U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	NDA 202236/S0 (Cross references: IND 77363)
Drug Name:	Dymista (MP29-02) (azelastine HCl and fluticasone propionate Nasal Spray)
Indication(s):	Treatment of Seasonal Allergic Rhinitis (SAR) In Patients 12 Years of Age and Older
Applicant:	Meda Pharmaceuticals, Inc.
Date(s):	Received 4/1/11; User Fee 2/1/12
Review Priority:	Standard
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Keywords: Clinical Studies, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Meda Pharmaceuticals proposes Dymista® (MP29-02) nasal spray for treatment of seasonal allergic rhinitis (SAR) in patients 12 years of age and older. Dymista consists of a fixed-dose combination of azelastine hydrochloride and fluticasone propionate, both approved medications in approved doses. Efficacy was assessed by a single primary endpoint, change from baseline in 12-hour reflective Total Nasal Symptom Score (rTNSS) over the 14-day treatment period. (b) (4)

The applicant claims that Dymista® is effective in decreasing in rTNSS compared to placebo and monotherapies (b) (4) and improving the quality-of-life compared to placebo in SAR patients aged 12 years and older. The applicant also clams that the onset of action was observed as early as 30 minutes following the initial dose of Dymista®.

My statistical review of the clinical studies supports the claim of relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. In all three studies, there is evidence that Dymista is effective in decreasing rTNSS compared to placebo, as well as to each monotherapy. There is also evidence that Dymista is effective in improving the quality-of-life compared to placebo, and the observed effects met the minimum clinically significant difference of -0.50. The onset of action was observed at 30 minutes following the initial dose of Dymista. (b) (4)

1.2 Brief Overview of Clinical Studies

Dymista® (MP29-02) nasal spray consists of a fixed-dose combination of azelastine hydrochloride and fluticasone propionate. Each actuation of the MP29-02 nasal spray pump delivers 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate such that 1 spray per nostril twice daily delivers a total daily dose of 548 mcg of azelastine hydrochloride and 200 mcg of fluticasone propionate.

In this submission, the data supporting the efficacy of MP29-02 consisted of four phase 3 studies (MP4001, MP4002, MP4004, and MP4006) and one phase 3 safety study (MP4000). The design of Study MP4001 is different from other three phase 3 studies. Study MP4001 used Astelin® and fluticasone propionate nasal spray commercially available generic product as the comparator, not truly individual components of MP29-02. Conclusion of efficacy of MP29-2 was mainly based on three efficacy studies (4002, 4004, and 4006).

The studies MP4002, 4004, and 4006 are similar in design. The objective of these clinical trials was to compare the efficacy and safety of the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray (MP29-02) compared to placebo and to each

component alone, in patients with symptomatic SAR. All treatments were administered at a dosage of 1 spray per nostril twice daily (total daily dose for MP29-02 was 548 mcg azelastine hydrochloride/ 200 mcg fluticasone propionate). The individual active controls (fluticasone propionate and azelastine hydrochloride) were formulated in the same delivery device as MP29-02. Efficacy was assessed by a single primary endpoint, change from baseline in 12-hour reflective Total Nasal Symptom Score (rTNSS) over the 14-day treatment period. Secondary endpoints included the change from Baseline in reflective and instantaneous Total Ocular Symptom Score (rTOSS and iTOSS, respectively); onset of action; the change from Baseline in the individual nasal symptom scores including nasal congestion and postnasal drip; and the change from Baseline in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

1.3 Statistical Issues and Findings

During my review of the clinical studies, I found no issues that could not be resolved by re-analyzing the data. The results generated by the applicant and by me are similar and do not change the overall conclusion.

The major efficacy findings are as follows:

- The treatment effect of MP29-02 nasal spray was measured by the change from baseline over the 14-day treatment period in combined AM+PM rTNSS. MP29-02 demonstrated statistically significant greater decrease in rTNSS than placebo and monotherapies except Study MP4004 (p=0.06). The treatment effects between MP29-02 and monotherapies and placebo ranged from 0.64 to 2.71 points with baseline score of 19 points (maximum of 24 points). All protocol pre-specified sensitivity analyses supported the primary analysis results using repeated-measures analysis of covariance based on non-imputed data. Therefore, there is replicate evidence of the superiority of MP29-02 over placebo, as well as over each of the monocomponents (ie. azelastine and fluticasone propionate).

- MP29-02 demonstrated statistically significant greater decrease in iTNSS compared to placebo and azelastine HCI only. The treatment effects between MP29-02 and azelastine HCI and placebo ranged from 0.70 to 2.63 points with baseline score of 18 points (maximum of 24 points).

- MP29-02 demonstrated statistically significant greater decrease in rTOSS than placebo in all three studies and fluticasone propionate and azelastine HCI only in one study (MP4004). The treatment effects between MP29-02 and placebo ranged from 1.06 to 1.56 points with baseline score of 12 points (maximum of 18 points). MP29-02 was numerically better than azelastine HCI in two studies. Although there is evidence that MP29-02 is superior to placebo in the ocular symptom endpoint (rTOSS), only one study showed factorial contributions of azelastine as well as fluticasone propionate to the combination, and this evidence was not replicated in the other two studies.

- Onset of action was a secondary endpoint for studies MP4002, MP4004, and MP4006. Beginning 45 minutes after the first dose, subjects who received MP29-02 in study MP4002 showed an improvement in iTNSS that was significantly better than the improvement seen by subjects who received placebo. For studies MP4004 and MP4006, a significant improvement over placebo was seen at 30 minutes in subjects who received MP29-02. For all studies, the significant improvement in MP29-02 over placebo was maintained at each time-point through the end of the 4-hour time course.

- In all three studies, the treatment difference in the overall RQLQ score for MP29-02 compared to placebo met the minimum clinically significant difference of -0.50 with baseline score of 4 points (maximum of 6 points). Therefore, there is evidence that MP29-02 is effective in improving the RQLQ score after 2-weeks of treatment in subjects aged 18 years and older with SAR.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Dymista® (MP29-02) nasal spray consists of a fixed-dose combination of azelastine hydrochloride and fluticasone propionate. Each actuation of the MP29-02 nasal spray pump delivers 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate such that 1 spray per nostril twice daily delivers a total daily dose of 548 mcg of azelastine hydrochloride and 200 mcg of fluticasone propionate.

Azelastine hydrochloride (Astelin® Nasal Spray; Meda Pharmaceuticals, Inc.), 137 mcg per spray, is a topical antihistamine, which was approved on November 1, 1996 in the United States (NDA 20-114) for treatment of seasonal allergic rhinitis (SAR) in patients 5 years of age and older and symptoms of non-allergic vasomotor rhinitis (VMR) in patients 12 years of age and older. The recommended dosage of azelastine hydrochloride in adults and children 12 years of age and older with seasonal allergic rhinitis is 1 or 2 sprays per nostril twice daily; for VMR, the dosage is 2 sprays per nostril twice daily (a total of 1096 mcg per day).

Fluticasone propionate nasal spray (Flonase®; GlaxoSmithKline), 50mcg per spray, is a nasal steroid, which was approved on October 1994 in the United States (NDA 20-121) for treatment of seasonal and perennial allergic and non-allergic rhinitis in patients 4 years of age and older. Adult dosage is 200 mcg once-daily regimens (two 50-mcg sprays in each nostril once daily).

The purpose of this submission is to obtain the approval of marketing in US of Dymista® nasal spray one spray per nostril twice daily for relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. The applicant claims that combining two agents with different mechanisms of action, ie, the antihistaminic action of intranasal azelastine hydrochloride (a selective histamine H1-receptor antagonist) and the anti-inflammatory effects of intranasal

fluticasone propionate (a glucocorticosteroid), would have the potential for greater efficacy when used in combination than when used alone.

2.1.2 History of Drug Development

The clinical development plan for Dymista® nasal spray was introduced to the Division of Pulmonary, Allergy, and Rheumatology Products by Meda Pharmaceuticals, Inc. via IND 77363 in April, 2007. Since then, the Division had several meetings and discussion with the applicant about their clinical program. On December 21, 2007, the applicant requested for a Special Clinical Protocol Assessment (Study MP4002). There was no statistical review was done and there was a no agreement reached. The Division provided the comments on January 17, 2008. The main points are as follows:

- As discussed in the June 25, 2007, teleconference and the September 10, 2007, meeting, we questioned the rationale of the proposed combination product, MP29-02 (azelastine hydrochloride/fluticasone propionate). According to 21 CFR 300.50, a combination product should be safe and effective for a significant patient population requiring such concurrent therapy. We do not believe that the proposed protocol MP4002 defines such a patient population, and you have not provided other evidence that such a significant population exists.

- The proposed fixed-combination product does not permit titration of the individual components as is possible with monotherapy treatment. This is especially concerning with intranasal corticosteroids, potentially exposing patients to excess corticosteroids and increased risk.

- The proposed efficacy study appears premature given the need for developing and characterizing appropriate monotherapy comparators to determine if a component interaction is present prior to a definitive Phase 3 study. Characterization should include *in vitro* performance comparison of the monotherapies compared to the combination product as well as pharmacokinetic comparisons.

A type-A meeting was held on April 29, 2008, to discuss the Division's SPA comments. The Pre-NDA meeting was held on August 17, 2010, the Division re-expressed its concerns about dose selection:

- A lower dose of MP29-02 is not required for NDA filing. However, we remain concerned about the lack of flexibility of dosage titration with the fixed dose combination. This lack of flexibility will be evaluated in the context of the available safety information, and will be a review issue.

- If the systemic exposure from MP29-02 is equal or less than the systemic exposures for fluticasone and azelastine, respectively, from the corresponding commercially marketed monotherapies, then the proposed pharmacokinetic assessments will facilitate bridging to the systemic safety profiles established for the commercial monotherapies. Accordingly, a separate HPA axis effect trial with MP29-02 will not be required if you provide robust pharmacokinetic exposure data. However, the proposed pharmacokinetic data do not account for formulation differences that may alter the efficacy and local safety of locally acting products. Given this limitation, the results from MP4001 will likely be viewed as secondary support for the factorial contribution of azelastine and fluticasone to the efficacy of MP29-02.

- The Division finds the proposed indication for the treatment of nasal (b) (4) symptoms associated with seasonal allergic rhinitis to be problematic. (b) (4)

- Include in your NDA submission a rationale for the large sample size in MP-4006, which enrolled approximately double the patients enrolled in trials MP-4002 and MP-4004.
- The protocol synopses for trials MP-4002, MP-4004, and MP-4006 do not state whether patients with a history of failed therapy with either Astelin or Flonase were excluded. Based on the information provided, we cannot ascertain whether an appropriate patient population requiring combination therapy was identified for these trials.

Below is an excerpt of the discussion between the applicant and the Division.

The Division recommended that Meda address the following issues in the NDA submission:

1) Explain the rationale for an additional trial when typically two trials would be sufficient for establishing efficacy, and
2) Explain the rationale for the large (doubled) sample size in trial MP-4006

Meda agreed that they will provide explanation in the application. They added that the rationale for the additional trial and increased sample size was based upon previous trial results. Regarding the decision to conduct trial MP-4006, MP-4001 had yielded striking results, however, the results of MP-4002, while statistically significant, were not of the same magnitude as those for MP-4001, which prompted the company to conduct an additional trial. In addition, the total ocular symptom score (TOSS) had not been prespecified as an endpoint in trial MP-4002, which supported the decision to conduct an additional trial.

The Division reminded Meda that in previous discussions there had been agreement on principles governing the issues of sample size, and asked for explanation of the large size of trial MP-4006. Meda responded that the results of trail MP-4002, which demonstrated a "delta" (effect size) that was smaller than anticipated, prompted the company's decision to increase the sample size in order to be on the safe side.

The Division stated that it will be important for Meda to make their case in their application, particularly given that there is no established minimum clinically important difference for seasonal allergic rhinitis. A product associated with a small treatment difference, but a significant p-value driven by a large sample size is undesirable. The Division recommended that Meda reflect back on the minutes of previous meetings during which this issue was discussed.

Meda stated that the treatment difference associated with the combination product as compared to the monocomponents is comparable to that for non-sedating products compared to placebo. The Division responded that cross-study comparisons are fraught with difficulty. Meda replied that they will address the issue of clinical significance to the best of their ability in the NDA submission. Meda also asked whether there were any concerns regarding MP-4002 and MP-4004, to which the Division replied, no.

2.1.3 Specific Studies Reviewed

In this submission, the applicant submitted four phase 3 efficacy studies (MP4001, 4002, 4004, and 4006) and one phase 3 safety study (MP4000). The design of Study MP4001 is different from other three phase 3 studies. Study MP4001 used Astelin® and fluticasone propionate nasal spray commercially available generic product as the comparator, not truly individual components of MP29-02. Conclusion of efficacy of MP29-02 was mainly based on three efficacy studies (4002, 4004, and 4006). My review of efficacy will exclude the Study MP4001. Throughout the review, seasonal allergic rhinitis will be referred to as SAR, reflective total nasal symptom score as rTNSS, reflective total ocular symptom score as rTOSS, fluticasone propionate as FP, Azelastine hydrochloride as AH.

2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location \\...\cdsesub1evsprod\NDA202236.enx. The information needed for this review was contained in modules 1, 2.7, and 5.3.5.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy Studies

3.1.1 Study Design

Table 1 presents the study design of these four studies which mainly collected efficacy and safety data to support MP29-02 in treatment of SAR in patients 12 years of age and older. The following review will only present the results from three studies (4002, 4004, and 4006).

Table 1: Design of key controlled efficacy studies

Study/Center /Study Period	Study Design	Key Inclusion Criteria	# Patients by Group Entered	Primary Endpoint
MP4001 Phase 3 8 sites during Texas Mountain Cedar allergy season 12/20/2007 to 2/19/2008	Randomized Double-blind Placebo-controlled Parallel group Multi-center Active-controlled 2-weeks treatment duration	Males and females, 12 years and older, with at least a 2-year history of SAR during Texas mountain cedar season	1) MP29-02 nasal spray, 1 spray per nostril BID: 153 2) Astelin® nasal spray, 1 spray per nostril BID: 152 3) Fluticasone propionate nasal spray (commercially available generic version), 1 spray per nostril BID: 153 4) Placebo nasal spray, 1 spray per nostril BID: 151	The overall change from Baseline at Day 14 in combined AM+PM rTNSS
MP4002 Phase 3 44 sites in US 3/10/2008 to 6/13/2008	Randomized Double-blind Placebo-controlled Parallel group Multi-center Active-controlled 2-weeks treatment duration	Males and females, 12 years and older, with at least a 2-year history of SAR and a positive skin test to a local spring pollen	1) MP29-02 nasal spray, 1 spray per nostril BID: 207 2) Azelastine hydrochloride nasal spray[a], 1 spray per nostril BID: 207 3) Fluticasone propionate nasal spray[b], 1 spray per nostril BID: 208 4) Placebo nasal spray, 1 spray per nostril BID: 210	The overall change from Baseline at Day 14 in combined AM+PM rTNSS
MP4004 Phase 3 41 sites in US 8/14/2008 to 11/3/2008	Randomized Double-blind Placebo-controlled Parallel group Multi-center Active-controlled 2-weeks treatment duration	Males and females, 12 years and older, with at least a 2-year history of SAR and a positive skin test to a local fall pollen	1) MP29-02 nasal spray, 1 spray per nostril BID: 195 2) Azelastine hydrochloride nasal spray[a], 1 spray per nostril BID: 194 3) Fluticasone propionate nasal spray[b], 1 spray per nostril BID: 189 4) Placebo nasal spray, 1 spray per nostril BID: 200	The overall change from Baseline at Day 14 in combined AM+PM rTNSS
MP4006 Phase 3 49 sites in US 4/8/2009 to 8/26/2009	Randomized Double-blind Placebo-controlled Parallel group Multi-center Active-controlled 2-weeks treatment duration	Males and females, 12 years and older, with at least a 2-year history of SAR and a positive skin test to a local spring pollen	1) MP29-02 nasal spray, 1 spray per nostril BID: 451 2) Azelastine hydrochloride nasal spray[a], 1 spray per nostril BID: 449 3) Fluticasone propionate nasal spray[b], 1 spray per nostril BID: 450 4) Placebo nasal spray, 1 spray per nostril BID: 451	The overall change from Baseline at Day 14 in combined AM+PM rTNSS

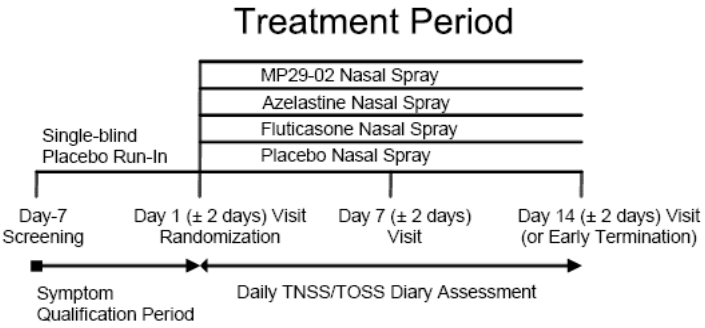
[a] Formulated as MP29-02 without fluticasone propionate.
[b] Formulated as MP29-02 without azelastine hydrochloride.

The studies MP4002, 4004, and 4006 are similar in design. The objective of these clinical trials was to compare the efficacy and safety of the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray (MP29-02) compared to placebo and to each component alone, in patients with symptomatic SAR. All treatments were administered at a dosage of 1 spray per nostril twice daily (total daily dose for MP29-02 was 548 mcg azelastine hydrochloride/ 200 mcg fluticasone propionate). The individual active controls (fluticasone propionate and azelastine hydrochloride) were formulated in the same delivery device as MP29-02.

Following a 7-day placebo run-in period, patients with allergy to prevailing individual seasonal pollen who met the minimum symptom severity requirement were randomized in a 1:1:1:1 ratio to receive MP29-02, azelastine hydrochloride, fluticasone propionate, or placebo. Patients were treated per protocol twice daily (AM and PM) for 14 days, during which they recorded nasal and ocular symptoms twice daily in a patient diary. The overall design of the study is depicted in Figure 1.

The eligible patients include male and female patients 12 years of age and older with a minimum 2-year history of SAR with a positive skin test to a local spring pollen during the previous year, who met all study inclusion/exclusion criteria, were eligible for randomization. All patients had moderate-to-severe symptomatic allergic rhinitis.

Figure 1: Study Design



3.1.2 Efficacy Endpoints and Assessment Schedule

The primary endpoint is the change from baseline to day 14 in the 12-hour reflective TNSS (combined AM+PM rTNSS) for entire double-blind period. The AM+PM rTNSS score ranges from 0 to 24.

Efficacy was assessed by patient ratings of symptom intensity as recorded in diaries for TNSS and TOSS, and by completion of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at specified intervals. Postnasal drip was scored at the same time, as a separate assessment. Patients were instructed to rate their nasal symptoms, ocular symptoms and postnasal drip, twice daily (AM and PM) in diaries prior to dosing.

The following are secondary endpoints that were evaluated:

1. Change from baseline in instantaneous TNSS (iTNSS) for the entire 14-day study period;
2. Onset of Action (in Studies MP4002, 4004, and 4006 only)
3. Change from baseline in 12-hours reflective individual symptom scores (including postnasal drip) for the entire 14-day stud period;
4. Daily change from baseline in 12-hour reflective and instantaneous TNSS;
5. Change from baseline in 12-hour reflective TOSS for the entire 14-day period;.
6. Change from baseline in 12-hour reflective and instantaneous individual ocular symptom scores for the entire 14-day study period;
7. Change from baseline to Day 14 in the RQLQ in patients 18 years of age and older;

Information recorded in the TNSS section of the diary included:

1. Runny Nose severity score
2. Sneezing severity score
3. Itchy Nose severity score
4. Nasal Congestion severity score
5. Time of dosing and number of sprays of study medications

The severity scale for TNSS symptoms and postnasal trip is defined as:

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

Information recorded in the TOSS section of the diary included:

1. Itchy eye severity score
2. Watery eye severity score
3. Eye redness severity score

The severity scale for evaluation of Itchy Eyes and Watery Eyes is same as TNSS's scale. The severity scale for Red eyes is defined as:

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

The RQLQ consisted of 7 domains which are rated on a 7-point scale with 0 being not troubled by the allergy symptoms during the past week, and 6 being extremely troubled (Table 1). The score of 9 was checked for Questions 1, 2 and 3, if the specified activity was not done. The total score for the questions within each domain was calculated. The RQLQ was only assessed at baseline and Day 14 in subjects aged 18 years and older. Domain score was calculated from the mean score of all items in the domain. Overall score was calculated from the mean score of all items and the maximum value is 6.

Table 1 Domain for RQLQ Questionnaire.

Domain	Question Numbers
Activities	1, 2, 3
Sleep	4, 5, 6
Non-nose/Eye Symptoms	7, 8, 9, 10,11,12, 13
Practical problems	14, 15, 16
Nasal symptoms	17, 18, 19, 20
Eye symptoms	21, 22, 23, 24
Emotional	25, 26, 27, 28

3.1.3 Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 2, a total of 3412 patients were enrolled at 134 centers in US; 3265 (96%) completed the 2 weeks of study. The reasons for discontinuation were similar among the 4 studies. The pooled results for reason of early discontinuation were displayed in Table 2.

Table 2: Patients' Accountability N (%)

Studies		***MP29-02***	***Azelastine***	***Fluticasone***	***Placebo***
MP4002	Randomized	207	208	207	210
	Completed	198 (96)	197 (95)	200 (97)	203 (97)
	Safety	207	208	207	210
	ITT	207	208	207	209
	PP	193 (93)	193 (93)	197 (95)	198 (94)
MP4004	Randomized	195	194	189	201
	Completed	183 (94)	186 (96)	180 (95)	190 (95)
	Safety	195	194	189	200
	ITT	193	194	189	200
	PP	180 (92)	179 (92)	173 (92)	189 (94)
MP4006	Randomized	451	449	450	451
	Completed	434 (96)	430 (96)	431 (96)	433 (96)
	Safety	451	449	450	451
	ITT	448	445	450	448
	PP	411 (91)	407 (91)	406 (90)	413 (92)
Total Randomized		853	851	846	862
Total Completed		815 (96)	813 (96)	811 (96)	826 (96)
Reason of early discontinuation (Pooled all 3 Studies)					
Adverse Event		10	6	4	9
Abnormal Test Procedure Results		0	1	0	0
Treatment Failure		1	1	2	5
Non-Compliance		1	4	10	4
Subject withdrew Consent		3	3	3	2
Lost to Follow-up		6	3	1	2
Administrative Problems		1	0	0	0
Protocol Violation		8	14	6	8
Other		8	6	9	6
Total		38 (4)	38 (5)	35 (4)	36 (4)

In general, demographic and baseline characteristics of patients were balanced among the treatment groups for each study (See Table 9, Table 9, Table 11, and Table 12 in Appendix for detail). As shown in Table 3, demographic and baseline characteristics of patients were similar across three studies. The majority of patients were Caucasian (80%) and female (64%) with median age of 36 years. The average duration of SAR history was 20 and ranged from 2 to 75 years. The mean baseline total TNSS ranged from 18.3 to 19.4 and mean baseline total TOSS ranged from 11.7 to 12.3.

Table 3: Patients' Demographic and Baseline Characteristics N (%)

	MP4002 (N=832)	***MP4004 (N=779)***	***MP4006 (N=1801)***	***Total (N=3412)***
Age (yrs)				
12 to < 18, N (%)	98 (12)	55 (7)	199 (11)	352 (10)
18 to < 65, N (%)	706 (85)	710 (91)	1557 (86)	2973 (87)
65 or older, N (%)	28 (3)	14 (2)	45 (3)	87 (3)
Mean (SD)	37.3 (14.7)	37.8 (13.5)	35.2 (14.5)	36.3 (14.4)
Median (Range)	38 (12, 77)	38 (12, 77)	34 (12, 83)	36 (12, 83)

Gender, N (%)				
Female	532 (64)	496 (64)	1102 (61)	2130 (62)
Male	300 (36)	283 (36)	699 (39)	1282 (38)
Race, N (%)				
Caucasian	655 (79)	613 (79)	1433 (80)	2701 (79)
Black	141 (17)	129 (17)	281 (16)	551 (16)
Asian	14 (2)	18 (2)	39 (2)	71 (2)
Other	22 (3)	19 (2)	48 (3)	89 (3)
Baseline total daily rTNSS (maximum value=24)				
N	831	775	1791	3397
Mean (SD)	18.3 (3.2)	18.4 (3.1)	19.4 (2.4)	18.9 (2.9)
Median (Range)	18.5 (6.7, 24)	18.6 (6.3, 24)	19.3 (7.6, 24)	19.0 (6.3, 24)
Baseline total daily iTNSS (maximum value=24)				
N	831	775	1791	3397
Mean (SD)	17.0 (4.1)	17.1 (4.0)	17.9 (3.5)	17.5 (3.8)
Median (Range)	17.3 (3.4, 24)	17.4 (5.2, 24)	18.0 (1.5, 24)	17.8 (1.5, 24)
Baseline total daily rTOSS (maximum value=18)				
N	831	775	1791	3397
Mean (SD)	11.7 (4.3)	11.7 (4.0)	12.3 (3.8)	12.0 (4.0)
Median (Range)	12.3 (0, 18)	12.4 (0, 18)	12.8 (0, 18)	12.6 (0, 18)
Baseline RQLQ (maximum value=6)				
N (N missing)	703 (123)	688 (85)	1552 (237)	3469 (524)
Mean (SD)	3.8 (0.9)	3.8 (1.0)	3.9 (1.0)	3.9 (1.0)
Median (Range)	3.9 (0.8, 6)	3.9 (0.6, 6)	3.9 (0.7, 6)	3.9 (0.6, 6)
Duration of SAR history (yrs)				
Mean (SD)	21.4 (13.6)	20.8 (13.2)	19.7 (12.7)	20.4 (13.1)
Median (Range)	18 (2, 75)	18 (2, 75)	17 (2, 68)	18 (2, 75)

3.1.4 Statistical Methodologies

The primary analysis for rTNSS is summarized as follows:

A repeated-measures analysis was performed on the primary efficacy variable to include all absolute changes in combined (AM+PM) rTNSS on each day from day 2 to day 14 as repeated measures in an analysis of covariance (ANCOVA) model for the ITT population. Note that for day 1, only the postdose PM score was available. The model contained study day as the within-patient effect, treatment group and site as the between-patient effect, and baseline as covariate. Baseline was defined as the average of all combined rTNS over the entire 7-day placebo run-in period, including the AM day 1 diary score (pre-dosing). The covariance matrix of the error terms over the treatment days was specified as unstructured and heterogeneous among treatment groups to allow all parameters to be estimated from the data and, thus, avoided potential misspecifications. A Satterthwaite approximation was applied to determine the degrees of freedom. Two-sided confidence intervals of differences in overall mean changes, ie, MP29-02 compared to placebo, MP29-02 compared to azelastine and MP29-02 compared to fluticasone propionate, were computed.

Assumptions of the ANCOVA model were checked including normality of the residuals and site by treatment interaction. Further sensitivity analyses comprised raw data analysis without imputation and analyses of the PP population. (See Appendix for detail of sensitivity analyses and analyses for other endpoints)

In order to adjust for multiplicity, a gate keeping strategy was employed by the applicant for the primary endpoint rTNSS (in all three studies) and for the secondary endpoint rTOSS (in studies 4004 and 4006).

> The MP29-02 vs. placebo comparison for rTNSS was first tested at the .05 significance level. If this was significant, then the MP29-02 vs. azelastine comparison was also done at the .05 level. If the MP29-02 – azelastine comparison was not significant at the .05 level, no comparison of MP29-02 to fluticasone was made; otherwise the comparison was made at the .05 level. Once these 3 test comparisons were shown to be significantly different in favor of MP29-02, the reflective TOSS was examined in the same order specified for TNSS. Although multiple efficacy, safety, and quality of life endpoints were examined and compared in studies, the only adjustment for multiplicity was on the primary endpoint (rTNSS), and the rTOSS.

The following describes the approach used by the applicant to handle missing data

> Missing TNSS values were imputed using the LOCF method. If a post-baseline TNSS score was missing, the last non-missing post-baseline TNSS score prior to the missing value was used for analysis (last observation carried forward, LOCF). Individual nasal symptom scores were not carried forward for calculating the total score, ie, the total score was always calculated using nasal symptom scores reported at the same time point. If any of the 4 nasal symptom scores were missing, the total score was set to missing, and then the LOCF method was used. The same methodology was applied to the TOSS assessments. The LOCF method was also applied for summaries of individual nasal symptom scores and the individual ocular symptom scores and postnasal drip score.
>
> For the RQLQ, a score of 9 for Questions 1, 2 and 3 was not included in the calculation of the total score for activity domain. For calculating domain scores and overall score, the standard scoring algorithm provided by (b) (4) was followed, including handling of missing or mismatching post-baseline activity score. Domain scores were calculated from the mean score of all items in the domain. Overall score was calculated from the mean score of all items. For missing data handling that was not specified by the standard scoring algorithm, the following rules were applied: if one score was missing, the change in domain score was calculated from the remaining scores of questions from that domain. If the score for more than one question in the domain was missing, then the domain score was set to missing. If any domain score was missing, the overall score was set to missing.

Efficacy analyses were performed on the intent-to-treat (ITT) population defined as all randomized patients with at least one post-baseline observation. As pre-specified in the protocol, missing TNSS values were imputed using the last observation carried forward (LOCF) method. Because the proportion of subjects who dropped out from treatment (and from study) is small (less than 4%), see Table 2, the amount of missing endpoint data is small. With that, we do not expect the results to be different when different imputation strategies for missing data are used.

Sample Size

For Studies MP 4002, 4004 and 4006, based on the applicant's sample size calculation, 95 patients per group were expected to provided 90% power to detect a treatment difference of 2.51 units in the absolute change from baseline over 2-weeks between MP29-02 and placebo; 195 patients per group were expected to provided 90% power to detect a treatment difference of 1.73 units in the absolute change from baseline over 2-weeks between MP29-02 and fluticasone; assuming a standard deviation of 5 units at a 2-sided and a significance level of 0.05.

The applicant changed the sample size of Study MP4002 from 600 to 780 in Amendment #2 (dated March 11, 2008) in order to increase the power from 80% to 90% and changed the sample size of Study MP4006 from 780 to 1800 in Amendment #1 (dated January 23, 2009). The applicant stated in the SCE (summary of clinical efficacy) "As a result, the Sponsor decided to increase the sample size in the design of MP4006 to 440 subjects per treatment arm to increase

the power to detect a clinically relevant difference and increase the precision of the estimates.". Protocol MP4002 was reviewed under Special Protocol Assessment (SPA), no agreement was reached.

3.1.5 Dose Selection

No dose-ranging study was conducted. The Division had a concern about the lack of flexibility of dosage titration with the fixed dose combination, and had expressed this concern with the applicant during the Pre-NDA meeting. This lack of flexibility will be evaluated in the context of the available safety information, and will be a review issue. Reader is referred to Dr. Lokesh Jain's review (the clinical pharmacology reviewer) and Dr. Jennifer Pippins's review (the clinical reviewer) for information regarding the dose selection.

3.1.6 Efficacy Results and Conclusions

Primary Efficacy Endpoint – Change from Baseline in rTNSS over 2-weeks

Treatment difference in the primary endpoint was analyzed using repeated-measures analysis of covariance by the applicant. As pre-specified in the protocol, missing TNSS values were imputed using the last observation carried forward (LOCF) method before applying the repeated measures analysis. Of note, carrying forward the last observed score for patient who drops out of the study and then applying repeated measures analysis is problematic. By applying this approach, patients will have the same score over a period of time after they dropout. In addition, patients who drop out for adverse events may have good scores carried forward even though they were not successfully treated. My comment was conveyed to the applicant in the 74 Days Letter (June, 13, 2011). In my review, I applied repeated measures analysis without imputation (i.e. one of applicant's sensitivity analyses) to evaluate the primary and secondary endpoints (TNSS and TOSS) on the ITT population. The applicant performed the same analysis in response to the 74 Day Letter (July 1, 2011).

The results based on the imputed and non-imputed results are generally similar for the primary endpoint (rTNSS).

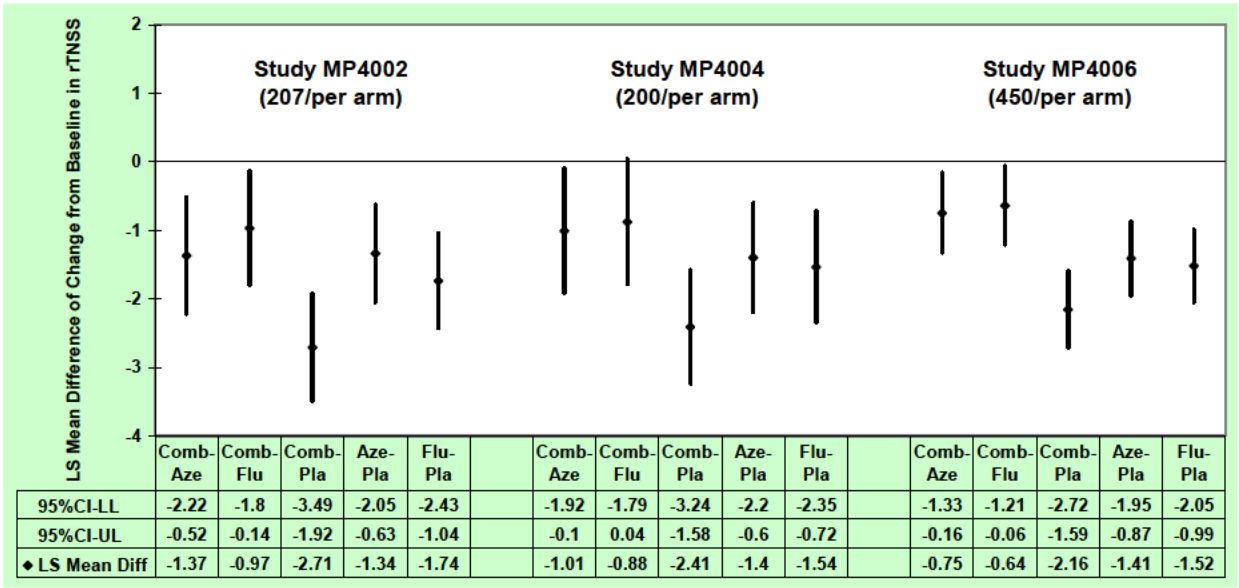
Table 4 displays the LS mean of absolute change from baseline over 2-weeks for rTNSS for all treatment groups for all three studies based on observed data. MP29-02 demonstrated statistically significant greater decrease in rTNSS than placebo and monotherapies except Study MP4004 (p=0.06). The treatment effects between MP29-02 and monotherapies and placebo ranged from 0.64 to 2.71 points with baseline score of 19 points (maximum of 24 points). All protocol pre-specified sensitivity analyses supported the primary analysis results (the results were not displayed here). Figure 2 displays the treatment difference and 95% confidence interval. The bars below zero indicate that MP29-02 is superior to the other treatment groups. As shown in Figure 3, the mean scores of rTNSS were consistently decreased over time.

Table 4: Results of Change from Baseline in rTNSS over 2-weeks (Reviewer's Analyses)

Treatment (one spray/nostril BID)	N	Baseline LS Mean (SE)	Change from Baseline LS Mean (SE)	Difference from MP29-02 LS Mean (SE)	95%CI	P value
Study MP4002						
MP29-02	207	18.27 (0.21)	-5.64 (0.33)	--	--	--
Azelastine HCl	208	18.26 (0.21)	-4.28 (0.29)	-1.37 (0.43)	(-2.22, -0.52)	0.002
Fluticasone Propionate	207	18.22 (0.21)	-4.67 (0.28)	-0.97 (0.42)	(-1.80, -0.24)	0.022
Placebo	209	18.61 (0.21)	-2.94 (0.24)	-2.71 (0.40)	(-3.49, -1.92)	<0.001
Study MP4004						
MP29-02	193	18.28 (0.22)	-5.54 (0.34)	--	--	--
Azelastine HCl	193	18.54 (0.22)	-4.53 (0.32)	-1.01 (0.46)	(-1.92, -0.10)	0.030
Fluticasone Propionate	188	18.64 (0.22)	-4.66 (0.34)	-0.88 (0.46)	(-1.79, 0.04)	0.060
Placebo	199	18.24 (0.21)	-3.12 (0.27)	-2.41 (0.42)	(-3.24, -1.58)	<0.001
Study MP4006						
MP29-02	448	19.34 (0.11)	-5.55 (0.22)	--	--	--
Azelastine HCl	443	19.47 (0.11)	-4.80 (0.21)	-0.75 (0.30)	(-1.33, -0.16)	0.012
Fluticasone Propionate	450	19.41 (0.11)	-4.91 (0.20)	-0.64 (0.29)	(-1.21, -0.06)	0.030
Placebo	448	19.44 (0.11)	-3.39 (0.19)	-2.16 (0.29)	(-2.72, -1.59)	<0.001

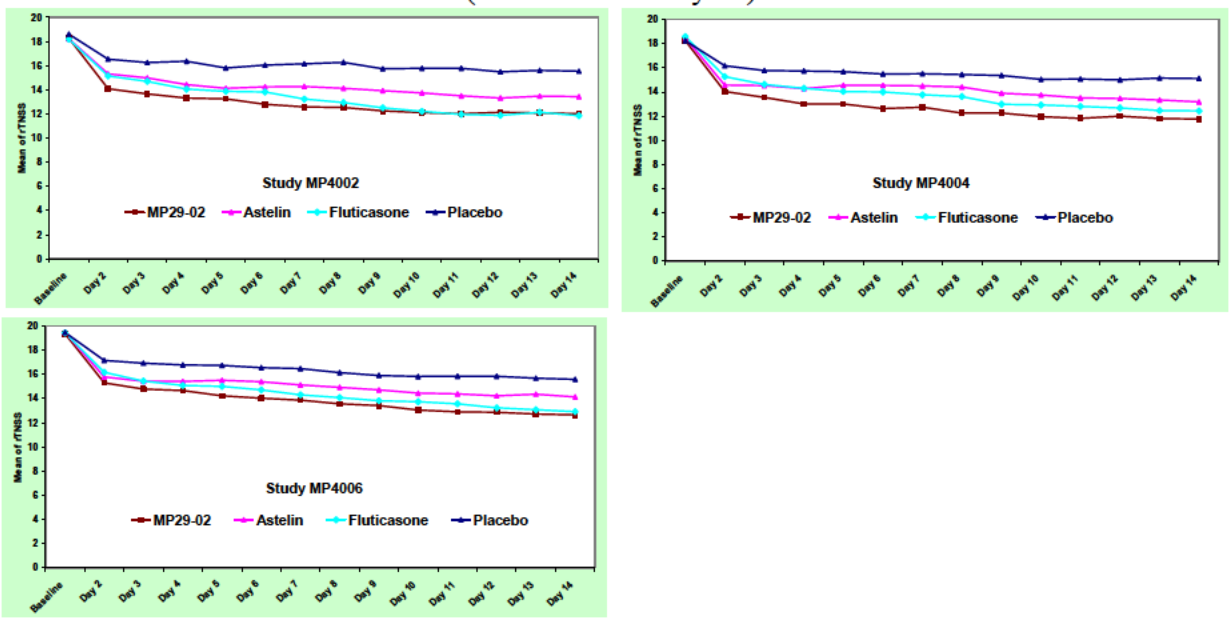
Repeated-measures analysis of covariance model contains study day as dependent variable with study day as the within-subject effect, treatment group and site as the between-subject effects, and baseline as a covariate and unspecified, heterogeneous covariance structure. Source: Diary_analy.sas;

Figure 2: Treatment Comparison of LS Mean of Change from Baseline of rTNSS over 2-Week (Reviewer's Analyses)



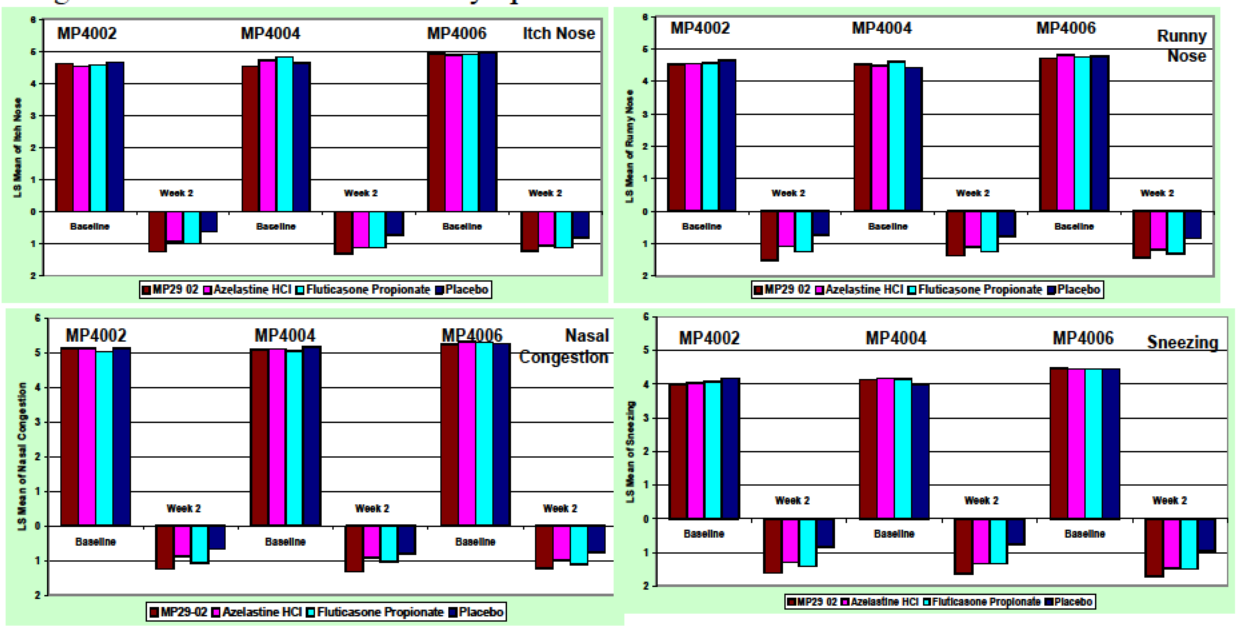
	Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla		Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla		Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla
95%CI-LL	-2.22	-1.8	-3.49	-2.05	-2.43		-1.92	-1.79	-3.24	-2.2	-2.35		-1.33	-1.21	-2.72	-1.95	-2.05
95%CI-UL	-0.52	-0.14	-1.92	-0.63	-1.04		-0.1	0.04	-1.58	-0.6	-0.72		-0.16	-0.06	-1.59	-0.87	-0.99
◆ LS Mean Diff	-1.37	-0.97	-2.71	-1.34	-1.74		-1.01	-0.88	-2.41	-1.4	-1.54		-0.75	-0.64	-2.16	-1.41	-1.52

Figure 3: Mean Score of rTNSS over 2-Week for Three Studies
(Reviewer's Analyses)



Four individual symptoms (itchy nose, nasal congestion, runny nose, and sneezing) were assessed over the course of the trial. These symptoms were assessed twice daily and combined to create the TNSS. When individual symptoms were assessed, subjects in the MP29-02 group reported greater improvements over placebo for the entire 14-day Treatment Period in every symptom evaluated, and these results were significant ($p < .001$). The benefit of the components to the efficacy of the combination was evident across all of the individual nasal symptoms. (Figure 4)

Figure 4: LS Mean of Individual Symptoms of rTNSS Score over 2-Week for three Studies



Secondary Efficacy Endpoint - Change from Baseline in iTNSS over 2-weeks

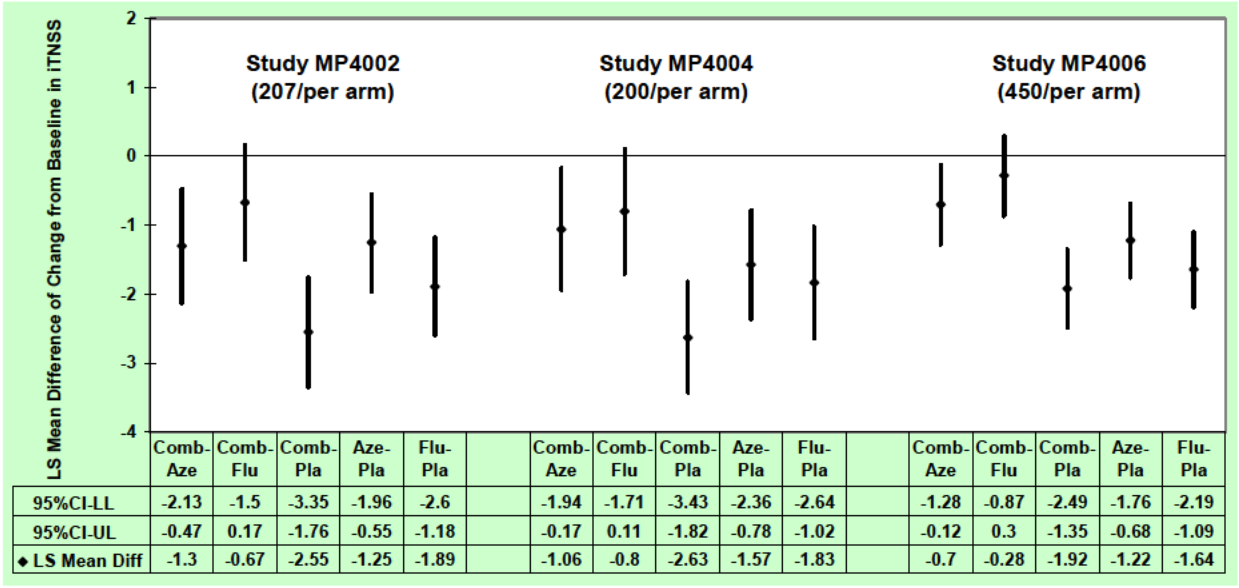
Table 5 and Figure 5 displays the LS mean of absolute change from baseline over 2-weeks for iTNSS for all treatment groups in three studies respectively. In all three studies, MP29-02 demonstrated greater decrease in iTNSS scores compared to placebo which confirm that the 12-hours dose interval is appropriate. The treatment effects between MP29-02 and Azelastine ranged from 0.7 to 1.3 points with baseline score of 18 points (maximum of 24 points).

Table 5: Results of Change from Baseline in iTNSS over 2-weeks (Reviewer's Analyses)

		Baseline	*Change from Baseline*	*Difference from MP29-02*		
Treatment (one spray/nostril BID)	***N***	***LS Mean (SE)***	***LS Mean (SE)***	***LS Mean (SE)***	***95%CI***	***P value***
Study MP4002						
MP29-02	207	17.16 (0.27)	-5.21 (0.33)	--	--	--
Azelastine HCl	208	16.84 (0.26)	-3.91 (0.28)	-1.30 (0.42)	(-2.13, -0.47)	0.002
Fluticasone Propionate	207	16.84 (0.27)	-4.54 (0.28)	-0.67 (0.42)	(-1.50, 0.17)	0.116
Placebo	209	17.26 (0.26)	-2.66 (0.24)	-2.55 (0.40)	(-3.35, -1.76)	<0.001
Study MP4004						
MP29-02	193	17.16 (0.27)	-5.19 (0.33)	--	--	--
Azelastine HCl	194	17.28 (0.27)	-4.14 (0.31)	-1.06 (0.45)	(-1.94, -0.17)	0.020
Fluticasone Propionate	188	17.19 (0.28)	-4.40 (0.34)	-0.80 (0.46)	(-1.71, 0.11)	0.084
Placebo	199	16.84 (0.27)	-2.57 (0.26)	-2.63 (0.41)	(-3.43, -1.82)	<0.001
Study MP4006						
MP29-02	448	17.91 (0.16)	-5.01 (0.22)	--	--	--
Azelastine HCl	445	18.00 (0.16)	-4.31 (0.20)	-0.70 (0.30)	(-1.28, -0.12)	0.019
Fluticasone Propionate	450	17.82 (0.16)	-4.73 (0.21)	-0.28 (0.30)	(-0.87, 0.30)	0.345
Placebo	448	17.90 (0.16)	-3.09 (0.19)	-1.92 (0.29)	(-2.49, -1.35)	<0.001

The analysis model is same as the primary efficacy analysis model. Source: Diary_analy.sas;

Figure 5: Treatment Comparison of LS Mean of Change from Baseline of iTNSS over 2-Week

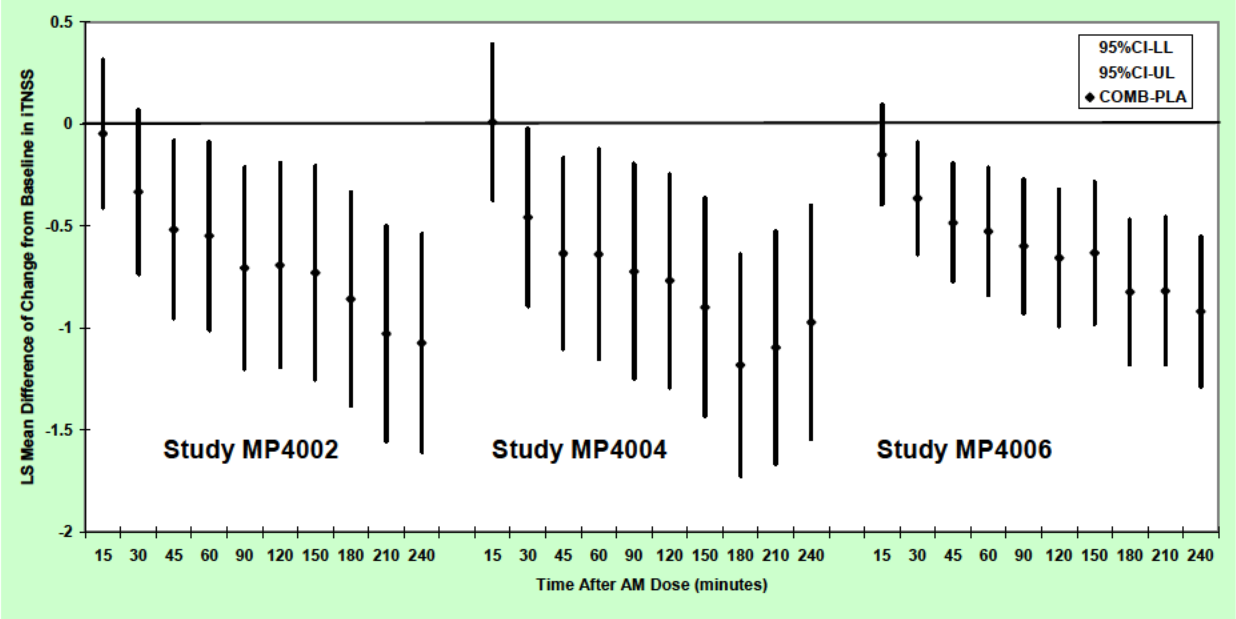


	Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla		Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla		Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla
95%CI-LL	-2.13	-1.5	-3.35	-1.96	-2.6		-1.94	-1.71	-3.43	-2.36	-2.64		-1.28	-0.87	-2.49	-1.76	-2.19
95%CI-UL	-0.47	0.17	-1.76	-0.55	-1.18		-0.17	0.11	-1.82	-0.78	-1.02		-0.12	0.3	-1.35	-0.68	-1.09
◆ LS Mean Diff	-1.3	-0.67	-2.55	-1.25	-1.89		-1.06	-0.8	-2.63	-1.57	-1.83		-0.7	-0.28	-1.92	-1.22	-1.64

Secondary Efficacy Endpoint - Onset on Action

Onset of action was assessed by measurements of instantaneous TNSS during the 4-hour period following the initial dose of study medication, and is defined as the first time point after initiation of treatment when MP29-02 demonstrated a statistically significant ($P < .05$) greater reduction from Baseline in iTNSS compared to the placebo treatment, which proved durable from this point. Two out of three studies, beginning 30 minutes after the first dose, subjects who received MP29-02 showed an improvement in TNSS was better than the improvement seen by subjects who received placebo. This difference was consistent through the end of the 4-hour evaluation period; (Figure 6).

Figure 6: Treatment Comparison of LS Mean of Change from Baseline of iTNSS over 2-Week



Secondary Efficacy Endpoint - Change from Baseline in rTOSS over 2-weeks

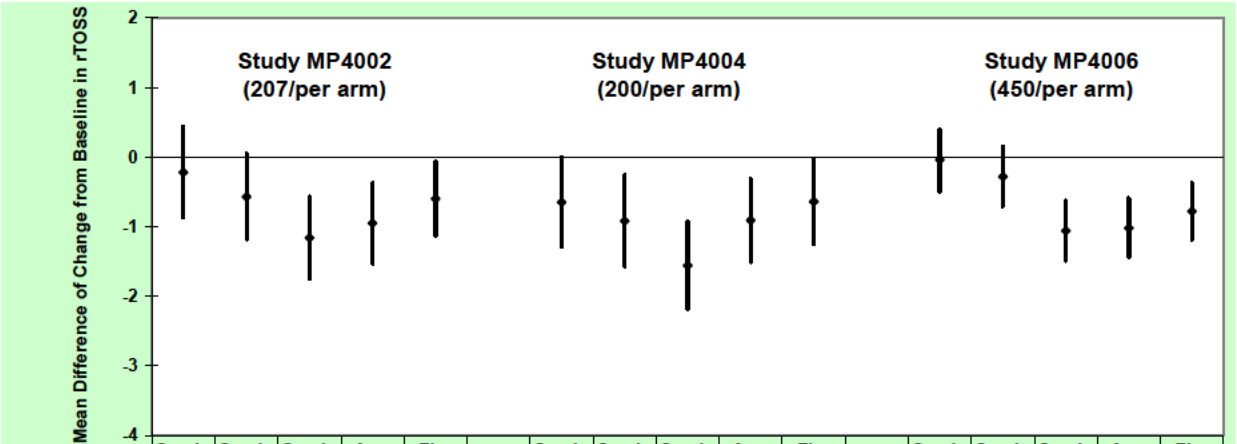
Figure 7 displays the LS mean of absolute change from baseline over 2-weeks for rTOSS for all treatment groups for all three studies respectively. MP29-02 demonstrated significant greater decrease in rTOSS compared to placebo, Azelastine, and Fluticasone propionate in Study MP4004. However, in the other two studies, only MP29-02 was significantly different to placebo, and it failed to show significant difference to Azelastine or Fluticasone propionate. Therefore, only one study showed factorial contributions of azelastine as well as fluticasone propionate to the combination, and this evidence was not replicated in the other two studies. The treatment effects between MP29-02 and placebo ranged from 1.06 to 1.56 points with baseline score of 12 points (maximum of 18 points).

Table 6: Results of Change from Baseline in rTOSS over 2-weeks (Reviewer's Analysis)

Treatment (one spray/nostril BID)	N	Baseline LS Mean (SE)	Change from Baseline LS Mean (SE)	Difference from MP29-02 LS Mean (SE)	95%CI	P value
Study MP4002						
MP29-02	207	11.88 (0.28)	-3.11 (0.25)	--	--	--
Azelastine HCl	208	11.49 (0.28)	-2.90 (0.23)	-0.22 (0.33)	(-0.87, 0.44)	0.516
Fluticasone Propionate	207	11.41 (0.28)	-2.55 (0.20)	-0.57 (0.31)	(-1.18, 0.05)	0.070
Placebo	209	12.07 (0.28)	-1.95 (0.19)	-1.16 (0.30)	(-1.75, -0.57)	<0.001
Study MP4004						
MP29-02	193	11.70 (0.28)	-3.62 (0.24)	--	--	--
Azelastine HCl	194	11.79 (0.28)	-2.97 (0.23)	-0.65 (0.33)	(-1.29, -0.00)	0.049
Fluticasone Propionate	189	12.01 (0.28)	-2.70 (0.24)	-0.92 (0.33)	(-1.57, -0.26)	0.006
Placebo	199	11.56 (0.27)	-2.06 (0.21)	-1.56 (0.32)	(-2.18, -0.93)	<0.001
Study MP4006						
MP29-02	448	12.29 (0.18)	-3.03 (0.17)	--	--	--
Azelastine HCl	445	12.40 (0.18)	-2.99 (0.16)	-0.04 (0.23)	(-0.49, 0.40)	0.845
Fluticasone Propionate	450	12.29 (0.18)	-2.76 (0.15)	-0.28 (0.22)	(-0.71, 0.15)	0.208
Placebo	448	12.22 (0.18)	-1.97 (0.15)	-1.06 (0.22)	(-1.49, -0.63)	<0.001

The analysis model is same as the primary efficacy analysis model. Source: Diary_analy.sas;

Figure 7: Treatment Comparison of LS Mean of Change from Baseline of rTOSS over 2-Week



	Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla		Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla		Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla
95%CI-LL	-0.87	-1.18	-1.75	-1.53	-1.13		-1.29	-1.57	-2.18	-1.51	-1.25		-0.49	-0.71	-1.49	-1.44	-1.19
95%CI-UL	0.44	0.05	-0.57	-0.37	-0.07		0	-0.26	-0.93	-0.31	-0.02		0.4	0.15	-0.63	-0.59	-0.37
◆ LS Mean Diff	-0.22	-0.57	-1.16	-0.95	-0.6		-0.65	-0.92	-1.56	-0.91	-0.64		-0.04	-0.28	-1.06	-1.02	-0.78

Secondary Efficacy Endpoint - Change from Baseline in RQLQ over 2-weeks

After consulting with the clinical team, it is my understanding that the division is interested in evaluating the difference in the improvement of RQLQ total scores after two weeks of treatment between MP29-02 and placebo, and not necessarily between MP29-02 and its monocomponents.

There were 9% to 19% of ITT patients across treatment groups in the three studies that were not

included in the applicant's RQLQ analyses. These patients were excluded either because they were under 18 years of age or they discontinue treatment and have no RQLQ scores over two weeks. (Table 7). There was no pattern to the missing data across treatment groups. The applicant's evaluation of RQLQ endpoint only included the observed data (

Table **8**). We commented it in the 74 Days Letter (June, 13, 2011): "*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."* The applicant acknowledged the comment regarding RQLQ analysis and noted that missing data were handled according to the algorithm provided by (b) (4) for missing or mismatching post-baseline activity scores in the 74 Day Letter (July 1, 2011).

In my review, I performed an analysis in all randomized patients aged 18 years and older. Change from baseline of RQLQ at day 14 for patients who have missing day 14 RQLQ value due to discontinuation were assigned a zero score (i.e. no change from baseline) (Figure 9). The results from the applicant's and my analyses are similar and do not change the overall conclusion. Figure 10 displays the responder profile of improvement of RQLQ from baseline in ITT population. Patients who have no day 14 RQLQ score will be coded as 0 (or non-responder). The x-axis indicates the categories of RQLQ improvement and the y-axis indicates the percentage of patients achieved different levels of response. There is separation between the MP29-02 (red line) and placebo (dark blue line), see Figure 10.

Based on the applicant's analyses of RQLQ, treatment difference in the overall score for MP29-02 compared to placebo met the minimum clinically significant difference of -0.50 with baseline score of 4 points (maximum of 6 points) in all three studies (

Table **8**). However, when I re-analyzed the data using all ITT patients, only two studies (MP4002 and MP4004) met the minimum clinically significant difference of -0.50. Nonetheless, all three studies showed highly significant treatment difference and showed consistent results. Therefore, based on the results of the analyses of RQLQ, there is evidence that MP29-02 is effective in improving the RQLQ score after 2-weeks of treatment, and is not likely due to chance.

Table 7: Patients' Who Were Excluded from the Applicant's RQLQ Analysis N (%)

	MP29-02	***Azelastine***	***Fluticasone***	***Placebo***
Study MP4002				
12 to < 18, N (%)	18 (62)	27 (84)	15 (65)	36 (92)
18 to < 65, N (%)	11 (38)	5 (16)	8 (35)	3 (8)
65 or older, N (%)	0	0	0	0
Total excluded	29 (14)	32 (15)	23 (11)	39 (19)
Study MP4004				
12 to < 18, N (%)	12 (71)	12 (63)	14 (70)	17 (59)
18 to < 65, N (%)	4 (24)	7 (37)	6 (30)	12 (41)
65 or older, N (%)	1 (6)	0	0	0
Total excluded	17 (9)	19 (10)	20 (5)	29 (15)
Study MP4002				
12 to < 18, N (%)	57 (86)	40 (78)	55 (85)	46 (84)
18 to < 65, N (%)	9 (14)	11 (22)	10 (15)	9 (16)

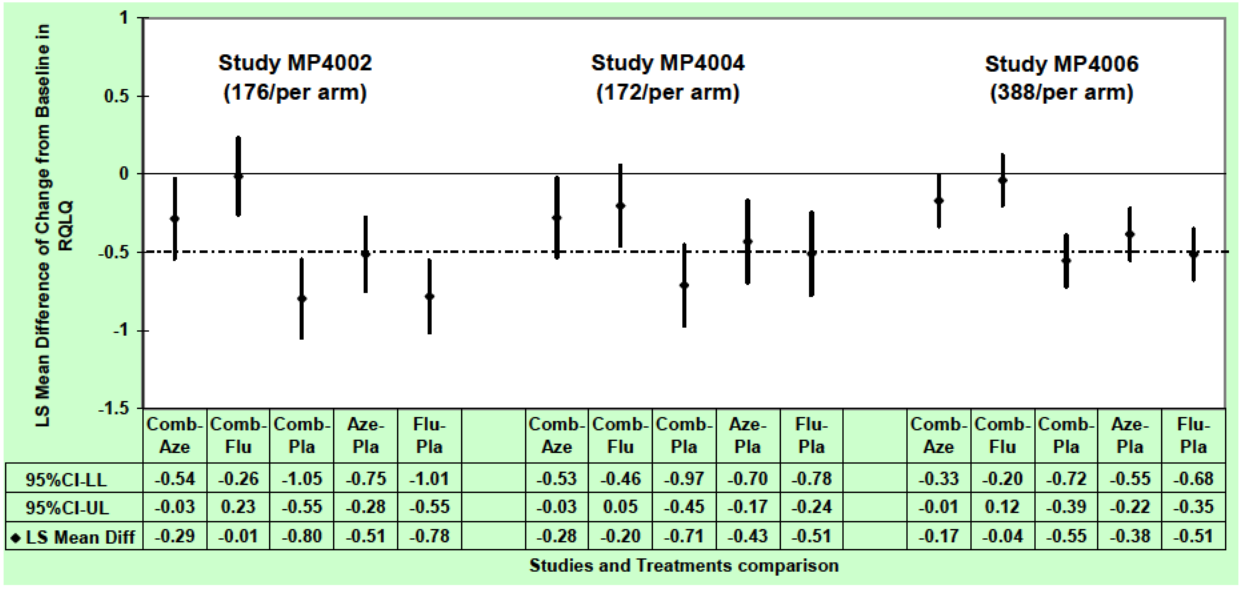
65 or older, N (%)	0	0	0	0
Total excluded	66 (15)	51 (12)	65 (14)	55 (12)

Table 8: Results of Change from Baseline in RQLQ over 2-weeks
(applicant's analysis – excluded patients with missing baseline value)

		Baseline	Change from Baseline	Difference from MP29-02		
Treatment (one spray/nostril BID)	**N**	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**P value**
Study MP4002						
MP29-02	176	3.87 (0.07)	-1.64 (0.10)	--	--	--
Azelastine HCl	174	3.80 (0.07)	-1.36 (0.09)	-0.29 (0.13)	(-0.54, -0.03)	0.029
Fluticasone Propionate	184	3.76 (0.07)	-1.63 (0.08)	-0.01 (0.13)	(-0.36, 0.23)	0.907
Placebo	169	3.87 (0.07)	-0.85 (0.08)	-0.80 (0.13)	(-1.05, -0.55)	<0.001
Study MP4004						
MP29-02	176	3.76 (0.08)	-1.68 (0.09)	--	--	--
Azelastine HCl	172	3.83 (0.07)	-1.40 (0.09)	-0.28 (0.13)	(-0.53, -0.03)	0.031
Fluticasone Propionate	169	3.78 (0.07)	-1.48 (0.10)	-0.20 (0.13)	(-0.46, 0.05)	0.123
Placebo	171	3.88 (0.07)	-0.97 (0.10)	-0.71 (0.13)	(-0.97, -0.45)	<0.001
Study MP4006						
MP29-02	381	3.87 (0.05)	-1.59 (0.06)	--	--	--
Azelastine HCl	394	3.92 (0.05)	-1.42 (0.06)	-0.17 (0.08)	(-0.33, -0.01)	0.043
Fluticasone Propionate	384	3.87 (0.05)	-1.55 (0.06)	-0.04 (0.08)	(-0.20, 0.12)	0.629
Placebo	393	3.88 (0.05)	-1.03 (0.05)	-0.55 (0.08)	(-0.72, -0.39)	<0.001

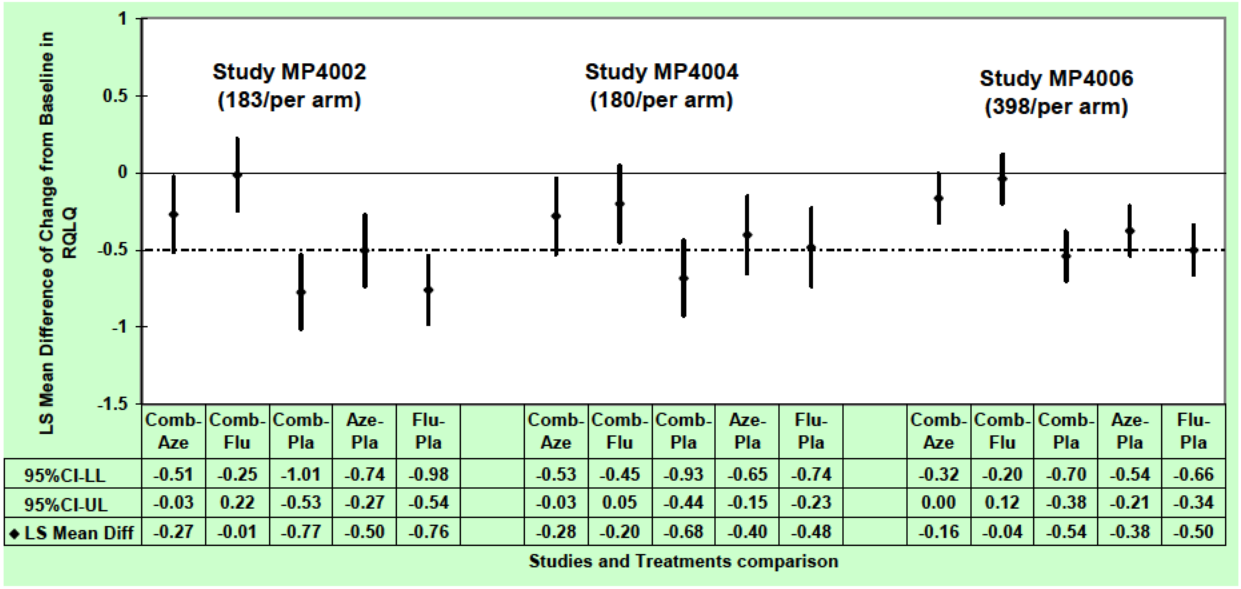
The analysis model is an ANCOVA model containing treatment group and site as fixed-effects and baseline as a covariate. Source: RQLQ_analy.sas;

Figure 8: Treatment Comparison of LS Mean of Change from Baseline of RQLQ over 2-Week
(applicant's analysis)



	Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla		Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla		Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla
95%CI-LL	-0.54	-0.26	-1.05	-0.75	-1.01		-0.53	-0.46	-0.97	-0.70	-0.78		-0.33	-0.20	-0.72	-0.55	-0.68
95%CI-UL	-0.03	0.23	-0.55	-0.28	-0.55		-0.03	0.05	-0.45	-0.17	-0.24		-0.01	0.12	-0.39	-0.22	-0.35
◆ LS Mean Diff	-0.29	-0.01	-0.80	-0.51	-0.78		-0.28	-0.20	-0.71	-0.43	-0.51		-0.17	-0.04	-0.55	-0.38	-0.51

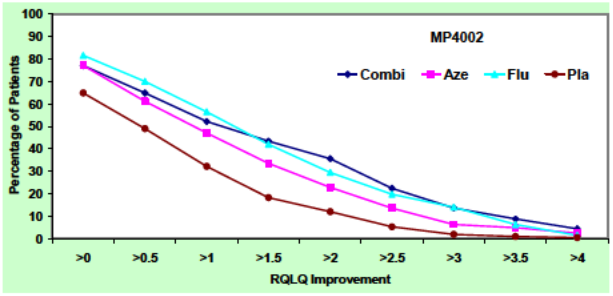
Figure 9: Treatment Comparison of LS Mean of Change from Baseline of RQLQ over 2-Week (Reviewer's analysis – ITT population (18+ years) with imputation for patients who were missing baseline value)

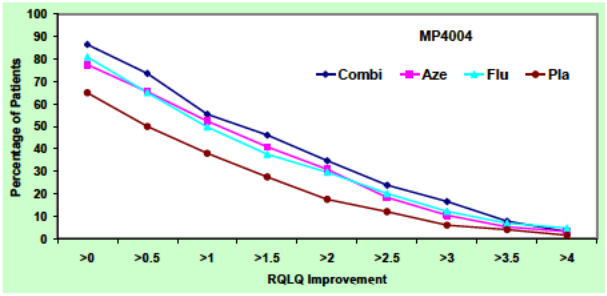


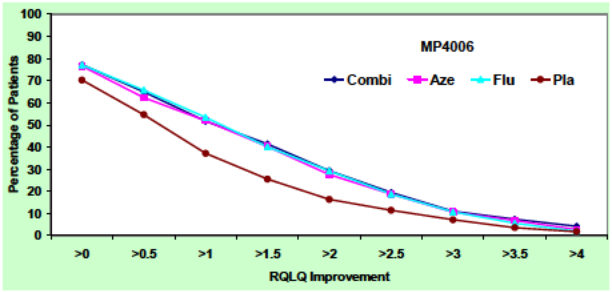
	Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla		Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla		Comb-Aze	Comb-Flu	Comb-Pla	Aze-Pla	Flu-Pla
95%CI-LL	-0.51	-0.25	-1.01	-0.74	-0.98		-0.53	-0.45	-0.93	-0.65	-0.74		-0.32	-0.20	-0.70	-0.54	-0.66
95%CI-UL	-0.03	0.22	-0.53	-0.27	-0.54		-0.03	0.05	-0.44	-0.15	-0.23		0.00	0.12	-0.38	-0.21	-0.34
◆ LS Mean Diff	-0.27	-0.01	-0.77	-0.50	-0.76		-0.28	-0.20	-0.68	-0.40	-0.48		-0.16	-0.04	-0.54	-0.38	-0.50

Studies and Treatments comparison

Figure 10: Responder Profile of Change from Baseline of RQLQ over 2-Week for Three Studies







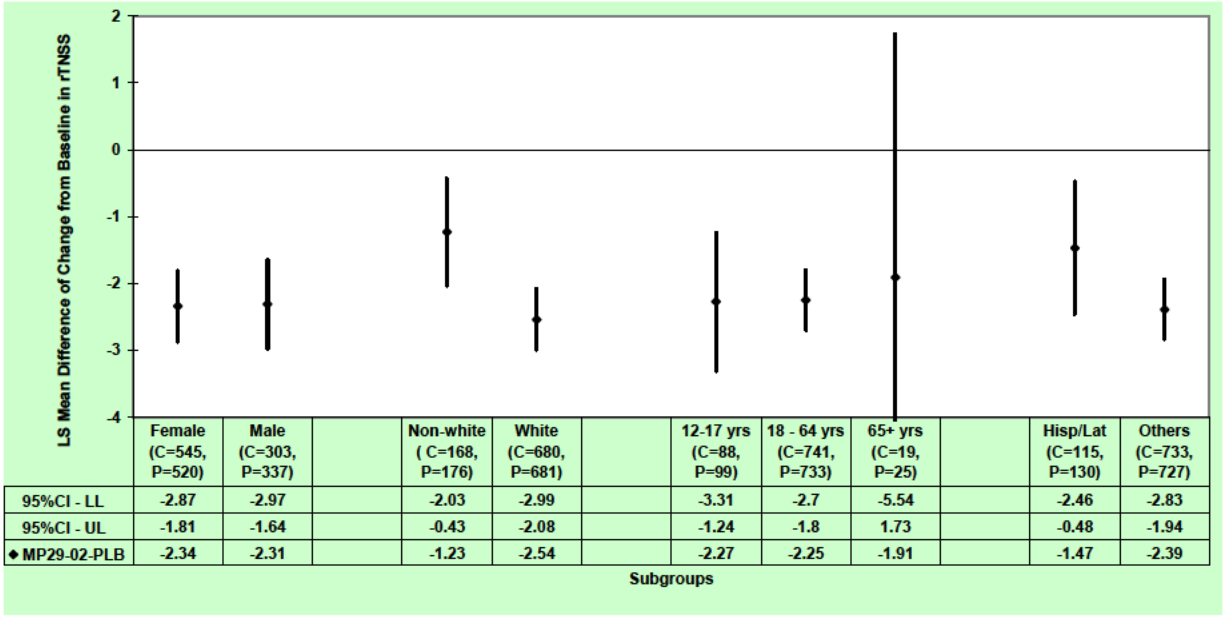
3.2 Evaluation of Safety

Dr. Jennifer Pippins, the Medical Reviewer, conducted the evaluation of the safety data separately. Reader is referred to Dr. Pippins's review for information regarding the safety profile of the drug.

4. FINDINGS IN SPECIFAL/SUBGROUP POPULATIONS

The applicant did not provide the results from subgroup analyses for each study (MP4002, MP4004, and MP4006). I performed the subgroup analysis by sex (female and male), age class (12 to <18 years, 18 to <65 years, and ≥65 years of age), and race (white and other), and ethnicity (Hispanic/Latino and no-Hispanic/Latino) based on the pooled population of studies MP4001, MP4002, MP4004, and MP4006; the results were reported in Figure 11 and Figure 12 for rTNSS and rTOSS respectively. The treatment comparison between MP29-02 and placebo among the subgroups were similar to the primary efficacy results in the ITT population.

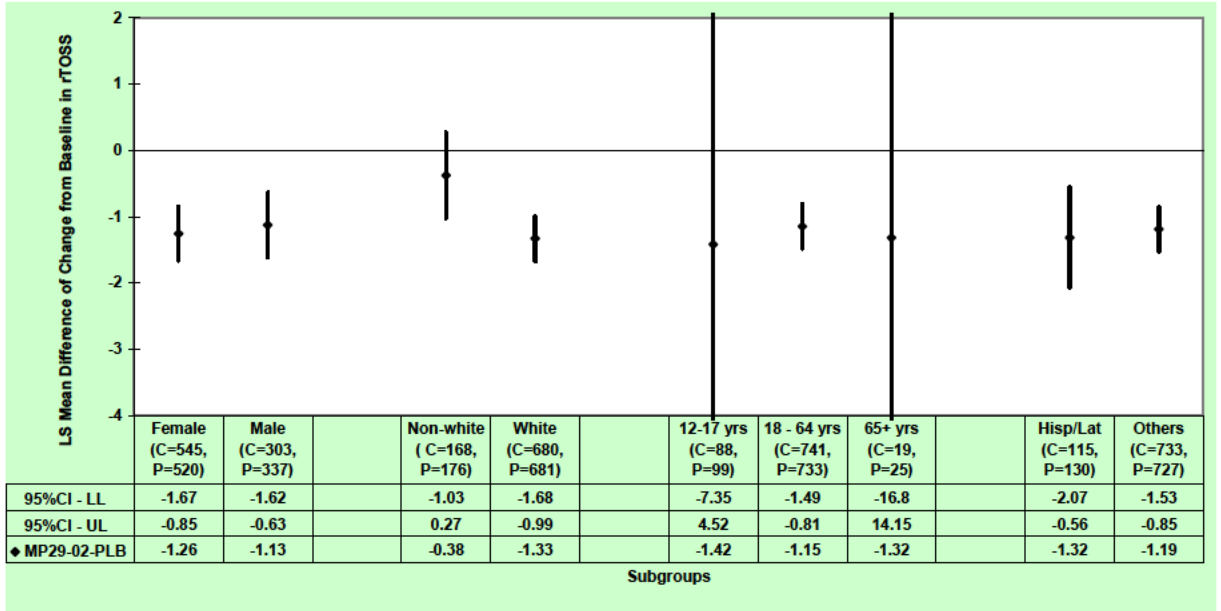
Figure 11: LS Mean Change from Baseline of rTNSS over 2-weeks by Subgroup



	Female (C=545, P=520)	Male (C=303, P=337)		Non-white (C=168, P=176)	White (C=680, P=681)		12-17 yrs (C=88, P=99)	18 - 64 yrs (C=741, P=733)	65+ yrs (C=19, P=25)		Hisp/Lat (C=115, P=130)	Others (C=733, P=727)
95%CI - LL	-2.87	-2.97		-2.03	-2.99		-3.31	-2.7	-5.54		-2.46	-2.83
95%CI - UL	-1.81	-1.64		-0.43	-2.08		-1.24	-1.8	1.73		-0.48	-1.94
◆ MP29-02-PLB	-2.34	-2.31		-1.23	-2.54		-2.27	-2.25	-1.91		-1.47	-2.39

Subgroups

Figure 12: LS Mean Change from Baseline of rTOSS over 2-weeks by Subgroup



	Female (C=545, P=520)	Male (C=303, P=337)		Non-white (C=168, P=176)	White (C=680, P=681)		12-17 yrs (C=88, P=99)	18 - 64 yrs (C=741, P=733)	65+ yrs (C=19, P=25)		Hisp/Lat (C=115, P=130)	Others (C=733, P=727)
95%CI - LL	-1.67	-1.62		-1.03	-1.68		-7.35	-1.49	-16.8		-2.07	-1.53
95%CI - UL	-0.85	-0.63		0.27	-0.99		4.52	-0.81	14.15		-0.56	-0.85
◆ MP29-02-PLB	-1.26	-1.13		-0.38	-1.33		-1.42	-1.15	-1.32		-1.32	-1.19

Subgroups

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

During my review of the clinical studies, I found no issues that that could not be resolved by re-analyzing the data. Two examples are the primary analysis model and evaluation of the RQLQ endpoint.

Treatment difference in the primary endpoint was analyzed using repeated-measures analysis of covariance by the applicant. This includes all absolute changes in AM+PM combined rTNSS on each study day from Day 2 to Day 14 as dependent variable with study day as the within-subject effect, treatment group and site as the between-subject effects, and Baseline as a covariate. The analysis was conducted on the ITT population defined as all randomized subjects with at least one post-baseline measure. The covariance matrix of the error terms over the treatment days was specified as unstructured. As pre-specified in the protocol, missing TNSS values were imputed using the last observation carried forward (LOCF) method before applying the repeated measures analysis.

Of note, carrying forward the last observed score for patient who drops out of the study and then applying repeated measures analysis is problematic. By applying this approach, patients will have the same score over a period of time after they dropout. In addition, patients who drop out for adverse events may have good scores carried forward even though they were not successfully treated. My comment was conveyed to the applicant in the 74 Days Letter (June, 13, 2011). In my review, I applied repeated measures analysis without imputation (i.e. one of the applicant's sensitivity analyses) to evaluate the primary and secondary endpoints (TNSS and TOSS) on the ITT population. The applicant performed the same analysis as response to the 74 Days Letter (July 1, 2011).

The results based on the imputed and non-imputed results are generally similar. This is expected because the proportion of subjects who dropped out from treatment (and from study) is small (less than 4%), therefore the amount of missing endpoint data is small. Therefore, we do not expect results to be different when different imputation strategies for missing data are applied. There were only 3 instances of a change in the statistical significance: Study MP4004 the comparison of combination versus fluticasone for rTNSS and iTNSS was statistically significant based on imputed scores (p=0.038 and p=0.049, respectively) but not based on raw scores (p=0.060 and p=0.084, respectively); Study MP4004 the comparison of combination versus azelastine for rTOSS was not statistically significant based on imputed scores (p=0.069) but was based on raw scores (p=0.049). However, each of these represents small numerical shifts in the pairwise differences in point estimate and does not change the overall interpretation of the results. (See Table 12 in Appendix for the details)

There were 9% to 19% of ITT patients across treatment groups in the three studies that were not included in the RQLQ analyses. Therefore, the applicant's evaluation of RQLQ endpoint only included the observed data. We commented it in the 74 Days Letter (June, 13, 2011): "*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." The applicant acknowledged the comment regarding RQLQ analysis and noted that missing data were handled according to the algorithm provided by (b) (4) for missing or mismatching post-baseline activity scores in the 74 Days Letter (July 1, 2011). Of note, majority of excluded patients in the RQLQ analysis are under the age of 18 and therefore not eligible to complete the questionnaire. In my review, I conducted an analysis in all randomized patients aged 18 years and up, and assigned a change from baseline of zero in RQLQ score at day 14 for patients who discontinue prior to day 14 (i.e. no change from baseline). . The results from the applicant's and my analyses are similar and do not change the overall conclusion.

The major efficacy findings are as follows:

- The treatment effect of MP29-02 nasal spray was measured by the change from baseline over the 14-day treatment period in combined AM+PM rTNSS. MP29-02 demonstrated statistically significant greater decrease in rTNSS than placebo and monotherapies except Study MP4004 (p=0.06). The treatment effects between MP29-02 and monotherapies and placebo ranged from 0.64 to 2.71 points with baseline score of 19 points (maximum of 24 points). All protocol pre-specified sensitivity analyses supported the primary analysis results using repeated-measures analysis of covariance based on non-imputed data. Therefore, there is replicate evidence of the superiority of MP29-02 over placebo, as well as over each of the monocomponents (ie. azelastine and fluticasone propionate).

- MP29-02 demonstrated statistically significant greater decrease in iTNSS compared to placebo and azelastine HCI only. The treatment effects between MP29-02 and azelastine HCI and placebo ranged from 0.70 to 2.63 points with baseline score of 18 points (maximum of 24 points).

- MP29-02 demonstrated statistically significant greater decrease in rTOSS than placebo in all three studies and fluticasone propionate and azelastine HCI only in one study (MP4004). The treatment effects between MP29-02 and placebo ranged from 1.06 to 1.56 points with baseline score of 12 points (maximum of 18 points). MP29-02 was numerically better than azelastine HCI in two studies. Although there is evidence that MP29-02 is superior to placebo in the ocular symptom endpoint (rTOSS), only one study showed factorial contributions of azelastine as well as fluticasone propionate to the combination, and this evidence was not replicated in the other two studies.

- Onset of action was a secondary endpoint for studies MP4002, MP4004, and MP4006. Beginning 45 minutes after the first dose, subjects who received MP29-02 in study MP4002 showed an improvement in iTNSS that was significantly better than the improvement seen by subjects who received placebo. For studies MP4004 and MP4006, a significant improvement over placebo was seen at 30 minutes in subjects who received MP29-02. For all studies, the significant improvement in MP29-02 over placebo was maintained at each time-point through the end of the 4-hour time course.

- In all three studies, the treatment difference in the overall RQLQ score for MP29-02 compared to placebo met the minimum clinically significant difference of -0.50 with

baseline score of 4 points (maximum of 6 points). Therefore, there is evidence that MP29-02 is effective in improving the RQLQ score after 2-weeks of treatment in patients 18 years and older.

5.2 Conclusions and Recommendations

My statistical review of the clinical studies supports the claim of relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. In all three studies, there is evidence that Dymista is effective in decreasing rTNSS compared to placebo, as well as to each monotherapy. There is also evidence that Dymista is effective in improving the quality-of-life compared to placebo, and the observed effects met the minimum clinically significant difference of -0.50. The onset of action was observed at 30 minutes following the initial dose of Dymista.

(b) (4)

6. LABELING

Based on review of the submitted data, I have some comments and edits to the proposed label under Section 14.

14 CLINICAL STUDIES

(b) (4)

2 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

7. APPENDIX

Table 9: Patients' Demographic and Baseline Characteristics N (%), Study MP4002

ITT Population		MP29-02	Azelastine	Fluticasone	Placebo
Demographics	**Category/Statistics**	**(N = 207)**	**(N = 208)**	**(N = 207)**	**(N = 209)**
Age (Years)	N	207	208	207	209
	Mean	37.3	36.2	38.6	37.3
	Standard Deviation	14.07	14.56	14.14	16.01
	Median	38.0	36.5	39.0	39.0
	Min - Max	12 - 77	12 - 77	12 - 76	12 - 74
	12 to < 18 [n (%)]	19 (9.2)	28 (13.5)	15 (7.2)	36 (17.2)
	18 to < 65 [n (%)]	183 (88.4)	172 (82.7)	185 (89.4)	165 (78.9)
	65 or older [n (%)]	5 (2.4)	8 (3.8)	7 (3.4)	8 (3.8)
Gender [n (%)]	Male	65 (31.4)	78 (37.5)	80 (38.6)	77 (36.8)
	Female	142 (68.6)	130 (62.5)	127 (61.4)	132 (63.2)
Race [n (%)]	White	162 (78.3)	162 (77.9)	161 (77.8)	169 (80.9)
	Black	34 (16.4)	37 (17.8)	38 (18.4)	32 (15.3)
	Asian	5 (2.4)	2 (1.0)	4 (1.9)	3 (1.4)
	Native Hawaiian or Other Pacific Islander	1 (0.5)	2 (1.0)	1 (0.5)	0 (0.0)
	American Indian or Alaska Native	1 (0.5)	0 (0.0)	2 (1.0)	0 (0.0)
	Other	4 (1.9)	5 (2.4)	1 (0.5)	5 (2.4)
Total Daily Reflective TNSS[a]	N	207	208	207	209
	Mean	18.3	18.2	18.2	18.6
	Standard Deviation	3.04	3.54	3.23	3.17
	Median	18.3	18.6	18.4	18.7
	Min - Max	9 - 24	7 - 24	9 - 24	8 - 24
Baseline Reflective TOSS[a]	N	207	208	207	209
	Mean	11.88	11.45	11.38	12.08
	Standard Deviation	3.902	4.539	4.418	4.284
	Median	12.18	12.35	12.00	12.33
	Min - Max	0.7 – 18	0.1 – 18	0 – 18	0 - 18
Duration of SAR History (Years)	N	207	208	207	209
	Mean	21.7	21.6	21.3	21.2
	Standard Deviation	13.24	13.61	13.46	14.03
	Median	19.0	18.0	20.0	17.0
	Min - Max	2 - 62	2 - 75	2 - 74	2 - 60

[a] Mean daily baseline scores over 7-day Lead-in Period, including Day 1 AM.

Table 10: Patients' Demographic and Baseline Characteristics N (%), Study MP4004

ITT Population		MP29-02	Azelastine	Fluticasone	Placebo
Demographics	Category/Statistics	(N = 193)	(N = 194)	(N = 189)	(N = 200)
Age (Years)	N	193	194	189	200
	Mean	38.8	38.2	37.0	37.2
	Standard Deviation	14.08	13.49	13.63	13.03
	Median	38.0	38.0	38.0	40.0
	Min - Max	12 - 73	12 - 77	12 - 72	12 - 68
	12 to < 18 [n (%)]	12 (6.2)	12 (6.2)	14 (7.4)	17 (8.5)
	18 to < 65 [n (%)]	176 (91.2)	178 (91.8)	172 (91.0)	181 (90.5)
	65 or older [n (%)]	5 (2.6)	4 (2.1)	3 (1.6)	2 (1.0)
Gender [n (%)]	Male	67 (34.7)	66 (34.0)	68 (36.0)	81 (40.5)
	Female	126 (65.3)	128 (66.0)	121 (64.0)	119 (59.5)
Race [n (%)]	White	154 (79.8)	153 (78.9)	140 (74.1)	164 (82.0)
	Black	30 (15.5)	35 (18.0)	38 (20.1)	25 (12.5)
	Asian	5 (2.6)	3 (1.5)	4 (2.1)	6 (3.0)
	Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
	American Indian or Alaska Native	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
	Other	4 (2.1)	1 (0.5)	5 (2.6)	5 (2.5)
Total Daily Reflective TNSS[a]	N	193	194	189	199
	Mean	18.2	18.5	18.6	18.2
	Standard Deviation	3.34	3.15	2.92	3.07
	Median	18.4	18.7	18.9	18.5
	Min - Max	6 - 24	9 - 24	10 - 24	7 - 24
Total Daily Reflective TOSS[a]	N	193	194	189	199
	Mean	11.67	11.75	11.98	11.58
	Standard Deviation	4.162	3.892	3.800	4.138
	Median	12.38	12.32	12.77	12.13
	Min - Max	0.4 – 18	0 – 18	0.7 – 18	0 - 18
Duration of SAR History (Years)	N	193	194	189	200
	Mean	21.5	19.7	21.1	21.0
	Standard Deviation	13.51	13.05	13.65	12.82
	Median	18.0	16.0	19.0	18.0
	Min - Max	3 - 61	2 - 75	2 - 61	3 - 58

[a] Mean daily baseline scores over 7-day Lead-in Period, including Day 1 AM.

Table 11: Patients' Demographic and Baseline Characteristics N (%), Study MP4006

ITT Population		MP29-02	Azelastine	Fluticasone	Placebo
Demographics	Category/Statistics	(N = 448)	(N = 445)	(N = 450)	(N = 448)
Age (Years)	N	448	445	450	448
	Mean	35.6	36.4	34.2	34.7
	Standard Deviation	14.53	14.83	14.45	14.05
	Median	36.0	35.0	32.0	34.0
	Min - Max	12 – 78	12 – 83	12 – 70	12 – 77
	12 to < 18 [N (%)]	57 (12.7)	38 (8.5)	56 (12.4	46 (10.3)
	18 to < 65 [N (%)]	382 (85.3)	390 (87.6)	390 (86.7)	387 (86.4)
	65 or older [N (%)]	9 (2.0)	17 (3.8)	4 (0.9)	15 (3.3)
Gender [n (%)]	Male	171 (38.2)	174 (39.1)	170 (37.8)	179 (40.0)
	Female	277 (61.8)	271 (60.9)	280 (62.2)	269 (60.0)
Race [n (%)]	White	364 (81.3)	357 (80.2)	356 (79.1)	348 (77.7)
	Black	70 (15.6)	62 (13.9)	73 (16.2)	75 (16.7)
	Asian	8 (1.8)	12 (2.7)	8 (1.8)	10 (2.2)
	Native Hawaiian or other Pacific Islander	2 (0.4)	4 (0.9)	6 (1.3)	2 (0.4)
	American Indian or Alaska Native	0 (0.0)	1 (0.2)	1 (0.2)	3 (0.7)
	Other	4 (0.9)	9 (2.0)	6 (1.3)	10 (2.2)
Total Daily Reflective TNSS [a]	N	448	445	450	448
	Mean	19.4	19.5	19.4	19.5
	Standard Deviation	2.43	2.52	2.38	2.36
	Median	19.3	19.3	19.3	19.3
	Min - Max	8 – 24	12 – 24	11 – 24	12 – 24
Total Daily Reflective TOSS [a]	N	448	445	450	448
	Mean	12.30	12.42	12.32	12.22
	Standard Deviation	4.013	3.990	3.623	3.717
	Median	12.79	13.25	12.58	12.83
	Min - Max	0 – 18	0 – 18	0 – 18	0.6 – 18
Duration of SAR History (Years)	N	448	445	450	448
	Mean	20.4	19.5	19.6	19.6
	Standard Deviation	13.04	12.88	12.45	12.39
	Median	17.0	16.0	17.0	16.0
	Min - Max	2 – 64	2 – 65	2 – 58	2 - 68

[a] Mean daily baseline scores over 7-day Single-blind Treatment Period, including Day 1 AM.

Table 12: Summary of Pairwise Comparisons Resulting from Repeated Measures Analysis Using Imputed Scores or Raw Scores

			Analysis Results Based on Imputed Scores*			Analysis Results Based on Raw Scores		
			CvF	CvA	CvP	CvF	CvA	CvP
4001	rTNSS*	Delta	-1.47	-2.06	-3.11	-1.45	-2.09	-3.12
		p-value	*.003*	*<.001*	*<.001*	*.003*	*<.001*	*<.001*
	iTNSS	Delta	-0.98	-1.42	-2.76	-0.89	-1.50	-2.79
		p-value	*.043*	*.003*	*<.001*	*.066*	*.001*	*<.001*
	rTOSS	Delta	-1.17	-0.72	-2.02	-0.96	-0.60	-1.96
		p-value	*.002*	*.071*	*<.001*	*.009*	*.123*	*<.001*
4002	rTNSS*	Delta	-0.90	-1.38	-2.69	-0.97	-1.36	-2.70
		p-value	*.034*	*.001*	*<.001*	*.022*	*.002*	*<.001*
	iTNSS	Delta	-0.71	-1.26	-2.59	-0.67	-1.30	-2.55
		p-value	*.100*	*.003*	*<.001*	*.116*	*.002*	*<.001*
	rTOSS	Delta	-0.52	-0.25	-1.17	-0.57	-0.22	-1.16
		p-value	*.097*	*.457*	*<.001*	*.070*	*.516*	*<.001*
4004	rTNSS*	Delta	-0.99	-1.00	-2.51	-0.88	-1.01	-2.42
		p-value	*.038*	*.032*	*<.001*	*.060*	*.030*	*<.001*
	iTNSS	Delta	-0.94	-1.00	-2.78	-0.80	-1.06	-2.63
		p-value	*.049*	*.029*	*<.001*	*.084*	*.020*	*<.001*
	rTOSS	Delta	-0.88	-0.60	-1.54	-0.92	-0.65	-1.56
		p-value	*.009*	*.069*	*<.001*	*.006*	*.049*	*<.001*
4006	rTNSS*	Delta	-0.64	-0.71	-2.13	-0.64	-0.75	-2.16
		p-value	*.029*	*.016*	*<.001*	*.030*	*.012*	*<.001*
	iTNSS	Delta	-0.28	-0.67	-1.92	-0.28	-0.70	-1.92
		p-value	*.348*	*.026*	*<.001*	*.345*	*.019*	*<.001*
	rTOSS	Delta	-0.25	-0.03	-1.07	-0.28	-0.04	-1.06
		p-value	*.247*	*.912*	*<.001*	*.208*	*.845*	*<.001*

C=Combination MP29-02, F=Fluticasone, A=Azelastine, P=Placebo

*The pre-stated primary efficacy endpoint in every study was rTNSS analyzed using imputed scores.

Appendix: Analysis Methods for Primary and Secondary Endpoints

Additional sensitivity analyses for the primary endpoint were performed on the ITT population and for LOCF, and it includes applying analysis of covariance (ANCOVA) model to compare scores over the entire 14-day study period. A reduced model without factor treatment day was used for the analyses by day. The analyses were done for both the combined AM and PM scores and for the AM and PM scores separately.

The following describes the analysis plan for the secondary endpoints. Of note, the analyses were based on absolute change from baseline and respective percent change:

- Further Analyses of 12-hour Reflective TNSS: Treatment comparison was performed by Day. Moreover, P values based on paired t-test were calculated for within-patient changes from baseline to each day postbaseline by treatment group.
- 12-hour Instantaneous TNSS: Analyses were conducted for the entire 14-day study period and by day.
- Onset of Action: Onset of action was evaluated based on periodic measurements of iTNSS during the 4-hour period following the initial dose of study medications for the ITT population. Onset of action was defined as the first time point after initiation of treatment when the drug demonstrated a greater reduction from baseline in iTNSS compared to eh placebo treatment that proved durable from this point. This endpoint was assessed in three of the four studies (MP4002, 4004, and 4006).
- 12-hour Reflective TOSS: Analyses were conducted for the entire 14-day study period and by day.
- 12-hour Instantaneous TOSS: Analyses were conducted for the entire 14-day study period and by day.
- Individual Symptom Scores: Individual nasal and ocular symptom scores were analyzed for the entire 14-day study period and by day. Here, only the combined scores were analyzed.
- 12-hour Reflective Postnasal Drip: Analyses were conducted for the entire 14-day study period and by day.
- Rhinoconjunctivitis Quality of Life Questionnaire: The total score as well as domains were analyzed by applying an ANCOVA model as for the other by-day analyses.

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SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Feng Zhou, M.S.

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/s/

FENG ZHOU
12/27/2011

JOAN K BUENCONSEJO
12/28/2011

I concur with Feng Zhou's conclusion and recommendation for NDA 202236 supporting the claim of relief of symptoms of SAR in patients 12 years and older.