the entire trial were all intranasal therapies (including saline), topical corticosteroids (except for the treatment of small, localized lesions), all eye ophthalmic drops (prescription and OTC), radiation therapy, the initiation of injectable immunotherapy, and any drug (investigational or marketed) being used in a clinical trial.

Visits and Schedule of Assessments

Each of the studies included a screening visit (Visit 1), followed by a 7-day single-blind treatment period. Patients meeting symptoms severity criteria were randomized 1:1:1:1 to one of the four study arms on Day 1 (Visit 2). Follow-up occurred on Day 7 (Visit 3), and the end of the study was on Day 14 (Visit 4). A schedule of trial procedures is provided in Table 6.

[7] Tacrolimus, pimecrolimus or similar drugs may be used if limited to small, localized lesions.

Table 6. Schedule of Trial Procedures, Trials MP-4001, MP-4002, MP-4004, and MP-4006

	Single-blind Placebo Run-in Period	Treatment Period		
Procedure	**Visit 1 Screening Day -7**	**Visit 2 Randomization Day 1 (± 2)[f]**	**Visit 3 Day 7 (± 2)[d]**	**Visit 4 or Early Termination Day 14 (± 2)[d]**
Written informed consent and pediatric assent, if appropriate	X			
TNSS qualification	X	X		
Inclusion/Exclusion criteria	X	X		
Skin test[a]	X			
Physical examination/ medical history	X			
Document inadequate response to previous rhinitis medication(s)	X (Not performed for Trial MP-4001)			
Focused Nasal Examination	X	X	X	X
Vital signs (blood pressure, pulse, respiration temperature)	X	X	X	X
Urine pregnancy test[b]	X	X		X
Assess concomitant medications	X	X	X	X
Instruct patients on proper use of trial medications and completion of TNSS Diary	X	X	X	
Dispense placebo run-in medication	X			
Dispense Diary	X	X	X	
RQLQ[e]		X		X
Rhinitis Diagnosis Screener		X (Not performed for Trial MP-4001)		
Dispense trial medication		X		
4 hour onset of action assessment		X (Not performed for		

		Trial MP-4001)		
Collect used run-in medication		X		
Collect used trial medication				X
Collect Diary		X	X	X
Adverse events assessment[c]		X	X	X

Source: Section 5.3.5.3.27, pg. 25 (Table 3)
[a]May be omitted if patient had positive skin test for a relevant allergen within the last year
[b]All female patients
[c] For Trials MP-4002, MP-4004, and MP-4006, any adverse event that occurs subsequent to the signing of the informed consent will be recorded in the patient's medical record and CRF. For Trial MP-4001, any adverse event that occurs subsequent to the initial dose of study medication during the lead-in period will be recorded in the subject's medical record and in the CRF.
[d]Visit 3 and Visit 4 visit windows are calculated from Visit 2 (Randomization Visit)
[e]Administered prior onset of action assessment at Visit 2 to patients 18 and older
[f]Protocols for Trials MP-4002, MP-4004, and MP-4006 specify that Visit 2 must occur prior to noon; the window for Visit 2 is ±3 days for Trial MP-4001

Single-blind Placebo Run-in Period

Prior to the conduct of assessments at Screening (Visit 1, Day -7), patients provided written informed consent and (if appropriate) pediatric assessment. The rTNSS was administered; subjects with a score greater or equal to 8, along with a congestion score of 2 or 3, were considered eligible for the single-blind placebo run-in period. Screening assessments included a general physical examination, a focused nasal examination, medical history, skin test (omitted if a patient had a positive test in the past year), and urine pregnancy test[8]. Also conducted at Screening were documentation of medication use in the past 30 days, confirmation of inclusion and exclusion criteria, and documentation of prior response to rhinitis medication(s)[9].

Patients who successfully completed all Visit 1 assessments and who continued to meet eligibility criteria were administered diary cards and placebo medication. The first dose of placebo medication was self-administered by patients at the clinic.

During the 7-day, single-blind placebo run-in period, patients were instructed to record symptoms scores twice daily (AM and PM), and to take placebo nasal spray twice daily (approximately every 12 hours).

Double-blind Treatment Period

Following the single-blind placebo run-in period, patients satisfying symptom severity criteria and continuing to meet trial inclusion/exclusion criteria were randomized 1:1:1:1 to one of the four treatment groups.

[8] Administered to all females.
[9] Investigators evaluated whether patients had a history of inadequate response to previous rhinitis medication(s) including intranasal corticosteroids, oral antihistamines, nasal antihistamine or subcutaneous immunotherapy within the previous 2 years. Not conducted for Trial MP-4001.

Prior to randomization the patient's diary was collected; failure to complete the diary[10] resulted in discontinuation from the trial. The placebo medication bottle was also collected and weighed. Additional assessments included vital signs, focused nasal examination, adverse events, concomitant medications, urine pregnancy test[11], adverse events, and concomitant medications.

After randomization (Visit 2) but before trial medication administration, patients 18 years of age and older were administered the Adult RQLQ. Patients were also instructed to record the iTNSS prior to the first dose of trial medication and then at 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes.[12] The first dose of trial medication was self-administered during the clinic visit. Prior to leaving the clinic, patients were dispensed a new diary. During the 14-day treatment period patients were instructed to record symptoms scores twice daily (AM and PM), and to take double-blind medication twice daily (after the recording of scores).

Patients underwent an interim evaluation (Visit 3) on Day 7 (± 2) of the treatment period. Assessments included collection and review of the patient diary, collection and assessment of returned trial medication, vital signs, focused nasal examination, adverse events, and concomitant medications. A new diary was dispensed.

The final end-of-study evaluation (Visit 4) took place on Day 14 (± 2) of the treatment period, or at the time of early termination. The first assessment conducted at Visit 4 was the RQLQ for adults. Additional assessments included collection and review of the patient diary, collection and assessment of returned trial medication, vital signs, focused nasal examination, urine pregnancy test[13], adverse events, and concomitant medications.

Pollen Counts

Pollen counts were performed each weekday, and when possible, each weekend day, either by trial site staff or by a community counting station located within 30 miles of the study site.

Safety

A summary of the safety evaluations conducted for the four 2-week efficacy and safety trials is provided in Section 7.1.1.

Planned Analyses

[10] Failure to complete the diary was defined as missing data for 2 consecutive (AM or PM) TNSS assessments or any 3 TNSS assessments (AM or PM) during the run-in period.
[11] Administered to all females.
[12] Not conducted for Trial MP-4001.
[13] Administered to all females.

Reference ID: 3107643

This section summarizes the Applicant's pre-specified statistical analytic approach based on information provided in the trials' protocols, as well as in the final Statistical Analysis Plans for each trial.

Analysis Populations

Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized patients with at least one post baseline efficacy observation. Members of the ITT population must also have taken the correct lead-in trial medication and at least one dose of double-blind mediation following randomization. All main efficacy analyses were to be conducted using the ITT population.

Per-protocol Population

The per-protocol (PP) population is defined as all patients completing the 2-week double-blind treatment period per protocol. Patients could be excluded due to noncompliance with treatment, taking prohibited medications, insufficient TNSS score, incorrect randomization, and out-of-window final trial visit. Additional efficacy analyses were planned for the PP population.

Safety Population

The safety population is defined as all randomized patients who receive at least 1 dose of trial medication. Safety analyses were planned for the safety population.

Statistical Testing

The chosen threshold for statistical significance was at the 0.05 level, and all statistical tests were 2-sided. The only planned adjustment for multiplicity was for the primary endpoint. A gatekeeping strategy for the adjustment of multiplicity was described.[14]

Missing Data

The statistical analysis plans pre-specified that missing TNSS values would be imputed using the last observation carried forward (LOCF) method.

Demographic and Background Data

Categorical variables were summarized using frequency distributions and continuous variables with descriptive statistics, for both the ITT and PP populations. Baseline comparability was evaluated using a two-way analysis of variance (ANOVA) model for continuous variables and the Chi-square test or Fisher's exact test for categorical variables.

[14] While the protocols for Trials MP-4001 and MP-4002 specified that no adjustments for multiple comparisons would be made, this statement was absent from the protocols for MP-4004 and MP-4006. The statistical analysis plans for all four trials specified the use of a gatekeeping strategy to adjust for multiplicity.

Reference ID: 3107643

Efficacy Analyses for the primary endpoint
The primary efficacy analysis was pre-specified to be a repeated measures analysis, using an ANCOVA model, for the ITT population. The model contained study day as the within-subject effect, treatment group and site as the between-subject effect, and baseline as a covariate. An additional analysis evaluated the primary endpoint for the PP population.

Efficacy Analyses for secondary endpoints
A summary of the main analyses planned by the Applicant for secondary endpoints discussed in this review is provided below. These analyses were conducted for the ITT population.

iTNSS
Change from baseline in iTNSS for the entire 14-day treatment period was analyzed using a repeated measures model.

rTOSS
Change from baseline in the rTOSS for the entire 14-day treatment period was analyzed using repeated measures technique.

RQLQ
The RQLQ was administered to patients 18 years of age or older. The protocols state that RQLQ scores would be summarized according to the method described in the literature[15] and treatment groups compared by ANCOVA.

Onset of action (Trials MP-4002, MP-4004, MP-4006)
Onset of action was evaluated by examining change from baseline in iTNSS over the 4-hour period following the initial administration of trial drug. The onset of action was defined as "the first time point after initiation of treatment when the drug demonstrates a greater reduction from baseline in instantaneous TNSS compared to the placebo treatment that proves durable from this point."

Treatment Compliance
Patients were instructed to record each dose of trial medication in their patient diary, and to return trial medication. Diary entries and bottle weight were compared and discrepancies were resolved prior to a patient's departure from the clinic; however, only information from the patient diary was used for data analysis.

Subgroup Analyses
Other than a potential subgroup analyses based on pollen counts (if necessary), no subgroup analyses were pre-specified.

[15] Juniper EF, et al. *Clin Exp Allergy.* 1991;21:77-83.

Reference ID: 3107643

Interim Analyses
There were no interim analyses planned for these trials.

Safety Analysis
A descriptive presentation of the safety data was planned.

Protocol Amendments
There were a number of protocol amendments for Trials MP-4001, MP-4002, and MP-4006. While these amendments do not raise any questions regarding study integrity, they did have the potential to impact results. One such example is the change in the definition of the patient population from individuals who "may benefit from combination therapy" to those who "have moderate-to-severe allergic rhinitis." This change was initiated with Trial MP-4002, and carried over into the subsequent efficacy and safety trials (MP-4004 and MP-4006). The pre-submission interaction around patient population, and the implications of how that population was ultimately defined, are discussed elsewhere in this section and this review (see also Sections 2.5 and 6.14).

Also notable was the increase in the number of planned patients that took place both for Trials MP-4002 and MP-4006. A discussion of the pre-submission interaction regarding sample size and the implications for the interpretation of efficacy data is provided elsewhere in this section and this review (see also Sections 2.5 and 6.14).

A detailed summary of the protocol amendments for the 2-week efficacy and safety trials follows below.

Trial MP-4001
Original protocol: October 24, 2007
Protocol Amendment 1: November 8, 2007
- Addition of urine pregnancy test to Day 1
- Editing of acceptable forms of contraception
- Deletion of requirement that patients with new nasal mucosal ulcerations or septal perforations be referred to an otorhinolaryngologist for further evaluation
- Bottle weights deleted from treatment compliance evaluation (now only diary data)

Protocol Amendment 2: November 20, 2007
- Run-in period changed from -5 days to -7 days ± 3 days
- Prohibited medications changed from "medicated" eye drops to "all" eye drops
- Clarification of contraception requirements
- Other minor editing changes

Trial MP-4002
Original protocol: December 21, 2007

Reference ID: 3107643

Protocol Amendment 1: February 8, 2008

- Description of patient population changed from "may benefit from combination therapy" to "have moderate-to-severe allergic rhinitis"
- Documentation of prior inadequate response to rhinitis medications added

Protocol Amendment 2: March 11, 2008

- Number of planned subjects planned changed from 600 to 780; power calculation now indicates 90% power
- Rhinitis Diagnosis Screener questionnaire added

Changes made to Trial MP-4002 apply to both Trials MP-4004 and MP-4006.

Trial MP-4004
Original protocol: June 5, 2008
No protocol amendments.

Trial MP-4006
Original protocol: December 29, 2008
Protocol Amendment 1: January 23, 2009

- Plan for 780 randomized patients changed to 1800 randomized; sample size calculation updated
- Exclusion criteria "members of the same household" deleted (had not been part of MP-4002 or MP-4004)

Protocol Amendment 2: March 25, 2009

- Randomization criteria changed from:
    - A 12-hour reflective TNSS (AM or PM) ≥ 8 on 3 separate symptoms assessments (one of which was within 2 days of Day 1, and could include the morning of Day 1) during the Lead-in Period; an AM or PM 12-hour reflective nasal congestion score of 2 or 3 must have been recorded on 3 separate symptom assessments (one of which was within 2 days of Day 1, and could include the morning of Day 1) to
    - Randomization Visit: For the 3 days prior to Randomization and on the morning of Randomization, the sum of the 7 consecutive reflective AM and PM TNSS assessments was ≥ 56, with a nasal congestion score ≥ 14; with a congestion score ≥ 2 at time point zero, prior to beginning the onset of action assessment
- Positive skin prick test changed from "wheal diameter of at least 3 mm larger than the negative control" changed to "wheal diameter of at least an average of 5x5 mm larger than the negative control and a positive wheal of at least an average of 5x5 to histamine."
- Original exclusion of patients who had participated in Trials MP-4001, MP-4002, or MP-4004 changed to the following: "in order to ensure an adequate safety database, sites should make every effort to ensure no more than 50% of their subjects have participated in protocol MP4001, MP4002 or MP4004."

Reference ID: 3107643

6 Review of Efficacy

Efficacy Summary

The NDA submission contains adequate data to support the efficacy of MP29-02 for the treatment of symptoms of seasonal allergic rhinitis in patients 12 years of age and older.

Evidence of efficacy comes primarily from Trials MP-4002, MP-4004, and MP-4006, which were randomized, double-blind, placebo- and active-controlled, with a 2-week treatment period. These trials employed a factorial design, evaluating the proposed product, MP29-02, along with placebo, as well as two investigational monotherapy comparators, azelastine hydrochloride and fluticasone propionate, each formulated (separately) in the MP29-02 vehicle. This factorial design allows for the evaluation of the contribution of each component to the efficacy of the novel combination product. In each of the three pivotal 2-week efficacy and safety trials, results for the analysis of the primary endpoint, change from baseline in the rTNSS (AM and PM combined) over the 14-Day treatment period, were statistically significant for the comparisons between MP29-02 and placebo, as well as the comparisons of MP29-02 to each of the monotherapy comparators. These results were robust to analyses using different approaches for the handling of missing data.

Overall, these results provide replicate evidence of efficacy for the proposed combination product; the factorial design also provides replicate evidence of the contribution of each component. Moreover, the effect sizes for the treatment difference between MP29-02 and placebo (approximately -2.16 to -2.70) are of reasonable magnitude when compared to other development programs for allergic rhinitis, and thus, likely to represent an outcome that is clinically meaningful.

Results for the secondary endpoints, including iTNSS which validates the twice-daily dosing interval, and RQLQ, were generally supportive of the primary analysis. In addition, the program provides replicate evidence for a 30-minute onset of action claim.

(b) (4)

6.1 Indication

The Applicant proposes that MP29-02 is indicated for (b) (4) This clinical review proposes that the indication be modified to "the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief." The intent of this modification is to aid clinicians in the selection of an appropriate population that is likely to benefit from combination therapy, and to limit exposure to patients for whom combination therapy is unnecessary.

6.1.1 Methods

Refer to Section 5.3 for a discussion of the protocols and planned analyses for the three 2-week efficacy and safety trials (MP-4002, MP-4004, and MP-4006). The designs of these trials are generally consistent with the principles laid out in the Agency's Draft Guidance on this topic[16], as well as with the programs conducted for other products approved for seasonal allergic rhinitis.

In addition to needing to meet the general requirements of a seasonal allergic rhinitis clinical development program, the MP29-02 program also must fulfill the requirements for a fixed combination dosage form, as outlined in regulation.[17] This includes meeting the condition of the Combination Rule that stipulates that "each component makes a contribution to the claimed effects." The Division's assessment is that this can be demonstrated through the use of appropriately designed and conducted trials where the proposed combination product is compared to each component, and the combination product is statistically superior to each component with an effect size that is clinically meaningful. Each component must also be demonstrated to be efficacious, i.e., through comparison to placebo. This factorial design requires that the monotherapy comparators be comparable to the monocomponents comprising the combination product, as differences can obscure the comparison of the combination to each of its components. To that extent, the December 7, 2011, submission providing additional CMC data including that addressing the comparability of the combination drug product used in clinical trials to the corresponding monocomparator drug products, was deemed to constitute a major amendment to the Application. As this major amendment was submitted within three months of the user fee goal date, it resulted in an extension of that date by three months to May 1, 2012. The CMC review of the December 7, 2011, submission concludes that the comparability of the monotherapies and the combination drug product evaluated in the pivotal clinical trials was acceptable; this conclusion lends

[16] Draft Guidance for Industry, "Allergic Rhinitis: Clinical Development Programs for Drug Products," April 2000. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071293.pdf. Accessed March 22, 2012.
[17] 21 CFR 300.50(a), commonly referred to as the "Combination Rule."

legitimacy to the Applicant's use of the factorial design in the pivotal clinical efficacy trials

6.1.2 Demographics

Demographics and baseline characteristics for the pooled ITT population (Trials MP-4002, MP-4004, and MP-4006) are provided in Table 7.

Table 7. Demographics and Baseline Characteristics for the pooled ITT population, Trials MP-4002, MP-4004, and MP-4006

Category	MP29-02 N=848	Placebo N=857	Azelastine hydrochloride N=847	Fluticasone propionate N=846
Age (Years)				
N	848	857	847	846
Mean (SD)	37 (14)	36 (14)	37 (15)	36 (14)
Median	37	36	37	36
Min-Max	12-78	12-77	12-83	12-76
12 to < 18 [n(%)]	88 (10)	99 (12)	78 (9)	85 (10)
18 to < 65 [n(%)]	741 (87)	733 (86)	740 (87)	747 (88)
65 or older [n(%)]	19 (2)	25 (3)	29 (3)	14 (2)
Sex [n(%)]				
Male	303 (36)	337 (39)	318 (38)	318 (38)
Female	545 (64)	520 (61)	529 (63)	528 (62)
Race [n(%)]				
White	680 (80)	681 (80)	672 (79)	657 (78)
Black	134 (16)	132 (15)	134 (16)	149 (18)
Asian	18 (2)	19 (2)	17 (2)	16 (2)
Native Hawaiian or other Pacific Islander	3 (0.4)	2 (0.2)	7 (0.8)	8 (0.9)
American Indian or Alaska Native	1 (0.1)	3 (0.4)	2 (0.2)	4 (0.5)
Other	12 (1)	20 (2)	15 (2)	12 (1)
Ethnicity [n(%)]				
Hispanic or Latino	115 (14)	130 (15)	122 (14)	114 (14)
Not Hispanic or Latino	733 (86)	727 (85)	725 (86)	732 (87)
Height (inches)				
N	847	856	847	846
Mean (SD)	66 (4)	66 (4)	66 (4)	66 (4)
Median	66	66	66	66
Min-Max	53-80	54-80	54-80	52-81
Weight (lb)				

N	847	856	847	846
Mean (SD)	177 (44)	176 (47)	173 (47)	176 (47)
Median	171	170	166	170
Min-Max	72-370	72-345	78-390	82-455
Total rTNSS Score[a]				
N	848	856	847	846
Mean (SD)	18.8 (2.9)	19.0 (2.8)	19.0 (3.0)	18.9 (2.8)
Median	18.9	19.1	18.9	19.0
Min-Max	6-24	7-24	7-24	9-24
Duration of SAR History (Years)				
N	848	857	847	846
Mean (SD)	21 (13)	20.3 (13)	20.1 (13)	20 (13)
Median	18	17	17.0	18
Min-Max	2-64	2-68	2-75	2-74

[a] Mean baseline rTNSS for the 7 days prior to randomization (including Day 1 AM) for Trials MP-4002 and MP-4004 or, for Trial MP-4006, the 3 days prior to randomization (including Day 1 AM)
Source: Applicant's submission dated October 25, 2011, Section 1.11.3, pg. 2-9 (Table 2.7.4.1.3-1)

The demographic and baseline characteristics are generally well balanced across treatment arms. Only 19 (2%) and 25 (3%) of patients treated with MP29-02 and placebo, respectively, were 65 years of age or older. Product labels for other intranasal sprays for seasonal allergic rhinitis (e.g. Astelin®, Astepro®, Veramyst®) specify that clinical trials did not include sufficient number of patients aged 65 and over to determine whether they respond differently from younger patients, and the proposed labeling for MP29-02 includes similar language.

A substantial percentage of patients (over 15%) of both the MP29-02 and placebo groups were of black race.

Subject Disposition

The disposition of subjects participating in the three 2-week efficacy and safety trials (MP-4002, MP-4004, and MP-4006) is provided in Table 8.

Table 8. Subject Disposition: Trials MP-4002, MP-4004, and MP-4006

Disposition	MP29-02	Placebo	Azelastine hydrochloride	Fluticasone propionate
All Randomized Subjects (N)	853	862	851	846
Number of Subjects who Completed, n (%)	815 (95.5)	826 (95.8)	813 (95.5)	811 (95.9)
Number of Subjects who Discontinued, n(%)	38 (4.5)	36 (4.2)	38 (4.5)	35 (4.1)
Primary Reason for Discontinuation, n (%)				
Adverse Event	10 (1.2)	9 (1.0)	6 (0.7)	4 (0.5)
Abnormal Test Result	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Treatment Failure	1 (0.1)	5 (0.6)	1 (0.1)	2 (0.2)
Protocol Violation	8 (0.9)	8 (0.9)	14 (1.6)	6 (0.7)
Noncompliance	1 (0.1)	4 (0.5)	4 (0.5)	10 (1.2)
Subject Withdrew Consent	3 (0.4)	2 (0.2)	3 (0.4)	3 (0.4)
Lost to Follow- up	6 (0.7)	2 (0.2)	3 (0.4)	1 (0.1)
Administrative Problem	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Other	8 (0.9)	6 (0.7)	6 (0.7)	9 (1.1)
Safety Population[a], n (%)	853 (100.0)	861 (99.9)	851 (100.0)	846 (100.0)
ITT Population[b], n (%)	848 (99.4)	857 (99.4)	847 (99.5)	846 (100.0)
PP Population[c], n (%)	784 (91.9)	800 (92.8)	779 (91.5)	776 (91.7)

Source: Applicant's submission dated October 18, 2011, Section 1.11.3, pg. 10 (Table 2.7.4.1.1)
[a] Safety population includes all randomized subjects who look at least one dose of the study drug.
[b] Intent-to-Treat population includes all subjects who were randomized and had at least one postbaseline efficacy observation.
[c] Per-Protocol population includes all subjects who completed the 2-week treatment period per protocol without major protocol violations.
Note: all percentages are based on all randomized subjects shown in the same column.

A total of 3412 patients were randomized across the three 2-week efficacy and safety trials; of these 3265 (95.7%) completed the trials, and 147 (4.3%) discontinued. The overall discontinuation rate of 4.3% is reasonable. Rates of discontinuation were generally balanced across treatment groups.

6.1.4 Analysis of Primary Endpoint(s)

The Applicant's pre-specified statistical approach to the analysis of the primary efficacy endpoint for the 2-week efficacy and safety trials is described in Section 5.3.

The results for the Applicant's analysis of the primary endpoint, change from baseline in the reflective combined AM + PM Total Nasal Symptom Score (rTNSS) over the entire 14-day treatment period, for the three pivotal efficacy and safety trials (MP-4002, MP-4004 and MP-4006), are provided in Table 9. See Section 6.1.10 for a description of the results from Trial MP-4001.

Table 9. rTNSS (AM and PM Combined), Change from Baseline over the 14-Day Treatment Period, ITT Population, Analysis using Imputed Scores

Treatment Arm	N	Baseline	Change from baseline	Treatment Difference from MP29-02		
		LS Mean (SD)	LS Mean (SD)	LS Mean	95% CI	P-value
Trial MP-4002						
MP29-02	207	18.27 (3.038)	-5.61 (5.235)	--	--	--
Azelastine hydrochloride	208	18.26 (3.538)	-4.23 (4.629)	-1.38	-2.22,-0.54	0.001
Fluticasone propionate	207	18.22 (3.233)	-4.71 (4.678)	-0.9	-1.74,-0.07	0.034
Vehicle Placebo	209	18.61 (3.175)	-2.92 (3.923)	-2.69	-3.48, -1.91	<0.001
Trial MP-4004						
MP29-02	193	18.28 (3.341)	-5.54 (5.183)	---	--	--
Azelastine hydrochloride	193	18.54 (3.147)	-4.54 (4.621)	-1.00	-1.90,-0.09	0.032
Fluticasone propionate	188	18.64 (2.918)	-4.55 (5.146)	-0.99	-1.91,-0.05	0.038
Vehicle Placebo	199	18.24 (3.067)	-3.03 (3.932)	-2.51	-3.33,-1.67	<0.001
Trial MP-4006						
MP29-02	448	19.34 (2.431)	-5.53 (5.180)	--	--	--
Azelastine hydrochloride	443	19.47 (2.520)	-4.82 (4.762)	-0.71	-1.30,-0.13	0.016
Fluticasone propionate	450	19.41 (2.378)	-4.89 (4.655)	-0.64	-1.22,-0.07	0.029
Vehicle Placebo	448	19.44 (2.363)	-3.40 (4.342)	-2.13	-2.70,-1.57	<0.001

Source: Section 2.7.3, pg. 17 (Table 4); Section 2.7.3, pg. 21 (Table 6); Section 2.7.3, pg. 26 (Table 8)

The Applicant used a LOCF approach to address the issue of missing data for the primary endpoint. As discussed by Feng Zhou in the Agency's Statistical Review, LOCF is not appropriate for use with a repeated measures model such as that being used for the analysis of rTNSS. One of the Applicant's sensitivity analyses utilized a repeated measures model without imputation of missing data. This analysis, based on raw scores, was generally consistent with the primary analysis based on imputed scores. The one notable discrepancy is in the comparison of MP29-02 to the fluticasone propionate monotherapy comparator in Trial MP-4004, which was statistically significant (p=0.038, effect size of -0.99) using the imputed data but not significant (p=0.060; effect size of -0.88) using the raw data. A comparison of the effect sizes and p values obtained using the two methods is provided in Table 10, and a discussion of the results obtained from the analysis using raw scores follows.

Table 10. rTNSS, Results Based on Imputed Scores vs. Raw Scores

		Analysis Using Imputed Scores			Analysis Using Raw Scores		
		MP29-02 vs. Placebo	MP29-02 vs. Azelastine	MP29-02 vs. Fluticasone	MP29-02 vs. Placebo	MP29-02 vs. Azelastine	MP29-02 vs. Fluticasone
Trial 4002	Effect Size	-2.69	-1.38	-0.90	-2.70	-1.36	-0.97
	p-value	<0.001	0.001	0.034	<0.001	0.002	0.022
Trial 4004	Effect Size	-2.51	-1.00	-0.99	-2.42	-1.01	-0.88
	p-value	<0.001	0.032	0.038	<0.001	0.030	0.060
Trial 4006	Effect Size	-2.13	-0.71	-0.64	-2.16	-0.75	-0.64
	p-value	<0.001	0.016	0.029	<0.001	0.012	0.030

Source: Applicant's submission dated July 1, 2011, Table 1 (Section 1.11.4, pg. 5)

In each of the three 2-week trials the treatment difference between MP29-02 and placebo for the primary endpoint is statistically significant, with a point estimate ranging from -2.16 to -2.70. The treatment difference between the azelastine hydrochloride monotherapy comparator and MP29-02 is also statistically significant in all three trials, with a point estimate ranging from -0.75 to -1.36.

For two of the three trials (MP-4002, MP-4006), the treatment difference between the fluticasone propionate monotherapy comparator and MP29-02 is statistically significant. In Trial MP-4004, the treatment difference between the fluticasone propionate monotherapy comparator and MP29-02 is not statistically significant for the analysis that appropriately accounts for missing data (i.e. the analysis based on raw scores).

As noted in Section 5.3, Trial MP-4006 employed a large (double) sample size compared to the other trials. To the extent that statistical significance is in part driven by sample size, the results from Trial MP-4006 need to be interpreted with some caution. This is particularly relevant given that there is no established minimal clinically important difference for the TNSS. It is this Reviewer's assessment that the general consistency of the effect size (for the comparison of MP29-02 to placebo) observed in MP-4006 with the results from the other two trials is reassuring.

Overall, the results from Trials MP-4002, MP-4004, and MP-4006 provide replicate evidence of efficacy for the proposed combination product; the factorial design also provides replicate evidence of the contribution of each component. The effect sizes for the treatment difference between MP29-02 and placebo are of reasonable magnitude when compared to other development programs for allergic rhinitis.

See Section 9.2 for the table of rTNSS results based on the Agency's statistical analysis (using raw scores), which is recommended for inclusion in the product label.

6.1.5 Analysis of Secondary Endpoints(s)

A description of secondary endpoints, and of the Applicant's pre-specified statistical approach to their analysis, for the three 2-week efficacy and safety trials, (MP-4002, MP-4004, and MP-4006), is provided in Section 5.3.

iTNSS and rTOSS
As was the case for rTNSS, the Applicant used a LOCF approach to address the issue of missing data for the endpoints iTNSS and rTOSS. As both of these secondary endpoints were analyzed using a repeated measures model, LOCF is not an appropriate choice of method to handle missing data in these instances. Unlike for rTNSS, the original submission did not include sensitivity analyses for iTNSS and rTOSS based on raw scores; these additional analyses were requested by the Agency in the 74-Day Letter and provided by the Applicant on July 1, 2011.

Results for the Applicant's original analysis of iTNSS are provided in Table 11 (iTNSS, imputed data only).

Table 11. iTNSS (AM and PM Combined), Change from Baseline over the 14-Day Treatment Period, ITT Population, Analysis using Imputed Scores

Treatment Arm	N	Baseline	Change from baseline	Treatment Difference from MP29-02		
		LS Mean (SD)	LS Mean (SD)	LS Mean	95% CI	P-value
Trial MP-4002						
MP29-02	207	17.16 (3.698)	-5.21 (5.294)	--	--	--
Azelastine hydrochloride	208	16.84 (4.225)	-3.95 (4.666)	-1.26	-2.09,-0.43	0.003
Fluticasone propionate	207	16.84 (4.157)	-4.51 (4.695)	-0.7[#]	-1.55,0.14	0.100
Vehicle Placebo	209	17.26 (4.145)	-2.63 (4.084)	-2.58[@]	-3.39, -1.79	<0.001
Trial MP-4004						
MP29-02	193	17.16 (4.091)	-5.23 (5.303)	---	--	--
Azelastine hydrochloride	193	17.28 (4.078)	-4.23 (4.632)	-1.00	-1.90,-0.10	0.029
Fluticasone propionate	188	17.19 (3.775)	-4.29 (5.155)	-0.94	-1.87,0.00	0.049
Vehicle Placebo	199	16.84 (3.878)	-2.45 (4.151)	-2.78	-3.61,-1.94	< 0.001
Trial MP-4006						
MP29-02	448	17.91 (3.516)	-5.00 (5.298)	--	--	--
Azelastine hydrochloride	443	18.00 (3.731)	-4.34 (4.887)	-0.66[^]	-1.25, -0.08	0.026
Fluticasone propionate	450	17.82 (3.371)	-4.72 (4.878)	-0.28	-0.87,0.31	0.348
Vehicle	448	17.90 (3.517)	-3.08 (4.405)	-1.92	-2.49, -1.36	< 0.001

Reference ID: 3107643

Placebo						

Source: Section 5.3.5.1.3 MP4002, pg. 176 (Table 14.2.7.2); Section 5.3.5.1.3 MP4004, pg. 206 (Table 14.2.7.2); Section 5.3.5.1.3 MP4006, pg. 206 (Table 14.2.7.2); Section 5.3.5.3.27, pg. 95 (Table 48)
 # Calculated by reviewer. Applicant's value is -0.71, as found in Section 5.3.5.3.27, pg. 95 (Table 48).
@ Calculated by reviewer. Applicant's value is -2.59, as found in Section 5.3.5.3.27, pg. 95 (Table 48).
^ Calculated by reviewer. Applicant's value is -0.67, as found in Section 5.3.5.3.27, pg. 95 (Table 48).

The analysis based on raw scores was generally consistent with the original analysis based on imputed scores. The one notable discrepancy is in the comparison of MP29-02 to the fluticasone monotherapy comparator in Trial MP-4004, which was of marginal statistical significance (p=0.049, effect size of -0.94) using the imputed data but not significant (p=0.084; effect size of -0.80) using the raw data. A comparison of the effect sizes and p values obtained using the two methods (imputed data vs. raw scores) is provided in Table 12, and a discussion of the results obtained from the analysis using raw scores follows.

Table 12. iTNSS, Results Based on Imputed Scores vs. Raw Scores

		Analysis Using Imputed Scores			Analysis Using Raw Scores		
		MP29-02 vs. Placebo	MP29-02 vs. Azelastine	MP29-02 vs. Fluticasone	MP29-02 vs. Placebo	MP29-02 vs. Azelastine	MP29-02 vs. Fluticasone
Trial 4002	Effect Size	-2.59	-1.26	-0.71	-2.55	-1.30	-0.67
	p-value	<0.001	0.003	0.100	<0.001	0.002	0.116
Trial 4004	Effect Size	-2.78	-1.00	-0.94	-2.63	-1.06	-0.80
	p-value	<0.001	0.029	0.049	<0.001	0.020	0.084
Trial 4006	Effect Size	-1.92	-0.67	-0.28	-1.92	-0.70	-0.28
	p-value	<0.001	0.026	0.348	<0.001	0.019	0.345

Source: Applicant's submission dated July 1, 2011, Section 1.11.4, pg. 5 (Table 1)

In each of the three 2-week trials the treatment difference between MP29-02 and placebo for the secondary endpoint iTNSS is statistically significant.

With regards to the treatment differences between MP29-02 and the monotherapies, the results are statistically significant across all three trials for the comparison to the azelastine hydrochloride monocomparator. The opposite is the case for the comparison to the fluticasone propionate monocomparator, with none of the trials demonstrating a statistically significant treatment difference.

The iTNSS is primarily used for the assessment of the appropriateness of dosing interval for the proposed product. Given the replicate evidence for the treatment difference between MP29-02 and placebo in iTNSS, one can conclude that the twice-daily dosing interval for the combination product is appropriate. Moreover, the results for the treatment differences between each monotherapy and placebo were statistically significant (p-values were provided by the Applicant for Trials MP-4004 and MP-4006, data not shown). This is noteworthy, since it supports the appropriateness of the twice-

daily dosing interval for each monocomponent, which increases confidence in the validity of the combination.

See Section 9.2 for the table of iTNSS results based on the Agency's statistical analysis (using raw scores), which is recommended for inclusion in the product label.

Results for the Applicant's original analysis of rTOSS are provided in Table 13 (rTOSS, imputed data only).

Table 13. rTOSS (AM and PM Combined), Change from Baseline over the 14-Day Treatment Period, ITT Population, Analysis using Imputated Scores

Treatment Arm	N	Baseline	Change from baseline	Treatment Difference from MP29-02		
		LS Mean (SD)	LS Mean (SD)	LS Mean	95% CI	P-value
Trial MP-4002						
MP29-02	207	11.88 (3.902)	-3.07 (3.990)	--	--	--
Azelastine hydrochloride	208	11.49 (4.539)	-2.82 (3.822)	-0.25	-0.90,0.41	0.457
Fluticasone propionate	207	11.41 (4.418)	-2.55 (3.451)	-0.52	-1.14,0.10	0.097
Vehicle Placebo	209	12.07 (4.284)	-1.90 (3.261)	-1.17	-1.77,-0.57	<0.001
Trial MP-4004						
MP29-02	193	11.70 (4.162)	-3.56 (3.863)	---	--	--
Azelastine hydrochloride	192	11.78 (3.892)	-2.96 (3.312)	-0.6	-1.25,0.05	0.069
Fluticasone propionate	188	12.01 (3.800)	-2.68 (3.570)	-0.88	-1.54,-0.23	0.009
Vehicle Placebo	199	11.56 (4.138)	-2.02 (3.060)	-1.54	-2.16,-0.92	<0.001
Trial MP-4006						
MP29-02	448	12.29 (4.013)	-3.02 (3.972)	--	--	--
Azelastine hydrochloride	443	12.40 (3.990)	-2.99 (3.812)	-0.03	-0.47,0.42	0.912
Fluticasone propionate	450	12.29 (3.623)	-2.76 (3.518)	-0.26[#]	-0.69,0.18	0.247
Vehicle Placebo	448	12.22 (3.717)	-1.95 (3.494)	-1.07	-1.50,-0.64	<0.001

Source: Section 2.7.3, pg. 18 (Table 5); Section 2.7.3, pg. 23 (Table 7); Section 2.7.3, pg. 27 (Table 9);
[#] Calculated by reviewer. Applicant's value is 0.25, as found in Section 2.7.3, pg. 27 (Table 9).

The analysis based on raw scores was generally consistent with the original analysis based on imputed scores. The one notable discrepancy is in the comparison of MP29-02 to the azelastine monotherapy comparator in Trial MP-4004, which was not statistically significant (p=0.069, effect size of -0.60) using the imputed data but became marginally statistically significant (p=0.049; effect size of -0.65) using the raw data. A comparison of the effect sizes and p values obtained using the two methods (imputed

data vs. raw scores) is provided in Table 14, and a discussion of the results obtained from the analysis using raw scores follows.

Table 14. rTOSS, Results based on Imputed Scores vs. Raw Scores

		Analysis Using Imputed Scores			Analysis Using Raw Scores		
		MP29-02 vs. Placebo	MP29-02 vs. Azelastine	MP29-02 vs. Fluticasone	MP29-02 vs. Placebo	MP29-02 vs. Azelastine	MP29-02 vs. Fluticasone
Trial 4002	Effect Size	-1.17	-0.25	-0.52	-1.16	-0.22	-0.57
	p-value	<0.001	0.457	0.097	<0.001	0.516	0.070
Trial 4004	Effect Size	-1.54	-0.60	-0.88	-1.56	-0.65	-0.92
	p-value	<0.001	0.069	0.009	<0.001	0.049	0.006
Trial 4006	Effect Size	-1.07	-0.03	-0.25	-1.06	-0.04	-0.28
	p-value	<0.001	0.912	0.247	<0.001	0.845	0.208

Source: Applicant's submission dated July 1, 2011, Table 1 (Section 1.11.4, pg. 5)

In each of the three 2-week trials the treatment difference between MP29-02 and placebo for the secondary endpoint rTOSS is statistically significant.

With regards to the treatment differences between MP29-02 and the monotherapies, a single trial (MP-4004) provides a statistically significant result for the comparison to fluticasone, and none of the trials provide convincing evidence of a statistically significant treatment difference for the comparison to azelastine (the p-value for trial MP-4004 is marginal at 0.049, and is accompanied by an unimpressive effect size).

(b) (4)

RQLQ

The Applicant's analysis of the RQLQ data is provided in Table 15. This analysis was conducted using only observed data, as was noted by the Division in the 74-Day Letter, which stated that "In the evaluation of the RQLQ endpoint, it appears that you only included the observed data in the analysis. This approach is not acceptable. The analysis should be conducted on all randomized patients (ITT population). An appropriate strategy to handle missing data should be in place. We will conduct

additional analyses during our review of the application." In the Applicant's response to the 74-Day Letter dated July 1, 2011, it was noted that the missing RQLQ data was handled according to the algorithm provided by [redacted] (b) (4). The Applicant's response also stated that 9-19% of ITT subjects across treatment groups were not included in the RQLQ analysis; of these, 57-84% were under the age of 18 and therefore not eligible for the RQLQ assessment. Additional analyses of the RQLQ data were conducted by the Agency's statistical reviewer, Feng Zhou, including an analysis for in all randomized patients 18 years and older. She concludes that "The results from the applicant's and my analyses are similar and do not change the overall conclusion" (Feng Zhou, M.S., Statistical Review and Evaluation, December 28, 2011).

Table 15. Change from Baseline to Day 14 in RQLQ Overall Score, ITT Population, Age 18 or older

Treatment Arm	N	Baseline	Change from baseline	Treatment Difference from MP29-02		
		LS Mean (SD)	LS Mean (SD)	LS Mean	95% CI	P-value
Trial MP-4002						
MP29-02	176	3.88 (0.900)	-1.64 (1.392)	--	--	--
Azelastine hydrochloride	174	3.78 (0.962)	-1.36 (1.127)	-0.28[@]	-0.54,-0.03	0.029
Fluticasone propionate	184	3.76 (0.922)	-1.63 (1.209)	-0.01	-0.26,0.23	0.907
Vehicle Placebo	169	3.87 (0.981)	-0.85 (1.071)	-0.79[#]	-1.05,-0.55	<0.001
Trial MP-4004						
MP29-02	176	3.76 (0.989)	-1.68 (1.255)	---	--	--
Azelastine hydrochloride	172	3.85 (0.933)	-1.40 (1.269)	-0.28	-0.53,-0.03	0.031
Fluticasone propionate	169	3.78 (0.979)	-1.48 (1.338)	-0.2	-0.46,0.05	0.123
Vehicle Placebo	171	3.88 (0.965)	-0.97 (1.285)	-0.71	-0.97,-0.45	<0.001
Trial MP-4006						
MP29-02	381	3.87 (0.958)	-1.59 (1.301)	--	--	--
Azelastine hydrochloride	394	3.92 (1.015)	-1.42 (1.299)	-0.17	-0.33,-0.01	0.043
Fluticasone propionate	384	3.88 (0.942)	-1.55 (1.226)	-0.04	-0.20,0.12	0.629
Vehicle Placebo	393	3.88 (0.965)	-1.03 (1.231)	-0.56[%]	-0.72,-0.39	<0.001

Source: Section 5.3.5.1.3 MP4002, pg. 293 (Table 14.2.15); Section 5.3.5.1.3 MP4004, pg. 375 (Table 14.2.15); Section 5.3.5.1.3 MP4006, pg. 375 (Table 14.2.15); Section 5.3.5.3.27, pg. 98 (Table 51)
[#] Calculated by reviewer. Applicant's value is -0.80, as found in Section 5.3.5.3.27, pg. 98 (Table 51).
[@] Calculated by reviewer. Applicant's value is -0.29, as found in Section 5.3.5.3.27, pg. 98 (Table 51).
[%] Calculated by reviewer. Applicant's value is -0.55, as found in Section 5.3.5.3.27, pg. 98 (Table 51).

In each of the three 2-week trials the treatment difference between MP29-02 and placebo for the secondary endpoint RQLQ is statistically significant, and greater than

the minimum clinically significant difference of -0.50. The results for the treatment difference between MP29-02 and the azelastine hydrochloride monocomparator are statistically significant across all three trials, while the opposite is true for the comparison to the fluticasone propionate monocomparator. It is not necessary for the Applicant to demonstrate statistical significance for the comparisons between MP29-02 and the monotherapies for this secondary endpoint; the data is of sufficient strength that one can conclude that the results for secondary endpoint are supportive of the primary endpoint, and it is recommended that a descriptive summary of the RQLQ data be included in the product label.

6.1.6 Other Endpoints

Onset of Action was evaluated as a secondary endpoint in the three 2-week efficacy and safety trials (MP-4002, MP-4004, and MP-4006). This evaluation involved the assessment of iTNSS over the 4-hour period following the initial administration of trial drug; onset of action was defined as the first time point at which patients receiving MP29-02 showed an improvement in iTNSS that was significantly better than that for patients receiving placebo. Results for this analysis are provided in Table 16

Table 16. Change from Baseline in 4-Hour iTNSS, ITT Population: Trials MP-4002, MP-4004, MP-4006

	Trial MP-4002		Trial MP-4004		Trial MP-4006	
Timepoint	**MP29-02**	**Placebo**	**MP29-02**	**Placebo**	**MP29-02**	**Placebo**
Baseline (BL), n	207	209	192	200	445	447
LS Mean (SD)	9.32 (1.348)	9.46 (1.308)	9.51 (1.361)	9.63 (1.412)	9.65 (1.366)	9.54 (1.353)
15 minutes						
Change* in LS Mean (SD)	-1.12 (1.954)	-1.08 (1.719)	-1.20 (1.899)	-1.20 (1.862)	-1.41 (2.133)	-1.26 (1.883)
p-value	0.814	--	0.993	--	0.240	--
30 minutes						
Change* in LS Mean (SD)	-2.01 (2.214)	-1.68 (1.941)	-2.27 (2.270)	-1.80 (2.039)	-2.20 (2.370)	-1.83 (2.077)
p-value	0.108	--	0.032	--	0.008	--
45 minutes						
Change* in LS Mean (SD)	-2.78 (2.417)	-2.27 (2.093)	-2.98 (2.603)	-2.34 (2.234)	-2.87 (2.475)	-2.37 (2.214)
p-value	0.021	--	0.008	--	< 0.001	--
60 minutes						
Change* in LS Mean (SD)	-3.29 (2.608)	-2.75 (2.205)	-3.62 (2.753)	-2.98 (2.463)	-3.40 (2.679)	-2.86 (2.395)
p-value	0.021	--	0.016	--	<0.001	--
90 minutes						
Change* in LS Mean (SD)	-3.80 (2.761)	-3.10 (2.35)	-4.00 (2.815)	-3.28 (2.612)	-3.80 (2.833)	-3.19 (2.447)
p-value	0.005	--	0.009	--	<0.001	--
120 minutes						

Change* in LS Mean (SD)	-4.12 (2.787)	-3.43 (2.470)	-4.39 (2.672)	-3.62 (2.697)	-4.15 (2.791)	-3.48 (2.541)
p-value	0.007	--	0.005	--	< 0.001	--
240 minutes						
Change* in LS Mean (SD)	-5.01 (3.032)	-3.94 (2.684)	-5.21 (3.060)	-4.23 (3.055)	-5.01 (3.014)	-4.09 (2.901)
p-value	< 0.001	--	0.001	--	< 0.001	--

Section 5.3.5.3.27, pg. 51 (Table 19), pg. 63 (Table 27), pg. 75 (Table 35)
***Change denotes change from baseline**
Note: p-value is for the comparison between MP29-02 and placebo.

The first time point at which patients receiving MP29-02 showed an improvement in iTNSS that was significantly better than that for patients receiving placebo is 45 minutes for Trial MP-4002, and 30 minutes for Trials MP-4004 and MP-4006 (results highlighted in red). The clinical program, therefore, has replicate evidence for onset of action at 30 minutes. Once achieved, the statistically significant improvement for MP29-02 as compared to placebo is maintained until the end of the 4-hour assessment period in all three trials.

6.1.7 Subpopulations

The Applicant conducted subgroup analyses (age, gender, race, and ethnicity), pooling across the four 2-week efficacy and safety trials (including Trial MP-4001), for the primary endpoint rTNSS, and a single secondary endpoint, rTOSS. This review focuses on the subgroup analyses for the primary endpoint only, (b) (4) . Race and ethnicity were analyzed as binary categories (White vs. Other Races; Hispanic/Latino vs. Non-Hispanic/Latino), given the predominance of White and Non-Hispanics/Latinos representation in the clinical program. Subgroup analyses for age, gender, race, and ethnicity are provided in Table 17, Table 18, Table 19, and Table 20, respectively. In general, the treatment differences are consistent across the subgroups analyzed.

Table 17. rTNSS (AM and PM Combined), Change from Baseline over the 14-Day Treatment Period, Pooled ITT Population by Age: Trials MP-4001, MP-4002, MP-4004, and MP-4006

	Treatment Difference, LS Mean (95% CI)		
Comparison	**12 to < 18 years n=393**	**18 to < 65 years n=3491**	**≥ 65 years n=115**
MP29-02 vs. Placebo	-2.22 (-3.23,-1.22)	-2.40 (-2.81,-1.99)	-3.42 (-6.12, -0.71)
MP29-02 vs. Azelastine Hydrochloride	-1.79 (-2.88,-0.69)	-1.02 (-1.45,-0.60)	-2.54 (-5.19,0.12)
MP29-02 vs. Fluticasone Propionate	-0.98 (-2.08,0.13)	-0.86 (-1.28,-0.44)	-3.42 (-6.55,-0.29)

Section 5.3.5.3.27, pg. 102 (Table 52)

Table 18. rTNSS (AM and PM Combined), Change from Baseline over the 14-Day Treatment Period, Pooled ITT Population by Gender: Trials MP-4001, MP-4002, MP-4004, and MP-4006

	Treatment Difference, LS Mean (95% CI)	
Comparison	**Males n=1485**	**Female n=2514**
MP29-02 vs. Placebo	-2.53 (-3.14,-1.91)	-2.38 (-2.86,-1.90)
MP29-02 vs. Azelastine Hydrochloride	-1.65 (-2.29,-1.02)	-0.82 (-1.33,-0.31)
MP29-02 vs. Fluticasone Propionate	-0.62 (-1.29,0.04)	-1.06 (-1.55,-0.57)

Section 5.3.5.3.27, pg. 104 (Table 54)

Table 19. rTNSS (AM and PM Combined), Change from Baseline over the 14-Day Treatment Period, Pooled ITT Population by Race: Trials MP-4001, MP-4002, MP-4004, and MP-4006

	Treatment Difference, LS Mean (95% CI)	
Comparison	**White n=3214**	**Other Races n=785**
MP29-02 vs. Placebo	-2.61 (-3.03,-2.20)	-1.37 (-2.18,-0.57)
MP29-02 vs. Azelastine Hydrochloride	-1.21 (-1.65,-0.77)	-0.38 (-1.20,0.44)
MP29-02 vs. Fluticasone Propionate	-1.07 (-1.51,-0.63)	+0.13 (-0.74,1.00)

Section 5.3.5.3.27, pg. 106 (Table 56)

Table 20. rTNSS (AM and PM Combined), Change from Baseline over the 14-Day Treatment Period, Pooled ITT Population by Ethnicity: Trials MP-4001, MP-4002, MP-4004, and MP-4006

	Treatment Difference, LS Mean (95% CI)	
Comparison	**Hispanic/Latino n=715**	**Not Hispanic/Latino n=3284**
MP29-02 vs. Placebo	-2.11 (-2.96,-1.25)	-2.51 (-2.93,-2.09)
MP29-02 vs. Azelastine Hydrochloride	-0.48 (-1.38,0.43)	-1.18 (-1.61,-0.75)
MP29-02 vs. Fluticasone Propionate	-0.82 (-1.75,0.10)	-0.99 (-1.42,-0.55)

Section 5.3.5.3.27, pg. 108 (Table 58)

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

The Applicant refers to its long-term safety trial (MP-4000) to support the long-term effectiveness (and lack of tolerance) of the proposed product, citing the results for change from baseline in mean PM rTNSS, which were decreased throughout the trial (e.g. mean change of -1.80 [SD=2.678] on Day 7, and -2.99 [SD=2.588] at Week 52). The Applicant also refers to Trial MP-4000 results for the change in RQLQ (overall score) from baseline to Month 12: -1.5 (±1.20), which exceeds the minimum clinically significant difference of -0.5, to support the persistence of efficacy/lack of tolerance.

The ability to generalize results regarding efficacy from Trial MP-4000, which enrolled a different patient population (perennial allergic rhinitis and vasomotor rhinitis/non-allergic rhinitis) than that intended for MP29-02 (seasonal allergic rhinitis), is limited. Nevertheless, the available data do suggest a persistence of effect.

6.1.10 Additional Efficacy Issues/Analyses

While MP-4001 is considered as secondary support for efficacy due to its inclusion of the commercial products rather than the investigational monotherapies, which prevents the trial from providing evidence of the contribution of each component to the combination product, a brief examination of the efficacy results from this trial is nonetheless warranted. The comparison of MP29-02 to the commercial products provided by Trial MP-4001 may be informative to the clinician choosing between combination therapy versus monotherapy with the currently available products. A summary of the Applicant's analysis (using imputed data) of the primary endpoint for Trial MP-4001 is provided in Table 21.

Table 21. rTNSS (AM and PM Combined), Change from Baseline over the 14-Day Treatment Period, ITT Population, Analysis using Imputed Scores, Trial MP-4001

Treatment Arm	N	Baseline	Change from baseline	Treatment Difference from MP29-02		
		LS Mean (SD)	LS Mean (SD)	LS Mean	95% CI	P-value
Trial MP-4001						
MP29-02	153	18.64 (3.110)	-5.31 (5.084)	--	--	--
Astelin	152	17.87 (3.656)	-3.25 (4.155)	-2.06	-2.98,-1.14	<0.001
Commercially Available generic fluticasone propionate	151	18.12 (3.470)	-3.84 (4.762)	-1.47	-2.44,-0.50	0.003
Vehicle Placebo	150	18.49 (3.451)	-2.20 (4.163)	-3.11	-4.03,-2.19	<0.001

Source: Section 2.7.3, pg. 13 (Table 2)

Similar to the other 2-week efficacy and safety trials, the results of Trial MP-4001 demonstrates a statistically significant treatment difference between MP29-02 and placebo for the primary endpoint. The treatment differences between MP19-02 and the commercial monotherapies are also statistically significant.

The point estimate for the treatment difference between MP29-02 and placebo is -3.11, which is larger that the point estimates for the Applicant's analysis (using imputed data) of the primary endpoint for Trials MP-4002, MP-4004, and MP-4006 (-2.13 to -2.69). The point estimates for the treatment difference between MP29-02 and each of the commercial monotherapies (-2.06 for the comparison to Astelin; -1.47 for the comparison to commercially available generic fluticasone propionate) are also larger that those for the other 2-week trials (-0.71 to -1.38 for the comparison to the investigational azelastine monotherapy; -0.64 to -0.99 for the comparison to the investigational fluticasone monotherapy). These results must be interpreted with some

caution, however, given that Trial MP-4001 enrolled a patient population with sensitivity to the Texas Mountain Cedar pollen, which is typically associated with higher estimates of efficacy as compared to populations with symptoms triggered by other seasonal allergens.

Overall, the results from Trial MP-4001 are consistent with those from the other 2-week efficacy and safety trials, and provide secondary support for the efficacy of MP29-02 in the treatment of the symptoms of seasonal allergic rhinitis.

7 Review of Safety

Safety Summary

The safety information for MP29-02 comes primarily from the three 2-week efficacy and safety trials (MP-4002, MP-4004, and MP-4006), as well as from the year-long safety trial (MP-4000). Pooling across trials MP-4002, MP-4004, and MP-4006 to examine the emergence of any safety signals was deemed acceptable as these trials were very similar in design. The fourth 2-week efficacy and safety trial, Trial MP-4001, is distinguished by its use of the commercial monotherapy comparators and was considered separately. In general, the results of Trial MP-4001 were similar to the results of the other pooled studies.

Safety assessments in the three 2-week trials and the long-term safety trial include vital signs, physical examinations (both general and focused nasal examinations), and adverse event monitoring. Additionally, the long-term safety trial included ophthalmic examinations, clinical laboratory testing, and 12-lead electrocardiograms. A substudy examining HPA-Axis effects was also conducted as part of the long-term safety trial.

The safety population pooled from the three 2-week efficacy and safety trials (MP-4002, MP-4004, and MP-4006) is comprised of 853 patients treated with MP29-02, 861 patients treated with placebo, 851 patients treated with the azelastine hydrochloride monotherapy comparator, and 845 patients treated with the fluticasone propionate monotherapy comparator. The mean treatment duration, mean total number of doses taken, and rate of compliance was comparable across treatment groups. The safety population from the long-term safety trial (MP-4000) was comprised of 404 patients treated with MP29-02, and 207 patients treated with commercially available generic fluticasone propionate. The mean treatment duration and rate of compliance was comparable across treatment groups in Trial MP-4000.

There were no deaths across the seven clinical trials comprising the development program for MP29-02. A total of 8 serious adverse events (SAEs) were reported across

Reference ID: 3107643

the clinical program, with 5 of the SAEs reported for patients treated with MP29-02. All SAEs were assessed by the Applicant as unlikely to be related to treatment.

Overall, the frequency of adverse events leading to discontinuation of treatment in the three 2-week trials was low and balanced between the MP29-02 and placebo treatment arms (1.2% and 1.0%, respectively), albeit somewhat higher than the monotherapy comparators (0.7% and 0.5% for azelastine hydrochloride and fluticasone propionate, respectively). Most events were reported only once or twice, without any apparent pattern of association with the treatment arms. Similarly, the overall frequency of adverse events leading to discontinuation of treatment in the long-term safety trial was balanced between the two treatment arms (2.7% and 2.9% for MP29-02 and commercially available generic fluticasone propionate, respectively), and most events were reported only once.

The clinical program evaluated a number of submission specific safety concerns including local nasal effects, ophthalmic effects, somnolence, and HPA-axis effects. There was only one instance of nasal ulceration (grade 3 nasal irritation) across the clinical development program, which was reported for a patient receiving placebo in one of the 2-week efficacy and safety trials. There were no instances of nasal septal perforation (grade 4 nasal irritation) reported for any of the clinical trials. The frequency of epistaxis on nasal examination was balanced across treatment groups in the 2-week efficacy and safety trials, with an overall rate ranging from approximately 1 to 2%. The rate of epistaxis on nasal examination was also comparable between treatment arms in the long-term safety trial: 0.9% and 1.2% of patients in the MP29-02 and active comparator treatment groups, respectively, at the 12 month/ET visit. The frequency of epistaxis TEAEs reported for patients in the three 2-week efficacy and safety trials was in the 1.6-1.9% range, and comparable across treatment groups; the frequency of epistaxis TEAEs reported for patients treated with MP29-02 in the long-term safety trial was similar at 2.0%.

Ophthalmic examinations in the long-term safety trial did not reveal any signals for either glaucoma or posterior subcapsular cataract formation. Across the clinical program, the rate of somnolence was low (0.7% for patients treated with MP29-02 in the three 2-week efficacy and safety trials and 0.2% for patients treated with MP29-02 in the year-long safety trial. Results from the HPA-Axis substudy, conducted as part of Trial MP-4000, indicate that the effect of MP29-02 is comparable to that of fluticasone, and that the impact on serum cortisol is not substantial.

Overall, the frequency of any adverse event in the three 2-week efficacy and safety trials was somewhat higher for the MP29-02 treatment group (15.9%) compared to the other treatment groups (11.5%, 14.6%, and 13.1% for placebo, azelastine, and fluticasone, respectively). The imbalance seems to be due in large part to an imbalance in the frequency of dysgeusia (3.5% for MP29-02 vs. 0.2% for placebo and 0.5% for the fluticasone monotherapy comparator; at 5.2%, the azelastine hydrochloride

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monotherapy comparator also had a high frequency of dysgeusia). The most common adverse events associated with MP29-02 were dysgeusia, headache, and epistaxis in the three 2-week trials. This adverse event profile is consistent with the adverse event profiles described in the current product labels for the related monoproducts.

Overall, the frequency of any adverse event in the year-long safety trial was balanced between treatment groups (46.5% and 44.4% for the MP29-02 and active comparator treatment groups, respectively). The most common adverse events associated with MP29-02 were headache, pyrexia, and cough in the year-long safety trial.

In summary, the clinical development program was adequate to assess the safety of MP29-02, and the overall safety profile of the proposed product is acceptable.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant's Integrated Summary of Safety (ISS) presents safety information from all seven trials comprising the clinical development program, as summarized in Table 3.

As described in Sections 5.2 and 5.3, the monotherapy comparators used in trial MP-4001 differed from those employed in the other three efficacy and safety trials. The focus of this safety review, therefore, is on the three 2-week efficacy and safety trials which employed the investigational monotherapy comparators (Trials MP-4002, MP-4004, and MP-4006), as well as the year-long safety trial (Trial MP-4000); Trial MP-4001 is considered as secondary support for safety. Safety information from the two pharmacokinetic trials (X-03065-3282 and X-03065-3283) is also included where available and relevant.

A summary of the safety evaluations conducted for the four 2-week efficacy and safety trials is provided below. This is followed by a description of the long-term safety trial (MP-4000).

Safety Evaluations, Trials MP-4001, MP-4002, MP4004, MP-4006
Safety evaluations performed in the 2-week efficacy and safety trials included vital signs, focused nasal examination, monitoring of concomitant medications, and assessment for adverse events, which were conducted according to the schedule provided in Table 6.

Focused Nasal Examination
The Focused Nasal Examination included an evaluation for nasal irritation, epistaxis, and additional nasal symptoms, graded according to the criteria provided in Table 22.

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Table 22. Focused Nasal Examination, Components and Grading

Finding	Grading Criteria
Nasal Irritation	0 = None
	Grade 1A = focal irritation[18]
	Grade 1B = superficial mucosal erosion
	Grade 2 = moderate mucosal erosion
	Grade 3 = ulceration
	Grade 4 = septal perforation
Epistaxis	None
	Mild = self-limited
	Moderate = significant, prevents daily activity
	Severe = ER visit or hospitalization
Mucosal Edema, Nasal Discharge, Mucosal Erythema, Mucosal Bleeding*, and Crusting of Mucosa	None
	Mild
	Moderate
	Severe

Source: Section 5.3.5.1.4 MP4001, pg. 121-122; Section 5.3.5.1.4 MP4002, pg. 121; Section 5.3.5.1.4 MP4004, pg. 15; Section 5.3.5.1.4 MP4006, pg. 125
*** The Application does not specify how mucosal bleeding is distinguished from epistaxis.**

Discontinuation of Therapy

The protocols specified that a trial medication may be discontinued for adverse events or abnormal test results, as well as for unsatisfactory therapeutic effect, protocol violation, loss to follow-up, administrative issues, and patient withdrawal of consent.[19]

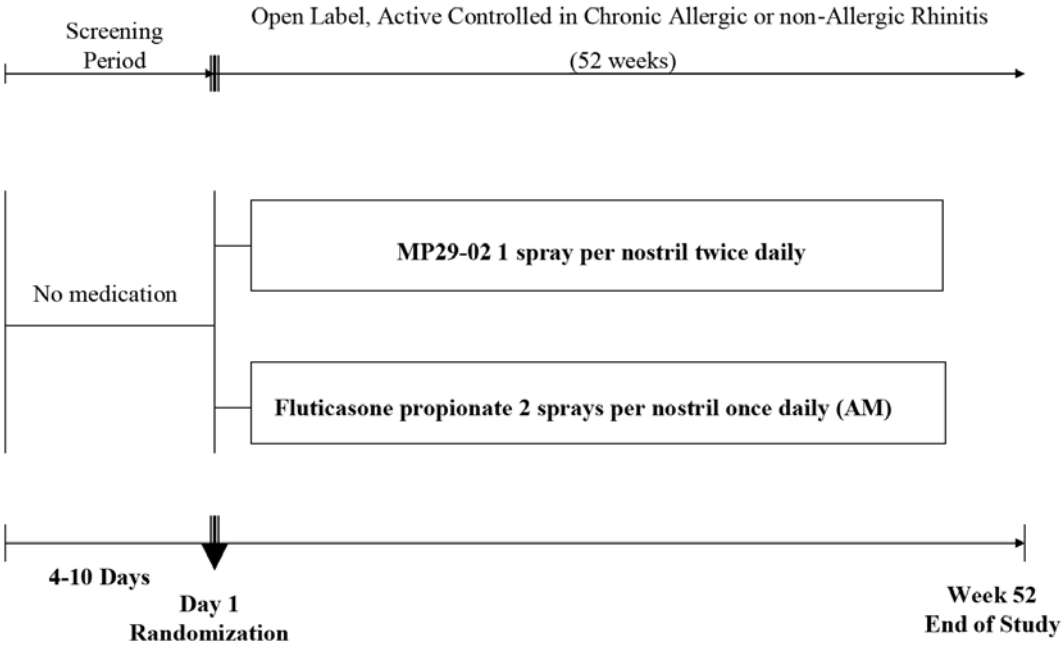
Year-Long Safety Trial: MP-4000

Trial MP-4000 was a year-long trial which had as its objective the evaluation of safety and tolerability with daily, chronic use of MP29-02 over a 1-year period in patients with chronic allergic or vasomotor rhinitis. Of note, the application does not include a rationale for assuming the applicability of foreign data to the US population. The relevance of the year-long safety trial, which was conducted entirely in India, is discussed further in Section 7.2.1.

[18] For protocols MP-4004 and MP-4006 this was described as "focal nasal mucosal inflammation, erythema or hyperemia."
[19] The protocols for MP-4004 and MP-4006 also specify that a patient may be discontinued due to non-compliance.

General Trial Design
MP-4000 was a randomized, open-label, active-controlled, parallel-group trial with a 52-week treatment period. A schematic of the general design of the trial is presented in Figure 2.

Figure 2. General Trial Design: Trial MP-4000



Source: 5.3.5.2.4, pg. 95 (MP4000 Study Flow Diagram)

Treatment arms
Trial MP-4000 evaluated two treatments: MP29-02, administered as 1 spray per nostril twice daily (total daily dose of 548 mcg azelastine hydrochloride and 200 mcg fluticasone propionate), and an active comparator, commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.), administered as 2 sprays per nostril once daily (total daily dose of 200 mcg). It is notable that the active comparator used, commercially available generic fluticasone propionate, is different from the fluticasone monotherapy comparator (formulated in the MP29-02 vehicle) evaluated in trials MP-4002, MP-4004, and MP-4006. This should be taken into account when comparing the safety results for the two treatments.

Safety Assessments
Trial MP-4000 including the following safety assessments, conducted according to the schedule provided in Table 24:

- Vital signs
- Physical Examination

- Focused Nasal Examination
  - The grading system used for the focused nasal examination is provided in Table 22
  - Typical fluctuations expected in the course of rhinitis were not considered adverse events
  - Patients with a new nasal mucosal ulceration (Grade 3) or nasal septal perforation (Grade 4) were referred to an otorhinolaryngologist for additional evaluation
- Eye Examination
- Laboratory Tests (hematology, chemistry, urinalysis)
- Urine pregnancy Test
- ECG
- Adverse Events

In addition, an evaluation of the Hypothalamic-Pituitary-Adrenal (HPA) axis was conducted in a subset of patients at a number of selected sites.

Assessment of Adherence
Adherence to treatment was evaluated using[20]:
- Diary data
- TNSS[21] (PM)
- RQLQ
  - Validated translations were provided in English and Hindi; patients unable to read either language were exempt from this assessment.

Population
Trial MP-4000 evaluated adults and adolescents with perennial allergic rhinitis or vasomotor rhinitis (VMR). Patients with a seasonal allergic component to their symptoms could be included, so long as they also had a history of perennial symptoms.

<u>Summary of Inclusion Criteria:</u>
- Males and females, 12 to 80 years of age
- Established history (≥ 1 year) of rhinitis due to perennial allergies or nonallergic rhinitis (VMR)[22]. Patients with a seasonal allergic component could also be included, provided that they have had significant symptoms outside of the allergy seasons.

[20] Medication bottles were weighed at each visit, but the protocol states that this was a secondary measure of compliance, and that the information was not entered into a database. Discrepancies between diary data and bottle weight were to be resolved prior to a patient leaving clinic.
[21] A description of the TNSS is provided in the preceding section summarizing the two-week efficacy and safety trials.
[22] The diagnosis of rhinitis was based on medical history, physical examination, rhinitis symptoms, skin testing or validated *in-vitro* tests for specific IgE such as RAST or PRIST, and could include nasal smears.

- Provides informed consent and, if applicable, pediatric assent
- Willing and able to comply with trial requirements, including daily use of medication for a one year period, even if symptoms are not bothersome
- General good health and free of any disease or concomitant treatment that could interfere with the interpretation of trial results as determined by the investigator or Applicant's medical officer.
- Patients have recorded in their diary the presence of nasal symptoms of rhinitis on at least 2 days during the screening period
- If receiving subcutaneous immunotherapy, on a stable regimen for at least 30 days prior to the first trial visit
- A 6-month washout period was required following the last dose of sublingual immunotherapy

Summary of Exclusion Criteria:

- On focused nasal examination, the presence of any nasal ulceration (Grade 3) or nasal septal perforation (Grade 4) at either the screening visit or randomization visit
- For patients participating in the HPA axis sub-study: Patients with a fasting morning plasma cortisol level less than or equal to 5 mcg per deciliter (or 150 nmol per liter)
- The use of any investigational drug within 30 days prior to screening
- Any nasal surgery or sinus surgery within 1 year prior to screening
- Presence of any hypersensitivity to azelastine or fluticasone propionate
- Women who were pregnant or nursing, or women of childbearing potential who were not abstinent or not practicing a medically acceptable method of contraception
- Chronic sinusitis – more than 3 episodes per year
- Acute sinusitis within the last 30 days
- Nasal disease(s) such as rhinitis medicamentosa, clinically significant nasal polyposis or nasal structural abnormalities
- Asthma (with the exception of intermittent asthma)
- Significant pulmonary disease including COPD
- Glaucoma
- Posterior subcapsular cataracts or any other lens opacity that might prevent the exclusion of the presence of a posterior subcapsular cataract

- Clinically significant arrhythmia or prolonged QTc (≥ 450 msec for males and ≥ 460 msec for females) on ECG or by history
- Known history of alcohol or drug abuse within 2 years
- Existence of any surgical or medical condition, which in the opinion of the investigator or sponsor, might significant alter the evaluation of the study
- Clinically relevant abnormal history and/or physical findings which, in the opinion of the investigator or sponsor, would interfere with the objectives of the study or that may preclude compliance with study procedures
- Employee (or employee's family member) of the study site, or individuals who would have access to the clinical study protocol
- Use of prohibited medications or therapies within the given time period prior to Screening, as described in Table 23.

Table 23. Prohibited medications and washout periods, Trial MP-4000

Medication	Time Period Prior to Screening
Systemic corticosteroids or omalizumab	30 days
Inhaled corticosteroids or combination inhaled corticosteroids/long-acting beta agonists	30 days
Sublingual immunotherapy	6 months

Source: Section 5.3.5.2.4, pg. 107

In addition, the following mediations were prohibited throughout the entire trial:

- Antihistamines, including ophthalmic preparations, sleep and diet aids, and cold preparations
- Oral and intranasal anticholinergic agents
- Topical decongestants
- Intranasal corticosteroids
- Leukotriene inhibitors
- Nasal saline or any intranasal medications
- Any anticoagulant at therapeutic doses
- Any other investigational or study drug

Oral decongestants for upper respiratory infection or breakthrough rhinitis symptoms were allowed for up to 5 consecutive days no more than twice a month.

Visits and Schedule of Assessments

The trial included a 4-10 day screening period, after which qualified patients were randomized 2:1 to either MP29-02 or commercially available generic fluticasone propionate for a 52-week open-label treatment period. Clinic visits took place at months 1, 3, 6, 9, and 12; phone contact was made at months 2, 4, 5, 7, 8, 10 and 11. A schedule of trial procedures is provided in Table 24.

Table 24. Schedule of Trial Procedures, Trial MP-4000

Procedure	S D-7	R D1	M1 D30 ± 5	M2 (P)	M3 D90 ± 7	M4 (P)	M5 (P)	M6 D180 ± 14	M7 (P)	M8 (P)	M9 D270 ± 14	M10 (P)	M11 (P)	M12 D365 ± 14
Consent/ Assent	X													
Inclusion/ Exclusion	X	X												
History	X													
Physical Examination	X		X		X			X			X			X
Focused Nasal Examination	X	X	X		X			X			X			X
Vital Signs	X	X	X		X			X			X			X
Height[a]	X	X	X		X			X			X			X
Body Weight	X	X	X		X			X			X			X
Laboratory Tests	X							X						X
ECG	X							X						X
Urine pregnancy[b]	X		X		X			X			X			X
Eye Exam[c]	X							X						X
HPA axis testing – Fasting AM plasma cortisol[d]	X							X						X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Instruct patients on proper use of medications		X	X		X			X			X			
Dispense SCREENING Diary	X													
Dispense TREATMENT		X	X		X			X			X			

Diary														
Dispense Diary Comment Card	X	X			X			X			X			
RQLQ[e]		X	X		X			X			X			X
Dispense trial medication		X	X		X			X			X			
Collect used trial medication			X		X			X			X			X
Collect SCREENING Diary		X												
Collect TREATMENT Diary			X		X			X			X			X
Assess compliance		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events assessment[f]		X	X	X	X	X	X	X	X	X	X	X	X	X

Source: 5.3.5.2.4, pg. 6 (Study Evaluation Schedule)
[a]Height will be taken at screening, for all patients. Height will only be taken at subsequent visits for subjects <18 years of age.
[b]All female patients.
[c]An ophthalmologist will examine for possible cataract formation and for glaucoma.
[d]Must be done between 8 and 9 AM. At selected sites only.
[e]RQLQ will be administered to subjects 18 years of age and older.
[f]Any adverse event that occurs subsequent to signing of informed consent will be recorded in the patient's medical record and in the CRF.
Key: D=Day, M=Month, P=phone contact, R=Randomization, S=Screening Visit

Screening Period

Prior to the conduct of assessments at Screening (Day -7), patients provided written informed consent and (if appropriate) pediatric assent. Screening assessments included a medical history, laboratory tests (hematology, chemistry, urinalysis), urine pregnancy test, ECG, general physical examination, focused nasal examination, eye examination by an ophthalmologist (including slit-lamp examination for cataracts and intra-ocular pressure for glaucoma). Concomitant medications were reviewed. Inclusion/exclusion criteria were verified.

At selected sites, patients in the HPA-Axis substudy had fasting AM plasma cortisol levels drawn. The planned enrollment for the HPA-Axis substudy was 200 total, distributed across the MP29-02 and commercially available generic fluticasone propionate treatment arms in a 2:1 ratio.

The patient was dispensed a screening diary and instructed to record AM and PM TNSS.

Open-label Treatment Period
Following the screening period, patients returned on Day 1 for the randomization visit, during which time patients' diaries were collected and reviewed; patients were required to exhibit nasal symptoms of rhinitis on at least 2 days during the screening period. Assessments on Day 1 included vital signs, focused nasal examination, review of concomitant medications, and assessment of adverse events. Inclusion/exclusion criteria were verified. The RQLQ was administered to patients 18 years of age and older. Treatment diary and diary comment cards were dispensed. Trial medication was dispensed and the first dose of trial medication was administered under supervision.

At months 1, 3, 6, 9, and 12 patients returned to the clinic. During these visits, patient diaries and comment cards were collected and reviewed and trial medication was collected and weighed. Assessments included vital signs, physical exam, focused nasal examination, urine pregnancy test, review of concomitant medications, and assessment of adverse events. Additionally, at months 6 and 12, the following assessments were conducted: laboratory tests (hematology, chemistry, urinalysis), ECG, eye exam, and for patients in the HPA-axis substudy, fasting morning plasma cortisol levels.

At months 2, 4, 5, 7, 8, 10, and 11 patients were contacted by telephone. Concomitant medications were reviewed and adverse events assessed. Patients were reminded of the importance of compliance.

Discontinuation of Treatment
The protocol specified that treatment could be discontinued for adverse events or abnormal test results, as well as for treatment failure, protocol violation, patient non-compliance, loss to follow-up, administrative issues, and patient withdrawal of consent.

Planned Analyses
Demographic and Background Data
Categorical variables were summarized using frequency distributions of patients and continuous variables with descriptive statistics. Baseline comparability was evaluated using a two-way analysis of variance (ANOVA) model for continuous variables and the Chi-square test or Fisher's exact test for categorical variables.

Safety
Safety analyses were conducted on all randomized patients who received any trial medication. The protocol called for a descriptive comparison of safety assessments to be made between MP29-02 and the active control.

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Efficacy
The analysis of RQLQ was performed on all randomized patients, 18 years of age and older, who received any trial medication. Changes in RQLQ from baseline to 6 and 12 months were summarized according to the method described in the literature.[23]

Total TNSS scores were summarized daily for Day 1 to 7, and using an average at 4-week intervals.

Subgroup Analyses
The statistical analysis plan pre-specified a subgroup analysis to be conducted according to the diagnosis of chronic rhinitis.

Interim
The statistical analysis plan pre-specified an interim analysis, to be conducted when all patients in the MP29-02 treatment group had completed the 6-month visit.

Protocol Amendments
There were several amendments to the protocol for Trial MP-4000, however, these did not raise any concerns for trial integrity. A summary of changes is provided below.

Original protocol: July 18, 2007
Protocol Amendment 1: November 29, 2007
- Synopsis changed as follows: size of patient population in HPA-Axis substudy changed from 100 patients per treatment arm to 200 patients distributed in a 2:1 ratio

Protocol Amendment 2: January 21, 2008
- Section 3.1 updated to reflect the 2:1 ratio described above

7.1.2 Categorization of Adverse Events

Adverse events were coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA). For pooling, the Applicant re-coded all AEs[24] to MedDRA Version 13.1.

The clinical program defined an adverse event as:

> *…any untoward medical occurrence in a subject…Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not*

[23] Juniper EF, et al. *Clin Exp Allergy.* 1991;21:77-83.
[24] Except for AEs reported for the two PK trials (Trials X-03065-3282 and X-03065-3283), which used MedDRA Version 13.0.

> *considered related to the investigational product was recorded as an AE…worsening of a prior condition was considered an AE.*[25]

An SAE was defined as:

> *…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 inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect.*[26]

The Applicant's analysis of AEs largely focuses on treatment-emergent adverse events (TEAEs), which are defined as:

> *…an adverse event (AE) with an onset date on or after the first dose of study drug, or an AE that is worsened (increased in severity or frequency) after taking the study drug."*[27]

These definitions are appropriate.

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

The Applicant's ISS includes a pooled safety analysis for the four 2-week efficacy and safety trials (MP-4001, MP-4002, MP-4004, and MP-4006). As described in Section 5.2 and 7.1.1, this review views Trial MP-4001, which included the commercial monotherapy treatment arms, as not being comparable to the other three 2-week efficacy and safety trials. As a result, this reviewer concluded that it is inappropriate to pool the data across these four trials, and the Applicant was asked to provide new pooled safety analyses based on only Trials MP-4002, MP-4004, and MP-4006, and excluding Trial MP-4001. Analyses for the duration of exposure and compliance, adverse events leading to discontinuation of treatment, results of nasal examinations, and common TEAEs were provided by the Applicant in a submission dated October 18, 2011, and are analyzed in this review of safety.

[25] Section 5.3.5.3.28 ISS, pg. 27
[26] Section 5.3.5.3.28 ISS, pg. 28
[27] Section 5.3.5.3.28 ISS, pg. 30

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7.2 Adequacy of Safety Assessments

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

The overall exposure to MP29-02 in the clinical development program was adequate for the pre-market evaluation of safety. Exposure in the three 2-week phase 3 efficacy and safety clinical trials and in the year-long safety trial are summarized in Table 25 and Table 26, respectively.

Table 25. Duration of Exposure and Compliance, Safety Population: Trials MP-4002, MP-4004, MP-4006

	MP29-02 N=853	Placebo N=861	Azelastine Hydrochloride N=851	Fluticasone Propionate N=846
Duration of Exposure (Days)	n=847	n=859	n=846	n=845
Mean (SD)	15 (2)	14 (2)	15 (2)	15 (2)
Median	15	15	15	15
Min-Max	2-29	1-18	1-20	2-19
Total No. of Doses* Taken	n=848	n=858	n=846	n=845
Mean (SD)	28 (3)	28 (4)	28 (3)	28 (3)
Median	29	28	29	29
Min-Max	3-50	1-33	1-45	6-36
Subjects Treatment Compliant#:				
Day 7 [n(%)]	822 (96)	834 (97)	826 (97)	817 (97)
Day 14/ET [n(%)]	825 (97)	835 (97)	823 (97)	823 (97)
Subjects with ≥ 80% Compliance [n(%)]@	839 (98)	850 (99)	837 (98)	838 (99)

Source: Applicant's submission dated October 18, 2011, Section 1.11.3, pg. 11 (Table 2.7.4.1.2)
*** One dose is equivalent to two sprays (one spray per nostril)**
 # Compliance was based on questions included in the CRF.
@ Compliance was calculated as follows: (total number of doses)/(duration of exposure x 2), using patient diary data

In the pooled safety population drawn from the three 2-week phase 3 efficacy and safety clinical trials, the mean duration of exposure was quite consistent across treatment groups, ranging 14 to 15 days. The mean number of doses taken was 28 and the percentage of patients compliant on Day 14 was 97% across all treatment groups.

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Table 26. Duration of Exposure and Compliance, Safety Population: Trial MP-4000

	MP29-02 N=404	Fluticasone Propionate* N=207
Duration of Exposure (Days)	n=375	n=188
Mean (SD)	340 (70)	329 (89)
Median	364	364
Min-Max	4-406	27-412
Total No. of Doses# Taken	n=386	n=196
Mean (SD)	633 (170)	302 (105)
Median	709	356
Min-Max	7-923	16-395
Subjects with ≥ 75% Compliance [n(%)]@	344 (85%)	169 (82%)

Source: Section 5.3.5.2.3, pg. 52 (Table 9)
*** Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)**
 # For MP29-02, one dose is equivalent to two sprays (one spray per nostril); for fluticasone propionate, one dose is equivalent to four sprays (two sprays per nostril)
@ Compliance was calculated as follows: MP29-02 -- (total number of doses)/(duration of exposure x 2), using patient diary data; fluticasone propionate -- (total number of doses)/(duration of exposure)

In the year-long safety trial (MP-4000), the mean duration of exposure was comparable for the two treatment groups (340 days for MP29-02 and 329 days for the active comparator. Compliance, based on patient diary data, was slightly higher for MP29-02 as compared to the active comparator, with 85% percent on MP29-02 of patients demonstrating ≥ 75% compliance as compared to 82% of patients on active comparator. In addition to diary data, Trial MP-4000 employed efficacy measures (e.g. 12-hour rTNSS, RQLQ [adult population]) as surrogate markers for compliance, the results of which are summarized in Table 27. Both mean 12-hour rTNSS and mean RQLQ (overall score) decreased over the course of the trial, adding further evidence for patient compliance.

Table 27. Surrogate markers for compliance, ITT Population: MP-4000

A. 12- hour rTNSS

Treatment Arm	N	Baseline	Change from baseline Mean (SD)
Baseline			
MP29-02	379	3.84 (2.487)	--
Fluticasone Propionate*	194	3.87 (2.326)	--
Day 7			
MP29-02	359	--	-1.80 (2.678)
Fluticasone Propionate*	185	--	-1.03 (2.673)
Week 4#			
MP29-02	372	--	-1.93 (2.383)

Fluticasone Propionate*	188	--	-1.36 (2.160)
Week 52@			
MP29-02	295	--	-2.99 (2.588)
Fluticasone Propionate*	148	--	-2.88 (2.543)

Source: Section 5.3.5.2.3, pg. 46-47 (Table 7)
*** Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)**
 # Week 4 includes PM TNSS scores from Day 1 to Day 28.
@ Week 52 includes PM TNSS scores from DAY 337 to Day 365.

B. RQLQ [Adult Population], Overall Score

Treatment Arm	N	Change from baseline Mean (SD)
Month 12 or Early Termination		
MP29-02	165	-1.5 (1.2)
Fluticasone Propionate	83	-1.6 (1.24)

Source: Section 5.3.5.2.3, pg. 47-48 (Table 8)
*** Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)**

Demographics

Demographic data for the three 2-week phase 3 efficacy and safety clinical trials is presented in Table 7. This data, provided for the ITT population, may be considered representative of the pooled safety population, given the high degree of overlap between the two populations.

Demographic data for the year-long safety trial (MP-4000) is provided in Table 28.

Table 28. Demographics and Baseline Characteristics for the Safety population, Trial MP-4000

Category	MP29-02 N=404	Fluticasone Propionate* N=207
Age (Years)		
N	404	207
Mean (SD)	33 (11)	35 (12)
Median	32	35
Minimum-Maximum	12-73	15-68
12 to <18 [n(%)]	28 (7)	8 (4)
18 to <65 [n(%)]	373 (92)	196 (95)
65 to older [n(%)]	3 (0.7)	3 (1)
Sex [n(%)]		
Male	240 (59)	110 (53)
Female	164 (41)	97 (47)
Race [n(%)]		
Asian	404 (100)	206 (100)
Black	0 (0)	1 (0.5)
Ethnicity [n(%)]		
Hispanic or Latino	0 (0)	0 (0)
Not Hispanic or Latino	404 (100)	207 (100)
Height (inches)		

N	403	207
Mean (SD)	64 (4)	64 (4)
Median	64	64
Minimum-Maximum	48-75	43-73
Weight (lb)		
N	404	207
Mean (SD)	136 (29)	136 (27)
Median	133	135
Minimum-Maximum	60-267	71-221
TNSS Total Score#		
N	393	202
Mean (SD)	3.8 (2.5)	3.9 (2.3)
Median	3.3	3.8
Minimum-Maximum	0-11	0-11
Duration of Chronic Allergic or Nonallergic Rhinitis (years)		
N	404	207
Mean (SD)	6 (5)	6 (6)
Median	4	4
Minimum-Maximum	1-31	1-42

Source: Section 5.3.5.2.3, pg. 43-44 (Table 6)
*** Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)**
 # Mean baseline TNSS over 7-day lead-in period, calculated using PM scores reported during this period.

There are a number of differences in the demographic profile of patients enrolled in the three 2-week phase 3 efficacy and safety clinical trials (MP-4002, MP-4004, and MP-4006) and the year-long safety trial (MP-4000). Most notably, the racial composition of Trial MP-4000 was almost entirely Asian, consistent with the trial's location in India. Caucasians constituted the majority race in the efficacy and safety trials, comprising 78-80% of the overall trial populations. In addition, there was a smaller percentage of adolescents and the elderly, and a greater percentage of males in Trial MP-4000 as compared to Trials MP-4002, MP-4004, and MP-4006. Patients enrolled in Trial MP-4000 were also somewhat shorter, weighed less, and had a shorter duration of illness. While these differences are noted, they are not viewed as prohibiting the generalization of these data to the United States population.

The overall number of adolescents exposed to MP29-02 in the long-term safety trial (n=28) is modest, however, given the overall benign safety profile and the extensive prior experience with the commercial monotherapies, it is acceptable. In the case of the elderly, the number exposed to MP29-02 in Trial MP-4000 (n=3) is quite limited. The proposed labeling for MP29-02 appropriately includes the following statement: "Clinical trials of DYMISTA Nasal Spray did not include sufficient numbers of patients 65 years of age and older to determine whether they respond different from younger patients."

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

Not applicable.

7.2.4 Routine Clinical Testing

The routine clinical testing conducted in the development program for MP29-02 was adequate and included: serum chemistry, hematology, urinalysis with microscopy, and 12-lead electrocardiograms (ECGs) conducted in the long-term safety trial (MP-4000). Urine pregnancy testing was performed in both the four 2-week efficacy and safety trials (MP-4001, MP-4002, MP-4004, and MP-4006) as well as the long-term safety trial (MP-4000).

7.2.5 Metabolic, Clearance, and Interaction Workup

The Applicant's proposed label relies on information available for Astelin, Astepro, and Flonase regarding metabolism, clearance, and drug-drug interactions. The proposed label also includes information regarding the clearance of azelastine obtained from pharmacokinetic Trial X-03065-3283.

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

The clinical program included monitoring for adverse events known to be associated with corticosteroids. Focused nasal examinations were conducted as part of both the 2-week efficacy and safety trials (at Screening, and Days 1, 7, and 14), and the year-long safety trial (at Screening, and Days 1, 30, 90, 180, 270, and 365). Ophthalmic exams were conducted as part of the year-long safety trial (at Screening, and Days 180, and 365). In addition, an HPA-axis study was conducted as a sub-study in Trial MP-4000.

The proposed product label also includes specific mention of somnolence, an adverse event known to be associated with antihistamines.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths across the seven clinical trials comprising the development program for MP29-02.

7.3.2 Nonfatal Serious Adverse Events

A total of 8 serious adverse events (SAEs) were reported across the clinical program, with 3 reported for the four 2-week phase 3 efficacy and safety clinical trials, and 5 for the year-long safety trial. Details of the SAEs are provided in Table 29 and Table 30. There were no SAEs reported for the two PK trials (Trials X-03065-3282 and X-03065-3283).

Table 29. SAEs for the Safety Population, Trials MP-4002, MP-4004, and MP-4006

Trial Site-Patient	Preferred Term	Day of Onset / Duration	Severity	Relationship* / Treatment
MP29-02				
MP-4004 419-012	Hepatitis C	Day 37 / Continuing	Mild	Unlikely related / None
MP-4006 621-071	Skin laceration	Day 8 / 2 days	Severe	Unlikely related / Hospitalization and/or significant intervention required
Placebo				
MP-4006 617-051	Arthritis bacterial	Day 1 / Continuing	Severe	Unlikely related / Hospitalization and/or significant intervention required

Source: Section 5.3.5.3.28 ISS, pg. 40 (Table 17)
*** Applicant's Assessment**

Table 30. SAEs for the Safety Population, Trials MP-4000

Site-Patient	Preferred Term	Day of Onset / Duration	Severity	Relationship# / Treatment
MP29-02				
318-013	Dengue Fever	Day 168 / 12 days	Severe	Unlikely / Hospitalization
321-012	Pyrexia	Day 13 / 8 days	Moderate	Unlikely related / Concomitant treatment and hospitalization
331-027	Appendicitis	Day 153 / 5 days	Severe	Unlikely related / Concomitant treatment and hospitalization
Fluticasone Propionate*				
335-013	Dehydration	Day 187 / 8 days	Moderate	Unlikely related / Concomitant treatment and hospitalization
335-013	Gastroenteritis	Day 187 / 8 days	Moderate	Unlikely related / Concomitant treatment and hospitalization

Source: Section 5.3.5.3.28 ISS, pg. 41 (Table 18)
***Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)**
 # Applicant's Assessment

Narratives for all SAEs were reviewed. In the four 2-week efficacy and safety trials, the two SAEs reported for the MP29-02 treatment group were Hepatitis C and Skin Laceration. While there is a known association between infection and corticosteroids, hepatitis C is an infection with a high background rate. The short duration of treatment decreases the likelihood that MP29-02 contributed to the development of the infection. The SAE of skin laceration is also unlikely to be due to MP29-02. In the year-long safety trial, the three SAEs reported for the MP29-02 treatment group were Dengue Fever, Pyrexia, and Appendicitis. Again, while there is a known association between infection and corticosteroids, it is important to note that dengue fever is an infection with a high risk of transmission in India. The ability to attribute causality for the event of "pyrexia" is hampered by limited information. With regards to appendicitis, this is also an event with a high background rate.

Overall, the number of SAEs in the clinical program was low, without any apparent imbalances between treatment groups.

7.3.3 Dropouts and/or Discontinuations

Adverse events leading to early discontinuation of treatment are summarized in Table 31 for the three 2-week efficacy and safety trials (MP-4002, MP-4004, and MP-4006) and in Table 32 for the year-long safety trial (MP-4000). There were no adverse events leading to discontinuation reported for the two PK trials (Trials X-03065-3282 and X-03065-3283).

Table 31. Adverse Events Leading to Discontinuation of Treatment, Safety Population, Trials MP-4002, MP-4004, and MP-4006

	MP29-02 N=853	Placebo N=861	Azelastine Hydrochloride N=851	Fluticasone Propionate N=846
Patients with any AE leading to discontinuation, n (%)	10 (1.2)	9 (1)	6 (0.7)	4 (0.5)
AE leading to discontinuation, n (%)				
Abdominal discomfort	--	--	1 (0.1)	--
Acute sinusitis	--	--	1 (0.1)	--
Arthritis bacterial	--	1 (0.1)	--	
Asthma	--	--	1 (0.1)	--
Cough	1 (0.1)	--	--	--
Dizziness	--	1 (0.1)	--	--
Dysgeusia	--	--	1 (0.1)	--
Epistaxis	2 (0.2)	--	1 (0.1)	--
Eustachian tube dysfunction	--	1 (0.1)	--	--
Headache	--	1 (0.1)	1 (0.1)	--
Mucosal erosion	1 (0.1)	1 (0.1)	--	2 (0.2)

Mucosal excoriation	--	--	1 (0.1)	--
Nasal mucosal disorder	--	1 (0.1)	1 (0.1)	--
Nausea	2 (0.2)	1 (0.1)	--	--
Oropharyngeal pain	--	--	1 (0.1)	--
Pain	--	--	--	1 (0.1)
Pharyngitis bacterial	1 (0.1)	--	--	1 (0.1)
Pharyngitis streptococcal	1 (0.1)	--	--	--
Photopsia	1 (0.1)	--	--	--
Sinusitis	--	4 (0.4)	--	--
Upper respiratory tract infection	--	--	--	1 (0.1)
Upper-airway cough syndrome	--	--	1 (0.1)	--
Viral upper respiratory tract infection	2 (0.2)	--	--	--
Vitreous floaters	1 (0.1)	--	--	--
Vomiting	--	1 (0.1)	--	--

Source: Applicant's submission dated October 18, 2011, Section 1.11.3, pg. 13-15 (Table 2.7.4.2.5-2)
*** Preferred Term**

Overall, the frequency of adverse events leading to discontinuation of treatment was low and balanced between the MP29-02 and placebo treatment arms (1.2% and 1.0%, respectively), albeit somewhat higher than the monotherapy comparators (0.7% and 0.5% for azelastine hydrochloride and fluticasone propionate, respectively). Most events were reported only once or twice, without any apparent pattern of association with the treatment arms.

Table 32. Adverse Events Leading to Discontinuation of Treatment, Safety Population, Trial MP-4000

	MP29-02 N=404	Fluticasone Propionate* N=207
Patients with any AE leading to discontinuation, n (%)	11 (2.7)	6 (2.9)
AE# leading to discontinuation, n (%)	--	--
Abdominal pain	1 (0.2)	--
Acne	2 (0.5)	--
Asthma	1 (0.2)	--
Blood cortisol decreased	3 (0.7)	--
Blood creatine phosphokinase Increased	--	1 (0.5)
Cataract	1 (0.2)	--
Cataract cortical	1 (0.2)	--
Cataract subcapsular	1 (0.2)	--
Dermatitis allergic	--	1 (0.5)
Dry mouth	--	1 (0.5)
Dysgeusia	--	1 (0.5)

Eye pain	--	1 (0.5)
Lenticular opacities	1 (0.2)	--
Nasal dryness	1 (0.2)	--
Pruritus generalized	--	1 (0.5)
Rash	--	1 (0.5)
Rhinorrhea	1 (0.2)	--
Visual field defect	1 (0.2)	--
Vomiting	1 (0.2)	--

Source: Applicant's submission dated October 10, 2011, Section 1.11.3, pg. 5-6 (Table B); Section 5.3.5.2.3, pg. 59 (Table 14)
[*]Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)
[#] Preferred Term

The frequency of adverse events leading to discontinuation was balanced between the two treatment arms (2.7% and 2.9% for MP29-02 and commercially available generic fluticasone propionate, respectively) in the long-term safety trial (Trial MP-4000). Most events were reported only once. One exception was the adverse event of "blood cortisol decreased," for which there were three reports for the MP29-02 treatment arm (0.7%) vs. none for the fluticasone propionate treatment arm. The results of the HPA-Axis Substudy, conducted as part of Trial MP-4000, are discussed in Section 7.4.5.

7.3.4 Significant Adverse Events

Given the formulation of the proposed product, the assessment of local nasal effects is warranted. Of note, there were no instances of nasal septal perforations in the clinical development program. A full discussion of the safety data regarding local nasal effects is provided in the following section.

Adverse events leading to withdrawal are discussed in Section 7.3.3. There were no events leading to dose reduction, as dose reduction was not performed in the clinical trials. Across Trials MP-4001, MP-4002, MP-4004, and MP-4006, the number of patients with any severe adverse event was comparable between MP29-02 and placebo (n=8 [0.8%] and n=10 [1.0%], respectively).[28] In Trial MP-4000, while there was an imbalance in the number of patients with any severe event (n=5 [1.2%] for the MP29-02 treatment arm and 0 for active control), the overall number of severe events was low.[29]

[28] Source: Section 5.3.5.3.28 ISS, pg. 30 (Table 7)
[29] Source: Section 5.3.5.3.28 ISS, pg. 37

Reference ID: 3107643

7.3.5 Submission Specific Primary Safety Concerns

Nasal Examinations

There was only one instance of nasal ulceration (grade 3 nasal irritation) across the clinical development program, which was reported for a patient receiving placebo in one of the 2-week efficacy and safety trials. There were no instances of nasal septal perforation (grade 4 nasal irritation) reported for any of the clinical trials. The frequency of epistaxis was balanced across treatment groups in the 2-week efficacy and safety trials, with an overall rate ranging from approximately 1 to 2%. The rate of epistaxis was also comparable between treatment arms in the long-term safety trial: 0.9% and 1.2% of patients in the MP29-02 and active comparator treatment groups, respectively, at the 12 month/ET visit. All cases of epistaxis on nasal examination across the phase 3 program were reported to be of mild or moderate intensity. A summary of nasal examination findings is provided for the three 2-week efficacy and safety trials (MP-4002, MP-4004, and MP-4006) in Table 33 and for the year-long safety trial (MP-4000) in Table 34. A discussion of nasal-related TEAEs follows each table.

Table 33. Results of Nasal Examinations at Day 14/ET, Safety Population: Trials MP-4002, MP-4004, MP-4006

	MP29-02 N=853 n (%)	Placebo N=861 n (%)	Azelastine Hydrochloride N=851 n (%)	Fluticasone Propionate N=846 n (%)
Epistaxis, n	845	856	837	843
None	826 (97.8)	844 (98.6)	829 (99.0)	828 (98.2)
Mild	17 (2.0)	12 (1.4)	8 (1.0)	14 (1.7)
Moderate	2 (0.2)	0	0	1 (0.1)
Severe	0	0	0	0
Nasal Irritation, n	845	856	837	842
None	775 (91.7)	806 (94.2)	783 (93.5)	780 (92.6)
Grade 1A	63 (7.5)	47 (5.5)	51 (6.1)	52 (6.2)
Grade 1B	5 (0.6)	2 (0.2)	2 (0.2)	9 (1.1)
Grade 2	2 (0.2)	0	1 (0.1)	1 (0.1)
Grade 3	0	1 (0.1)	0	0
Grade 4	0	0	0	0
Mucosal Edema, n	845	856	837	843
None	94 (11.1)	84 (9.8)	65 (7.8)	99 (11.7)
Mild	379 (44.9)	327 (38.2)	361 (43.1)	387 (45.9)
Moderate	321 (38.0)	374 (43.7)	339 (40.5)	307 (36.4)
Severe	51 (6.0)	71 (8.3)	72 (8.6)	50 (5.9)
Nasal Discharge, n	845	856	837	843
None	238 (28.2)	196 (22.9)	216 (25.8)	243 (28.8)
Mild	433 (51.2)	441 (51.5)	432 (51.6)	432 (51.2)
Moderate	159 (18.8)	200 (23.4)	178 (21.3)	153 (18.1)
Severe	15 (1.8)	19 (2.2)	11 (1.3)	15 (1.8)

Mucosal Erythema, n	845	856	837	843
None	518 (61.3)	522 (61.0)	483 (57.7)	506 (60.0)
Mild	249 (29.5)	235 (27.5)	247 (29.5)	247 (29.3)
Moderate	75 (8.9)	97 (11.3)	102 (12.2)	85 (10.1)
Severe	3 (0.4)	2 (0.2)	5 (0.6)	5 (0.6)
Mucosal Bleeding*, n	845	856	837	843
None	819 (96.9)	838 (97.9)	815 (97.4)	812 (96.3)
Mild	22 (2.6)	16 (1.9)	20 (2.4)	30 (3.6)
Moderate	4 (0.5)	2 (0.2)	1 (0.1)	1 (0.1)
Severe	0	0	1 (0.1)	0
Crusting of Mucosa, n	845	856	837	843
None	778 (92.1)	799 (93.3)	776 (92.7)	785 (93.1)
Mild	52 (6.2)	49 (5.7)	50 (6.0)	51 (6.0)
Moderate	15 (1.8)	8 (0.9)	10 (1.2)	6 (0.7)
Severe	0	0	1 (0.1)	1 (0.1)

Source: Applicant's submission dated October 18, 2011, Section 1.11.3, pg. 23-30 (Table 2.7.4.4.2)
*** The Application does not specify how mucosal bleeding is distinguished from epistaxis.**

Nasal-related TEAEs reported for Trials MP-4002, MP-4004, and MP-4006[30]
The frequency of epistaxis TEAEs reported for patients in Trials MP-4002, MP-4004, and MP-4006 was comparable across treatment groups (1.9%, 1.7%, 1.6%, and 1.7% for MP29-02, placebo, azelastine hydrochloride, and fluticasone propionate, respectively). The frequency of rhinalgia, nasal dryness, and nasal mucosal disorder were also generally comparable across treatment groups. The frequency of mucosal erosion and nasal discomfort was higher for MP29-02 as compared to placebo, but comparable to the frequency reported for at least one of the two monotherapy comparators. There was one case of mucosal excoriation reported for the azelastine hydrochloride treatment arm, with no cases reported for the other treatment groups.

[30] **Applicant's submission dated October 18, 2011, Section 1.11.3, pg. 16-22 (Table 2.7.4.2.2)**

Table 34. Results of Nasal Examinations, Safety Population: Trial MP-4000

Parameter	MP29-02 N=404			Fluticasone Propionate* N=207		
n (%)	Day 1	Month 6	Month 12/ET	Day 1	Month 6	Month 12/ET
Epistaxis						
n	404	355	334	207	169	163
None	399 (98.8)	354 (99.7)	331 (99.1)	205 (99.0)	168 (99.4)	161 (98.8)
Mild	5 (1.2)	1 (0.3)	3 (0.9)	2 (1.0)	1 (0.6)	2 (1.2)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Nasal Irritation						
n	404	355	334	207	169	163
None	250 (61.9)	293 (82.5)	294 (88.0)	128 (61.8)	133 (78.7)	140 (85.9)
Grade 1A	127 (31.4)	51 (14.4)	31 (9.3)	69 (33.3)	32 (18.9)	20 (12.3)
Grade 1B	25 (6.2)	10 (2.8)	9 (2.7)	10 (4.8)	3 (1.8)	3 (1.8)
Grade 2	2 (0.5)	1 (0.3)	0	0	1 (0.6)	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Mucosal Edema						
n	404	355	334	207	169	163
None	88 (21.8)	238 (67.0)	281 (84.1)	38 (18.4)	111 (65.7)	135 (82.8)
Mild	186 (46.0)	101 (28.5)	48 (14.4)	103 (49.8)	49 (29.0)	21 (12.9)
Moderate	130 (32.2)	16 (4.5)	5 (1.5)	62 (30.0)	9 (5.3)	6 (3.7)
Severe	0	0	0	4 (1.9)	0	1 (0.6)
Nasal Discharge						
n	404	355	334	207	169	163
None	51 (12.6)	216 (60.8)	276 (82.6)	31 (15.0)	100 (59.2)	135 (82.8)
Mild	180 (44.6)	119 (33.5)	53 (15.9)	91 (44.0)	56 (33.1)	21 (12.9)
Moderate	166 (41.1)	20 (5.6)	5 (1.5)	80 (38.6)	13 (7.7)	6 (3.7)
Severe	7 (1.7)	0	0	5 (2.4)	0	1 (0.6)
Mucosal Erythema						
n	404	355	334	207	169	163
None	170 (42.1)	241 (67.9)	265 (79.3)	87 (42.0)	105 (62.1)	130 (79.8)
Mild	174 (43.1)	105 (29.6)	65 (19.5)	88 (42.5)	58 (34.3)	28 (17.2)
Moderate	60 (14.9)	8 (2.3)	4 (1.2)	32 (15.5)	5 (3.0)	4 (2.5)
Severe	0	1 (0.3)	0	0	1 (0.6)	1 (0.6)
Mucosal Bleeding*						
n	404	355	334	207	169	163
None	398 (98.5)	353 (99.4)	331 (99.1)	201 (97.1)	169 (99.4)	162 (99.4)
Mild	3 (0.7)	1 (0.3)	3 (0.9)	4 (1.9)	0	1 (0.6)
Moderate	1 (0.2)	0	0	0	0	0
Severe	2 (0.5)	1 (0.3)	0	2 (1.0)	1 (0.6)	0
Crusting of Mucosa						
n	404	355	334	207	169	163

None	343 (84.9)	332 (93.5)	316 (94.6)	175 (84.5)	159 (94.1)	156 (95.7)
Mild	41 (10.1)	17 (4.8)	15 (4.5)	21 (10.1)	7 (4.1)	4 (2.5)
Moderate	18 (4.5)	5 (1.4)	3 (0.9)	10 (4.8)	2 (1.2)	2 (1.2)
Severe	2 (0.5)	1 (0.3)	0	1 (0.5)	1 (0.6)	1 (0.6)

Source: Section 5.3.5.3.28 ISS, pg. 51-52 (Table 22)
[*]Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)
[*] The Application does not specify how mucosal bleeding is distinguished from epistaxis.

Nasal-related TEAEs reported for Trial MP-4000
The frequency of epistaxis TEAEs reported for patients receiving M29-02 (2.0%) in Trial MP-4000 was higher than that for patients receiving fluticasone (0.5%)[31]. The frequency of nasal discomfort, nasal dryness, and nasal vestibulitis were similar between treatment groups (1.2% vs. 1.0%, 0.2% vs. 0%, and 0.2% vs. 0% for patients receiving MP29-02 and fluticasone, respectively).[32]

While there are limitations to cross-study comparisons, it is notable that the rate of epistaxis reported in the Flonase product label (6.9%) exceeds that reported for MP29-02, either on nasal examination or on review of adverse events. The rate of epistaxis reported in the Astelin product label[33] (2.0%) is comparable to that reported in the clinical development program for MP29-02. The Flonase product label reports the occurrence of nasal ulceration and nasal septal perforation (rarely) in the postmarketing setting; there are no reports of such events described in the Astelin product label.

Overall, the results for local nasal effects observed in the MP29-02 clinical development program are reassuring.

Ophthalmic Examinations

Ophthalmic examinations screening for glaucoma and posterior subcapsular cataracts were conducted as part of the long-term safety trial.

There was one instance of glaucoma, noted at Month 6 for a patient receiving MP29-02; there were no instances of glaucoma in the active comparator group. There were 4 instances (three at Month 6 and one at Month 12/ET) of posterior subcapsular cataracts among patients receiving MP29-02, and 5 instances among patients receiving active comparator; 2 of the 5 cases in the active comparator group were indentified at screening and should have resulted in exclusion from the trial. Results from the ophthalmic examinations are provided in Table 35.

[31] Section 5.3.5.2.3, pg.164-170 (Table 14.3.1.2.1). The 0.5% rate of epistaxis TEAEs reported for patients in the fluticasone treatment arm of Trial MP-4000 seems low, compared to the totality of the data (e.g. frequency of epistaxis noted on nasal examination for patients receiving fluticasone in Trial MP-4000 [1.0% on Day 1, 0.6% at Month 6 and 1.2% at Month 12/ET]).
[32] Section 5.3.5.2.3, pg.164-170 (Table 14.3.1.2.1).
[33] This rate is for an Astelin dose of 2 sprays per nostril twice daily, which is higher than the azelastine hydrochloride dose provided by MP29-02.

Table 35. Results of Ophthalmic Examinations, Safety Population: Trial MP-4000

Parameter	MP29-02 N=404			Fluticasone Propionate* N=207		
n (%)	Screening	Month 6	Month 12/ET	Screening	Month 6	Month 12/ET
Glaucoma						
Yes	0	1 (0.2)	0	0	0	0
No	399 (98.8)	354 (87.6)	333 (82.4)	203 (98.1)	168 (81.2)	162 (78.3)
Posterior Subcapsular Cataracts						
Yes	0	3 (0.7)	1 (0.2)	2 (1.0)#	0	3 (1.4)
No	404 (100.0)	352 (87.1)	332 (82.2)	205 (99.0)	168 (81.2)	159 (76.8)

Source: Section 5.3.5.2.3, pg. 827 (Table 14.3.9)
***Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)**
 # These two patients were randomized in error

While there is an imbalance (1 vs. 0) in the occurrence of glaucoma between the MP29-02 and active comparator treatment groups (1 vs. 0, respectively), the overall incidence is low. The incidence of cataract formation between the MP29-02 and active comparator treatment groups (4 vs. 3 [excluding the two cases at screening for the active comparator], respectively) is generally balanced. Overall, these results are reassuring.

Somnolence

Somnolence, known to be associated with antihistamine use including intranasal azelastine, was reported as a TEAE at a frequency of 0.7% for patients treated with MP29-02 in the three 2-week efficacy and safety trials, as summarized in Table 36. This was somewhat higher than the frequency for the other treatment groups, including azelastine (0.4%). For the year-long safety trial, the frequency of somnolence was 0.2% for the MP29-02 treatment group, and 0.5% for the active comparator treatment group.[34] Overall, the rate of somnolence across the clinical program was low.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, the frequency of any adverse event in the three 2-week efficacy and safety trials was somewhat higher for the MP29-02 treatment group (15.9%) compared to the other treatment groups (11.5%, 14.6%, and 13.1% for placebo, azelastine, and fluticasone, respectively). The most commonly reported AEs were dysgeusia (ranging from 0.2-5.2% across treatment groups), and headache (1.2-2.4%), and epistaxis (1.6-1.9% across treatment groups). A summary of common adverse events reported for

[34] Section 5.3.5.2.3, pg.167 (Table 14.3.1.2.1)

pooled safety population (Trials MP-4002, MP-4004, and MP-4006) is provided in Table 36.

Table 36. TEAEs with an Incidence ≥ 0.5% in MP29-02 Treatment Group, by Decreasing Order of Frequency, Safety Population: Trials MP-4002, MP-4004, MP-4006

Preferred Term	MP29-02 n=853	Placebo n=861	Azelastine Hydrochloride n=851	Fluticasone Propionate n=846
Any Adverse Event	136 (15.9)	99 (11.5)	124 (14.6)	111 (13.1)
Dysgeusia	30 (3.5)	2 (0.2)	44 (5.2)	4 (0.5)
Headache	18 (2.1)	10 (1.2)	20 (2.4)	20 (2.4)
Epistaxis	16 (1.9)	15 (1.7)	14 (1.6)	14 (1.7)
Oropharyngeal Pain	7 (0.8)	4 (0.5)	6 (0.7)	13 (1.5)
Mucosal erosion	6 (0.7)	1 (0.1)	0 (0.0)	7 (0.8)
Somnolence	6 (0.7)	1 (0.1)	3 (0.4)	1 (0.1)
Upper respiratory tract infection	6 (0.7)	6 (0.7)	4 (0.5)	4 (0.5)
Nasal discomfort	5 (0.6)	0 (0.0)	10 (1.2)	3 (0.4)
Nausea	5 (0.6)	4 (0.5)	3 (0.4)	3 (0.4)
Cough	4 (0.5)	2 (0.2)	3 (0.4)	2 (0.2)
Dry mouth	4 (0.5)	0 (0.0)	2 (0.2)	2 (0.2)
Nasopharyngitis	4 (0.5)	6 (0.7)	3 (0.4)	5 (0.6)

Source: Applicant's submission dated October 18, 2011, Section 1.11.3, pg. 16 (Table 2.7.4.2.2)

The imbalance in the overall frequency of AEs (15.9% for MP29-02 vs. 11.5%, 14.6%, and 13.1% for placebo, azelastine, and fluticasone) seems to be due in large part to an imbalance in the frequency of dysgeusia (3.5% for MP29-02 vs. 0.2% for placebo and 0.5% for fluticasone; at 5.2%, azelastine also has a high frequency of dysgeusia), which is to be expected given the prior experience with azelastine. The frequency of the other common AEs is generally balanced across treatment groups. The AE of somnolence is of special interest, since it carries a known association with antihistamine use, and is discussed above in Section 7.3.5.

Overall, the frequency of any adverse event in the year-long safety trial was balanced between treatment groups (46.5% and 44.4% for the MP29-02 and active comparator treatment groups, respectively). AEs that demonstrated an imbalance (with a greater frequency for the MP29-02 treatment arm) include: cough (5% vs. 2.4%), dysgeusia (2.7% vs. 0.5%), upper respiratory tract infection (2.5% vs. 1.9%), diarrhea (2.0% vs. 1.4%), and epistaxis (2.0% vs. 0.5%). A summary of common adverse events reported for Trial MP-4000 is provided in Table 37.

Table 37. TEAEs with an Incidence ≥ 2.0% in MP29-02 Treatment Groups, by Decreasing Order of Frequency, Safety Population: Trial MP-4000

Preferred Term	MP29-02 n=404	Fluticasone Propionate* n=207
Any Adverse Event	188 (46.5)	92 (44.4)
Headache	50 (12.4)	28 (13.5)
Pyrexia	34 (8.4)	22 (10.6)
Cough	20 (5.0)	5 (2.4)
Nasal Congestion	12 (3.0)	8 (3.9)
Rhinitis	11 (2.7)	5 (2.4)
Dysgeusia	11 (2.7)	1 (0.5)
Viral Infection	10 (2.5)	6 (2.9)
Upper Respiratory Tract Infection	10 (2.5)	4 (1.9)
Pharyngitis	9 (2.2)	5 (2.4)
Pain	8 (2.0)	6 (2.9)
Diarrhea	8 (2.0)	3 (1.4)
Epistaxis	8 (2.0)	1 (0.5)

Source: Section 5.3.5.3.28 ISS, pg. 33 (Table 11)
***Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)**

The imbalance in the frequency of dysgeusia is expected, given the known association between azelastine and dysgeusia, and is consistent with the pooled safety results from the 2-week efficacy and safety trials. Cough is a somewhat nonspecific AE, making interpretation of causality and the imbalance difficult. The imbalances for upper respiratory infection and diarrhea are modest in magnitude, and may be due to chance; of note, both MP29-02 and the active comparator have the potential for increased susceptibility to infections, given what is known about corticosteroids. The imbalance in epistaxis is of notable magnitude, but not unexpected, given that the combination's two monocomponents each carry an association with epistaxis. It is also possible that the magnitude of this imbalance may be due, at least in part, to an aberrantly low rate of epistaxis in the active comparator arm, as the rate of epistaxis for the fluticasone treatment group in the 2-week efficacy and safety trials was substantially higher (1.7% compared to 0.5% for the year-long safety trial).

Overall, the frequency of TEAEs in the two pharmacokinetic trials (Trials X-03065-3282 and X-03065-3283) was balanced between treatment groups for each of the two trials individually. The most common AEs reported for MP29-02 were headache and fatigue for both trials. A summary of TEAEs reported for Trials X-03065-3282 and X-03065-3283 is provided in Table 38.

Table 38. TEAEs Reported for X-03065-3282 and X-03065-3283

	X-03065-3282		X-03065-3283	
	MP29-02	Fluticasone Propionate*	MP29-02	Azelastine Hydrochloride*
Subjects with TEAEs#	8 (26.7)	7 (23.3)	13 (43.3)	12 (40.0)
Headache	3 (10.0)	4 (13.3)	7 (23.3)	4 (13.3)
Fatigue	2 (6.7)	0	2 (6.7)	2 (6.7)
Vessel Puncture Site Hematoma	1 (3.3)	0	1 (3.3)	1 (3.3)
Dermatitis Contact	0	0	1 (3.3)	2 (6.7)
Diarrhea	0	0	1 (3.3)	0
Dizziness	0	0	1 (3.3)	0
Dysgeusia	1 (3.3)	0	0	1 (3.3)
Dyspnea	0	0	1 (3.3)	0
Migraine	0	0	1 (3.3)	0
Nasal Discomfort	1 (3.3)	0	0	1 (3.3)
Ocular Hyperemia	1 (3.3)	0	0	0
Oropharyngeal Pain	0	0	1 (3.3)	0
Vessel Puncture Site Reaction	1 (3.3)	0	0	0

Section 5.3.5.3.28 ISS, pg. 38 (Table 15)
*** Investigational monotherapy**
 # TEAEs were defined as any AE occurring between administration of the treatment and Day 2 (for X-03065-3282) or Day 6 (for X-03065-3283)

The TEAE profiles for Trials X-03065-3282 and X-03065-3283 do not raise any specific concerns.

7.4.2 Laboratory Findings

Routine clinical testing was conducted in the long-term safety trial (MP-4000). Overall, mean baseline and mean changes in hematology, chemistry, and urinalysis parameters did not demonstrate clinically significant change and were similar across treatment groups. When results for laboratory tests were examined by shifts (values were categorized into low, normal, and high ranges, and comparisons made for screening vs. month 6 and screening vs. month 12/ET), a few imbalances in hematology (Table 39) and chemistry (Table 40) values were observed. Overall, the magnitude of these imbalances is modest and these results are not likely to be of clinically significance.

Table 39. Shifts in Hematology Laboratory Parameters, Safety Population: Trial MP-4000

Parameter	Visit	MP29-02 n=404	Fluticasone Propionate* n=207	Comments
Eosinophils (%)	Month 12/ET	N→H 7.1%	N→H 10.0%	Same pattern at Month 6
Hemoglobin (g/dL)	Month 12/ET	N→L 5.5%	N→L 8.7%	
Lymphocytes (%)	Month 12/ET	N→H 4.9%	N→H 1.9%	Same pattern at Month 6
White Blood Cell Count (thou/ÂµL)	Month 12/ET	N→H 3.0%	N→H 6.8%	Same pattern at Month 6

Source: Section 5.3.5.2.3, pg. 749-757 (Table 14.3.5.1.2)
***Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)**

Table 40. Shifts in Chemistry Laboratory Parameters, Safety Population: Trial MP-4000

Parameter	Visit	MP29-02 n=404	Fluticasone Propionate* n=207	Comments
Alanine Aminotransferase (U/L)	Month 12/ET	N→H 6.1%	N→H 4.3%	
Alkaline Phosphatase (U/L)	Month 12/ET	N→H 4.6%	N→H 2.5%	Reverse pattern at Month 6
Aspartate Aminiotransferase (U/L)	Month 12/ET	N→H 4.9%	N→H 8.1%	Same pattern at Month 6
Bilirubin Total (mg/dL)	Month 6	N→H 4.3%	N→H 1.8%	No difference at Month 12
Creatine Kinase (U/L)	Month 12/ET	N→H 7.6%	N→H 9.9%	Reverse pattern at Month 6
Glucose Fasting (mg/dL)	Month 12/ET	N→L 0.6% N→H 13.1%	N→L 2.5% N→H 16.9%	
Phosphorous (mg/dL)	Month 12/ET	N→H 3.4%	N→H 6.9%	
Protein Total (g/dL)	Month 12/ET	N→H 9.2%	N→H 5.6%	
Serum Calcium, Total (mg/dL)	Month 12/ET	N→L 3.7% N→H 1.2%	N→L 5.7% N→H 0.6%	Reverse pattern at Month 6
Sodium (mmol/L)	Month 12/ET	N→L 1.8% N→H 0.9%	N→L 2.5% N→H 0.0%	Same pattern at Month 6
Uric Acid (mg/dL)	Month 12/ET	N→H 6.7%	N→H 5.6%	Same pattern at Month 6

Source: Section 5.3.5.2.3, pg. 774-781 (Table 14.3.5.2.2)
***Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)**

7.4.3 Vital Signs

No clinically significant mean changes in systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, body temperature, or body weight were observed during the four 2-week efficacy and safety trials (MP-4001, MP-4002, MP-4004, and MP-4006). Mean baseline and mean change values for systolic and diastolic blood pressure, as well as heart rate, are provided in Table 41.

Table 41. Baseline and Changes in Vital Signs, Safety Population: Trials MP-4001, MP-4002, MP-4004, MP-4006

	MP29-02 N=1006		Placebo N=1012		Azelastine Hydrochloride N=851		Fluticasone Propionate N=846	
SBP (mmHg)								
Day 1 (Baseline)	Actual		Actual		Actual		Actual	
N	1006		1012		851		846	
Mean	117.1		117.6		116.4		116.2	
SD	12.70		12.89		12.31		12.59	
Median	117.0		118.0		116.0		116.0	
Min-Max	84-170		86-161		80-164		86-159	
Day 14 (End of Treatment)	Actual	Change*	Actual	Change*	Actual	Change*	Actual	Change*
N	997	997	1005	1005	839	839	843	843
Mean	117.7	0.6	117.3	-0.3	116.4	0.1	117.1	1.0
SD	12.97	10.70	13.00	10.63	12.54	10.03	13.19	10.06
Median	118.0	0.0	117.0	0.0	116.0	0.0	118.0	0.0
Min-Max	86-172	-52-48	80-175	-41-32	86-160	-31-42	80-167	-36-41
DBP (mmHg)								
Day 1 (Baseline)	Actual		Actual		Actual		Actual	
N	1006		1012		851		846	
Mean	73.7		73.8		73.0		73.2	
SD	9.32		9.09		9.18		9.46	
Median	74.0		74.0		72.0		72.0	
Min-Max	43-110		35-102		48-110		40-102	
Day 14 (End of Treatment)	Actual	Change*	Actual	Change*	Actual	Change*	Actual	Change*
N	997	997	1005	1005	839	839	843	843
Mean	73.6	-0.1	73.5	-0.3	72.7	-0.2	73.8	0.6
SD	9.48	8.44	9.21	8.86	9.17	8.22	9.71	7.67
Median	74.0	0.0	73.0	0.0	72.0	0.0	74.0	0.0
Min-Max	48-102	-32-30	45-98	-34-49	46-110	-34-28	49-108	-26-32
HR (bpm)								
Day 1 (Baseline)	Actual		Actual		Actual		Actual	
N	1005		1012		850		846	
Mean	73.3		73.8		72.9		72.6	
SD	9.86		9.68		9.80		9.25	
Median	72.0		72.0		72.0		72.0	
Min-Max	42-109		47-126		40-106		40-101	
Day 14 (End of Treatment)	Actual	Change*	Actual	Change*	Actual	Change*	Actual	Change*
N	997	996	1005	1005	839	838	843	843
Mean	74.0	0.7	74.0	0.2	74.1	1.1	73.2	0.7

SD	10.14	9.71	10.21	10.80	9.53	9.51	9.84	9,47
Median	73.0	0.0	73.0	0.0	74.0	1.0	72.0	0.0
Min-Max	44-112	-31-34	46-118	-55-40	51-119	-36-39	44-109	-32-33

Source: Section 5.3.5.3.28 ISS, pg. 248-253 (Table 2.7.4.4.1)
***Change from baseline, where baseline was measured on Day 1 prior to trial drug being dispensed.**
Note: Includes information for MP29-02 and placebo from Trial MP-4001. Monocomparator data (commercial products) omitted for Trial MP-4001.
Key: BPM=beats per minute, HR=heart rate, SBP=systolic blood pressure, SD=standard deviation

No clinically significant mean changes in systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, or body temperature were observed during the year-long safety trial (MP-4000). Over the course of the year-long trial, patients in both treatment groups experienced a 2-3 lb mean weight gain. This weight gain may be related to treatment, or, alternatively, it may reflect natural trends over time. Mean baseline and mean change values for systolic and diastolic blood pressure, as well as heart rate, are provided in Table 42.

Table 42. Baseline and Changes in Vital Signs, Safety Population: Trial MP-4000

	MP29-02 N=404		**Fluticasone Propionate# N=207**	
SBP (mmHg)				
Day 1 (Baseline)	Actual		Actual	
N	404		207	
Mean	117.7		119.0	
SD	10.34		9.42	
Median	120.0		120.0	
Min-Max	93-160		100-140	
Month 12 (End of Treatment)	Actual	Change*	Actual	Change*
N	334	334	163	163
Mean	118.5	1.0	119.2	0.3
SD	9.66	10.00	9.69	9.64
Median	120.0	0.0	120.0	0.0
Min-Max	90-144	-30-33	90-140	-20-26
DPB (mmHg)				
Day 1 (Baseline)	Actual		Actual	
N	404		207	
Mean	77.4		78.2	
SD	7.03		7.21	
Median	80.0		80.0	
Min-Max	55-100		59-94	
Month 12 (End of Treatment)	Actual	Change*	Actual	Change*
N	334	334	163	163
Mean	77.5	0.2	78.4	0.4
SD	6.67	7.67	6.99	7.65
Median	80.0	0.0	80.0	0.0
Min-Max	55-95	-21-32	55-90	-20-20
HR (BPM)				
Day 1 (Baseline)	Actual		Actual	

N	404		207	
Mean	78.6		79.3	
SD	7.19		7.59	
Median	80.0		80.0	
Min-Max	54-98		60-100	
Month 12 (End of Treatment)	Actual	Change*	Actual	Change*
N	334	334	163	163
Mean	77.7	-1.1	78.0	-1.3
SD	6.90	8.04	6.91	7.08
Median	78.0	0.0	80.0	-1.0
Min-Max	52-106	-30-26	58-101	-25-17

Source: Section 5.3.5.2.3, pg. 795-800 (Table 14.3.6)
***Change from baseline, where baseline was measured on Day 1 prior to trial drug being dispensed.**
#Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)
Key: BPM=beats per minute, HR=heart rate, SBP=systolic blood pressure, SD=standard deviation

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were obtained in the long-term safety trial (MP-4000) at screening to confirm eligibility, and again at months 6 and 12. Results were categorized as “within normal limits”, “abnormal/not clinically significant”, and “abnormal/clinically significant.” The Applicant did not provide any summaries of the data or treatment group comparisons, citing the rationale that ECG abnormalities were not anticipated based on prior experience with azelastine and fluticasone. The Astelin product label states that a study evaluating the impact of Astelin on cardiac repolarization did not demonstrate an effect on corrected QT interval (QTc). No studies evaluating ECGs are described in the Flonase product label.

This Reviewer examined the line listings provided for the ECG data obtained in Trial MP-4000. There were no reports of “abnormal/clinically significant” ECGs at either Month 6 or Month 12. The number (percentage) of patients with abnormal ECGs reported at Month 6 and/or Month 12 was 29 (8%) for the MP29-02 treatment group and 9 (5%) for the fluticasone treatment group. There were no ECG-related AEs reported. Overall, this information is reassuring.

7.4.5 Special Safety Studies/Clinical Trials

The year-long safety trial (MP-4000) included an evaluation of the HPA-Axis in a subset of patients, as described in Section 7.1.1.

Change in fasting serum cortisol, from baseline to Month 6 and baseline to Month 12 or Early Termination (ET), is summarized in Table 43. The number and percentage of patients falling into various categories of percent change in fasting serum cortisol (e.g. ≤ -30%, ≥ 30%) is provided in Table 44. Shifts in serum cortisol (between low, normal, and high values) are summarized in Table 45.

Table 43. Fasting Serum Cortisol, Safety Population: Trial MP-4000 (HPA-Axis Substudy)

	MP29-02 N=404 Mean ± SD (n)[#]	Fluticasone Propionate[*] N=207 Mean ± SD (n)[#]
Month 6 Evaluation		
Baseline	12.21 ± 4.196 (154)	12.53 ± 4.650 (78)
Value at Month 6	11.89 ± 4.547 (154)	11.61 ± 4.616 (78)
Change	-0.31 ± 5.142 (154)	-0.92 ± 5.319 (78)
Month 12/ET Evaluation		
Baseline	12.19 ± 4.209 (137)	12.52 ±4.531 (73)
Month 12/ET	12.11 ± 4.873 (137)	11.48 ± 4.653 (73)
Change	-0.08 ± 5.533 (137)	-1.04 ± 4.959 (73)

Source: Section 5.3.5.3.28, pg. 53 (Table 23)
[*]Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)
[#] n=number of patients with a baseline and postbaseline value for each visit
Key: ET=Early Termination

Table 44. Percent Change in Fasting Serum Cortisol, Safety Population: Trial MP-4000 (HPA-Axis Substudy)

MP29-02 N=404							
	≤ -30%	> -30% to ≤ -20%	> -20% to ≤ -10%	> -10% to < 10%	≥ 10% to < 20%	≥ 20% to < 30%	≥ 30%
Month 6 n=163	38 (23.3)	13 (8.0)	16 (9.8)	27 (16.6)	16 (9.8)	10 (6.1)	43 (26.4)
Month 12/ET n=139	32 (23.0)	11 (7.9)	11 (7.9)	28 (20.1)	11 (7.9)	11 (7.9)	35 (25.2)
Fluticasone Propionate* N=207							
	≤ -30%	> -30% to ≤ -20%	> -20% to ≤ -10%	> -10% to < 10%	≥ 10% to < 20%	≥ 20% to < 30%	≥ 30%
Month 6 n=79	18 (22.8)	5 (6.3)	13 (16.5)	19 (24.1)	4 (5.1)	7 (8.9)	13 (16.5)
Month 12/ET n=73	21 (28.8)	4 (5.5)	8 (11.0)	17 (23.3)	7 (9.6)	3 (4.1)	13 (17.8)

Source: Section 5.3.5.3.28, pg. 54 (Table 24)
[*]Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)
Note: n=number of patients with an observation
Key: ET=Early Termination

Table 45. Shifts in Serum Cortisol, Safety Population: Trial MP-4000 (HPA-Axis Substudy)

	MP29-02 N=404			Fluticasone Propionate* N=207		
	Screening					
	Low	Normal	High	Low	Normal	High
Month 6	n=163			n=79		
Low	0 (0.0)	5 (3.1)	1 (0.6)	0 (0.0)	2 (2.5)	0 (0.0)
Normal	0 (0.0)	153 (93.9)	2 (1.2)	1 (1.3)	72 (91.1)	2 (2.5)
High	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.3)
Month 12/ET						
Low	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	4 (5.5)	0 (0.0)
Normal	0 (0.0)	131 (94.2)	1 (0.7)	1 (1.4)	64 (87.7)	2 (2.7)
High	0 (0.0)	3 (2.2)	1 (0.7)	0 (0.0)	2 (2.7)	0 (0.0)

Source: Section 5.3.5.3.28, pg. 55 (Table 25)
***Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)**
Note: n=number of patients with an observation
Key: ET=Early Termination

Baseline values in fasting serum cortisol were comparable between the MP29-02 and fluticasone treatment groups, as was the magnitude of change from baseline to Month 6 and to Month 12. When examined by categories of percent change, the number and percentage of patients experiencing a decrement of greater than or equal to 30% was comparable for the two treatment groups at both Month 6 and Month 12. Similarly, the number and percentage of patients experiencing a shift from normal at screening to low (at Month 6 and at Month 12) was comparable between the MP29-02 and fluticasone treatment groups. Overall these results indicate that the effect of MP29-02 is comparable to that of fluticasone, and that the impact on serum cortisol is not substantial.

There are limitations to the Applicant's assessment of HPA-Axis. The MP-4000 substudy only evaluates one morning sample at Screening, Month 6, and Month 12, which is inconsistent with FDA recommendations for 12- or 24-hour urine free cortisol or serum cortisol AUC assessments.[35] Such assessments are recommended for new formulations causing higher systemic exposure compared to already marketed formulations for which the HPA axis has been already assessed. As noted in Section 4.4 of this review, the systemic exposure for fluticasone propionate associated with MP29-02 is higher than that for Flonase®. This deficiency was noted in the Agency's Filing Communication dated June 13, 2011. The Applicant responded on August 1, 2011, citing evidence that the systemic exposure to fluticasone from MP29-02 is less than that from other marketed products containing fluticasone (e.g. low dose Flovent HFA), for which HPA-axis evaluations are reassuring. Overall, the totality of the data suggests that the systemic exposure to fluticasone associated with MP29-02 falls within

[35] Draft Guidance, "Allergic Rhinitis: Clinical Development Programs for Drug Products," April 2000. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071293.pdf. Accessed December 7, 2011.

the range of fluticasone exposures associated with other products for which no substantial effect on HPA axis has been identified.

7.4.6 Immunogenicity

As each monocomponent of the combination product is a small molecule, immunogenicity is not anticipated and was not assessed.

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

Time dependency for adverse events was not specifically assessed by the Applicant. A comparison of the adverse event data from the short-term efficacy and safety trials (MP-4002, MP-4004, and MP-4006) as compared to the long-term trial (MP-4000) reveals an increase in the percentage of patients treated with MP29-02 who experienced any adverse event (15.9% and 46.5% for the short and long-term safety trials, respectively). This increase in the number of adverse events may reflect the longer duration of exposure provided by the long-term trial.

7.5.3 Drug-Demographic Interactions

A summary of AEs by demographic characteristics (age, sex, race, and ethnicity) is provided in Table 46.

Table 46. Frequency of AEs by Demographic Characteristics, Safety Population: Trials MP-4001, MP-4002, MP-4004, MP-4006

Demographic Characteristic	N		Any AE*, %	
	MP29-02	Placebo	MP29-02	Placebo
All	1006	1012	16.4	11.6
Age				
12 to <18 Years	97	112	6.2	8.9
18 to < 65 Years	882	868	17.6	12.1
≥ 65 Years	27	32	14.8	6.3

Reference ID: 3107643

Sex				
Male	362	387	17.1	12.7
Female	644	625	16.0	10.9
Race				
White	815	816	17.8	11.8
Black	151	149	10.6	11.4
Ethnicity				
Hispanic/Latino	180	189	19.4	13.2
Non-Hispanic/Latino	826	823	15.7	11.2

Source: Section 5.3.5.3.28 ISS, pg. 73 (Table 31)
*** A patient with multiple AEs was counted only once for the "Any AE" tabulation.**
Note: Includes information for MP29-02 and placebo from Trial MP-4001.

In general, the distribution of AEs with regards to demographic characteristics was similar for MP29-02 and placebo. Exceptions include age, for which the difference in the frequency of AEs between elderly vs. non-elderly adults was greater for placebo (6.3%:12.1%, elderly:non-elderly adults) as compared to MP29-02 (14.8%:17.6% elderly:non-elderly adults), however, the overall size of the elderly population enrolled in the four two-week efficacy and safety trials was small, limiting the interpretability of the data. Also noted is a greater difference in the frequency of AEs between patients of black vs. white race for MP29-02 (10.6%:17.8% black:white race) as compared to placebo (11.4%:11.8% black:white race), which is of unclear significance.

7.5.4 Drug-Disease Interactions

Allergic Rhinitis Subtypes
There was no subgroup analysis of AEs by disease severity conducted for the three 2-week efficacy and safety trials.

The long-term safety trial (Trial MP-4000) evaluated patients with one of two disease entities: perennial allergic rhinitis, and vasomotor rhinitis. An overview of adverse events, by disease subgroup, is provided in Table 47. The overall frequency of any TEAE, any SAE, and any TEAE leading to discontinuation was comparable between disease subgroups. Two out of the three most common TEAS (headache and pyrexia) were the same for the two disease subgroups. These data suggest that adverse experiences appear to be consistent across the different rhinitis entities, and support generalization to the seasonal allergic rhinitis population.

Table 47. Overview of AEs by Disease Subgroup, Safety Population: Trial MP-4000

	PAR N=278	VMR/NAR N=126
Number (%) of Subjects with Any TEAE, n (%)	138 (49.6)	50 (39.7)
Number (%) of Subjects with Any SAE, n (%)	1 (0.4)	2 (1.6)
Number (%) Subjects with TEAEs Leading to Discontinuation	7 (2.5)	4 (3.2)
3 most common TEAEs, n (%)	Headache, 38 (13.7) Pyrexia 24 (8.6) Cough, 20 (7.2)	Headache, 12 (9.5) Pyrexia, 10 (7.9) Epistaxis, 5 (4.0)

Source: Section 5.3.5.2.3, pg. 158 (Table 14.3.1.1.1), pg. 161 (Table 14.3.1.1.2), pg. 171 (Table 14.3.1.2.1.1), pg. 177 (14.3.1.2.1.2)
Key: PAR=Perennial Allergic Rhinitis; VMR/NAR=Vasomotor Rhinitis/Non-Allergic Rhinitis

Renal and Hepatic Impairment
No specific evaluations were done for MP29-02 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, as noted in the Astelin® Prescribing Information. The proposed label also notes that the pharmacokinetics of azelastine hydrochloride are not influenced by hepatic impairment, as noted in the Astelin® Prescribing Information.

7.5.5 Drug-Drug Interactions

The MP29-02 clinical development program did not include a specific evaluation for interactions between MP29-02 and other drugs. The proposed label includes information regarding known interactions for Astelin® (alcohol and other CNS depressants, cimetidine, ketoconazole) and Flonase® (ritonavir and ketoconazole).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Nonclinical carcinogenicity studies were not conducted for MP29-02, given reassuring results from past evaluations of azelastine and fluticasone. There were no adverse events of tumor reported for the clinical program.

7.6.2 Human Reproduction and Pregnancy Data

Urine pregnancy testing were performed in both the four 2-week efficacy and safety trials (MP-4001, MP-4002, MP-4004, and MP-4006) as well as the long-term safety trial (MP-4000). There were no positive results in any of these trials.

7.6.3 Pediatrics and Assessment of Effects on Growth

The clinical development program for MP29-02 did not include an evaluation in children less than 12 years of age.

Effects on Growth
The proposed label includes class labeling describing the association between intranasal corticosteroids and the reduction of growth velocity in pediatric patients, and recommends that the growth of pediatric patients receiving MP29-02 be monitored routinely.

Request for Waiver of Pediatric Studies
The NDA includes a request for waiver of pediatric studies, (b) (4) Each actuation of MP29-02 delivers 50 mcg of fluticasone propionate and 137 mcg of azelastine hydrochloride. (b) (4) (b) (4)

The Applicant's (b) (4) waiver proposal was discussed at the Pediatric Review Committee (PeRC) on November 30, 2011. The conclusion reached between the Division and PeRC was as follows:

- To grant the waiver of studies in the 0 to < 2 years age group, based on the rationale that the existence of seasonal allergic rhinitis in patients < 2 years of age is uncertain, making studies impossible or highly impractical.

- To grant the waiver of studies in the 2 to < 4 years age group, based on the rationale that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a

substantial number of pediatric patients falling into this age range. Regarding the first criterion, it is unlikely that the proposed product would represent a meaningful therapeutic benefit over existing therapies, given that the efficacy of fluticasone propionate in children less than 4 years was not demonstrated in a growth study conducted as part of a Written Request for this moiety. Regarding the second criterion, it is unlikely that combination therapy would be adopted broadly for children in the 2 to < 4 years age range.

(b) (4)

The Applicant [redacted] (b) (4) was instructed to submit a pediatric plan, which they did on December 16, 2011. After receiving feedback from the Division during teleconferences on February 27, 2012, and March 12, 2012, the Applicant submitted a revised pediatric plan on March 13, 2012. The Applicant's plan provides for the following:

1) A deferred efficacy and safety trial in children 4-11 years of age with seasonal allergic rhinitis.

   Protocol Submission: September 2012
   Study Completion: July 2013
   Study Report Submission: January 2014

2) A deferred long-term safety trial in children 4-11 years of age with seasonal or perennial allergic rhinitis.

   Protocol Submission: January 2013
   Study Completion: September 2014
   Study Report Submission: March 2015

This revised pediatric plan was discussed at the Pediatric Review Committee (PeRC) on March 21, 2012, and found to be acceptable. Finalization of the timelines is pending at the time of this review.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Application does not address the issue of overdose, but does comment that no withdrawal or rebound effects would be predicted for MP29-02, based on past experience with azelastine and fluticasone. *The Applicant's assessment is reasonable; other than somnolence, there are no systemic adverse events likely to occur with an overdose of azelastine hydrochloride, and the bioavailability of fluticasone propionate delivered intranasally averages less than 2%.*[36]

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120-Day Update on August 1, 2011, informing the Agency that there was no new safety data.

[36] As described in the Flonase product label.

Reference ID: 3107643

8 Postmarket Experience

There has been no postmarket experience with Dymista (Azelastine Hydrochloride and Fluticasone Propionate) Nasal Spray, 137 mcg/50 mcg per spray. An azelastine hydrochloride/fluticasone propionate combination product (Duonase) is available in India, however, its formulation differs from that of the proposed product.

9 Appendices

9.1 Literature Review/References

A PubMed search conducted by this Reviewer on March 19, 2012, [search term: azelastine and fluticasone; limits: human, clinical trial, meta-analysis, randomized clinical trial, English language], for the time period from March 19, 2007, to March 19, 2012. The search yielded three references, and a brief review of these reports was performed. In a trial evaluating various treatments including the concurrent administration of fluticasone nasal spray (50 mcg) and azelastine hydrochloride (0.1%) for 14 days to patients 12 years of age and older with seasonal allergic rhinitis, there was one report of a nasal ulceration in the azelastine + fluticasone treatment arm.[37] As has been previously noted, there was only one occurrence of nasal ulceration in the MP29-02 clinical program, which occurred in a patient treated with placebo. As intranasal corticosteroids are known to be associated with nasal ulceration, it is recommended that the labeling for MP29-02 include class language for local nasal effects (see Section 9.2). In addition to the ulceration, this paper by LaForce and colleagues also notes the occurrence of olfactory changes in patients treated with the azelastine and fluticasone concurrently. In the MP29-02 clinical program olfactory disturbances were reported for the fluticasone monotherapy, but not for the proposed combination product. The labels for both of the approved monotherapy products note an association with olfactory disturbances; these adverse events are also described in the proposed label for MP29-02, which references the Prescribing Information for the approved monotherapy products.

9.2 Labeling Recommendations

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

- Section 1, Indications and Usage: The recommended indication is “the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.”
- Section 5, Warnings and Precautions:

[37] 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; 31:132-40.

    - Class language for corticosteroids (local nasal effects, effect on growth) added
- Section 6. Adverse Reactions
    - Class language for corticosteroids (local nasal effects) added
- Section 6.1, Clinical Trials Experience
    - The safety data are revised to reflect the findings of the three clinical trials (MP-4002, MP-4004, and MP-4006) which used the appropriate (investigational) comparators, and not the commercial monoproducts.
- Section 14, Clinical Studies
    - Efficacy data (rTNSS, iTNSS) for Trials MP-4001 and MP-4004 removed from tables
        - Trial MP-4001 was removed given that it evaluated the commercial monotherapies, which are not appropriate comparators for the purpose of satisfying the Combination Rule
        - Trial MP-4004 was removed given space considerations; Trials MP-4002 and MP-4006 were chosen for inclusion given that they provide replicate evidence for the factorial contribution of each monocomponent with statistically significant results
    - Results for rTNSS and iTNSS combined into a single table (see Table 48)
    - (b) (4)
    - Table of RQLQ results replaced by an abbreviated summary
- Section 17 Patient Counseling Information
    - Class language for corticosteroids (local nasal effects) added

Reference ID: 3107643

Table 48. Table of rTNSS and iTNSS Results Proposed for Inclusion in the Product Label

Table 2. Mean Change from Baseline in Efficacy Variables over 2 Weeks in Adults and Children ≥ 12 years with Seasonal Allergic Rhinitis						
		Baseline	*Change from Baseline*	*Difference from Dymista*		
Treatment (one spray/nostril twice daily)	*N*	*LS Mean*	*LS Mean*	*LS Mean*	*95%CI*	*P value*
Sum of AM and PM Reflective Total Nasal Symptom Scores (Maximum Score=24)						
Trial 1 (MP4002)						
Dymista	*207*	*18.27*	*-5.64*	*--*	*--*	*--*
Azelastine HCl	*208*	*18.26*	*-4.28*	*-1.37*	*(-2.22, -0.52)*	*0.002*
Fluticasone Propionate	*207*	*18.22*	*-4.67*	*-0.97*	*(-1.80, -0.24)*	*0.022*
Placebo	*209*	*18.61*	*-2.94*	*-2.71*	*(-3.49, -1.92)*	*<0.001*
Trial 2 (MP4006)						
Dymista	*448*	*19.34*	*-5.55*	*--*	*--*	*--*
Azelastine HCl	*443*	*19.47*	*-4.80*	*-0.75*	*(-1.33, -0.16)*	*0.012*
Fluticasone Propionate	*450*	*19.41*	*-4.91*	*-0.64*	*(-1.21, -0.06)*	*0.030*
Placebo	*448*	*19.44*	*-3.39*	*-2.16*	*(-2.72, -1.59)*	*<0.001*
Sum of AM and PM Instantaneous Total Nasal Symptom Scores (Maximum Score=24)						
Trial 1 (MP4002)						
Dymista	*207*	*17.16*	*-5.21*	*--*	*--*	*--*
Azelastine HCl	*208*	*16.84*	*-3.91*	*-1.30*	*(-2.13, -0.47)*	*0.002*
Fluticasone Propionate	*207*	*16.84*	*-4.54*	*-0.67*	*(-1.50, 0.17)*	*0.116*
Placebo	*209*	*17.26*	*-2.66*	*-2.55*	*(-3.35, -1.76)*	*<0.001*
Trial 2 (MP4006)						
Dymista	*448*	*17.91*	*-5.01*	*--*	*--*	*--*
Azelastine HCl	*445*	*18.00*	*-4.31*	*-0.70*	*(-1.28, -0.12)*	*0.019*
Fluticasone Propionate	*450*	*17.82*	*-4.73*	*-0.28*	*(-0.87, 0.30)*	*0.345*
Placebo	*448*	*17.90*	*-3.09*	*-1.92*	*(-2.49, -1.35)*	*<0.001*

9.3 Advisory Committee Meeting

As azelastine hydrochloride and fluticasone propionate are well-characterized pharmaceutical entities, an advisory committee meeting was not held for this application. An internal Regulatory Briefing was previously held to discuss the application of the Combination Rule in this program and is described in Section 2.5.

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/s/

JENNIFER R PIPPINS
03/27/2012

SUSAN L LIMB
03/27/2012