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/BLA #:	NDA 22-203
Supplement #:	0050
Drug Name:	Astepro (azelastine hydrochloride) Nasal Spray
Indication(s):	Perennial Allergic Rhinitis in children ages ≥6 to <12
Applicant:	MEDA Pharmaceuticals
Date(s):	Submission Date: July 17, 2012
	PDUFA Date: September 6, 2013
Review Priority:	Standard
Biometrics Division:	DB2
Statistical Reviewer:	Ruthanna Davi, Ph.D., Statistical Reviewer
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Keywords: pediatrics

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1 EXECUTIVE SUMMARY

The phase 3 study provided demonstrates a statistically significant effect on the primary efficacy endpoint, the change from baseline in the 12-hour reflective TNSS (AM and PM combined) over the 28-day treatment period, for both MP03-36 and MP03-33 relative to placebo. The magnitude of the benefit of MP03-36 over placebo is estimated to be 1.0 unit with a 95% confidence interval from 0.3 to 1.7. The magnitude of the benefit of MP03-33 over placebo is estimated to be 0.9 units with a 95% confidence interval from 0.2 to 1.6. Analysis of individual symptoms from the rTNSS indicated that no single symptom appeared to be overly-influential in these primary efficacy results. In addition, no reversals in any individual component of the rTNSS score were noted.

No significant difference between either MP03-36 and placebo or MP03-33 and placebo in the key secondary efficacy endpoint, the change from baseline in 12-hour reflective TOSS (AM and PM combined) over the 28-day treatment period, was identified.

No statistically significant differences in the treatment effect in terms of the primary efficacy endpoint across age, gender, race (white/other), or seasonal allergic rhinitis classification (positive/negative) categories were identified.

2 INTRODUCTION

Astepro Nasal spray received FDA approval on August 31, 2009 for the treatment of seasonal and perennial allergic rhinitis in patients aged 12 years and older. The Pediatric Research Equity Act (PREA) and the complete response letter associated with the referenced approval require, as a post-marketing commitment, a confirmatory efficacy and safety study of Astepro for the treatment of perennial and/or seasonal allergic rhinitis in pediatric patients aged 6 years to less than 12 years.

2.1 Overview

In the current submission, the sponsor has provided the results of a single phase 3 study titled, "Randomized, Double-blind, Placebo-Controlled Trial of the Safety and Efficacy of MP03-36 (0.15% solution) and MP03-33 (0.1% solution) in Children Ages ≥6 to <12 with Perennial Allergic Rhinitis" and numbered MP441, to fulfill the post-marketing requirement for an efficacy and safety study of Astepro for treatment of perennial and/or seasonal allergic rhinitis in pediatric patients aged 6 years to less than 12 years.

Communication with the sponsor regarding this protocol is documented under IND 69785. The pediatric clinical study protocol and protocol amendments were submitted for review on July 1, 2009 (as a Special Protocol Assessment), October 21, 2009 and September 20, 2010. Statistical review of the protocol was conducted and is dated August 13, 2009. No agreement on the Special Protocol Assessment was granted. Comments regarding this protocol were sent to the

sponsor on August 14, 2009 and April 20, 2010. Statistical comments were made with regard to the definition of the intent-to-treat (ITT) population, adjusting for multiplicity in doses, and agreement that the last-observation-carried-forward (LOCF) imputation for missing data was appropriate as long as the early discontinuation rate was less than 12.5% otherwise different imputation methods were to be considered. With the exception of the LOCF imputation, all of these comments were implemented by the sponsor in study MP441. (The reader is referred to section 3.2.2 of this document for description of the missing data methods pre-specified in the final protocol and statistical analysis plan.)

2.2 Data Sources

The study report, protocol, and statistical analysis plan for study MP441 were utilized in the review of this submission. The following data sets were submitted electronically and utilized in the review of this submission.

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality and integrity of the submitted data (i.e. study report, protocol, statistical analysis plan, and electronic data sets) were adequate for review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study MP441 was a randomized, double-blind, parallel-group study in pediatric subjects 6 to 12 years of age with moderate-to-severe symptomatic perennial allergic rhinitis (PAR). The objective of this study was to compare the efficacy and safety of each of MP03-36 and MP03-33 to placebo.

After a seven-day single-blind placebo run-in period (used to evaluate symptom severity and compliance with reporting for subject eligibility), subjects were randomly assigned (stratified by age, 6 to <9 years of age versus 9 to <12 years of age) to one of the following three treatment groups for the four-week double-blind treatment period.

- MP03-36 (0.15% solution) formulation, 1 spray per nostril twice daily (AM & PM)
- MP03-33 (0.10% solution) formulation, 1 spray per nostril twice daily (AM & PM)
- Placebo nasal spray, 1 spray per nostril twice daily (AM & PM)

The primary efficacy variable was the change from baseline in the 12-hour combined AM+PM reflective total nasal symptom score (rTNSS) for the entire 4-week study period. Subjects/caregivers were to record symptom scores twice daily, once prior to the AM dose and once prior to the PM dose of study medication on each study day. For reflective scores, subjects were asked to rate their symptoms over the past 12 hours. Individual symptoms/signs of the rTNSS were each scored on a 4-point scale where 0=no symptoms, 1=mild symptoms, 2=moderate symptoms, and 3=severe symptoms. Symptoms contributing to the rTNSS were runny nose, sneezing, nasal itching, and nasal congestion. The maximum combined AM and PM TNSS was 24. Baseline rTNSS was defined as the average of all non-missing rTNSS over the last 3.5 days of the placebo run-in period.

The key secondary efficacy variable was the change from baseline in the 12-hour combined AM+PM reflective total ocular symptom scores (rTOSS) for the entire 4-week study period. Symptoms contributing to the rTOSS were itchy eyes, watery eyes, and eye redness. The maximum combined AM and PM rTOSS was 18.

3.2.2 Statistical Methodologies

The protocol specified that the efficacy analyses were to be performed using the intent-to-treat population (ITT) defined as all randomized subjects with at least one post-baseline efficacy observation. The primary analyses of the primary efficacy variable, rTNSS, and the key secondary efficacy variable, rTOSS, were protocol-defined as a mixed model for repeated measures (MMRM) with baseline as a covariate and no imputation for missing values as long as the early discontinuation rate did not exceed 12.5%. Subsequently but also prior to study unblinding, the statistical analysis plan specified the use of categorical effects for treatment, day, age group (stratification factor), and site as well as an unstructured covariance matrix which was to be allowed to vary among treatment groups. If convergence was not achieved with the unstructured covariance matrix, a compound symmetry covariance matrix was to be assumed. Data from subjects randomized into all three treatment groups were to be included in these analyses and the comparison for each of MP03-36 and MP03-33 to placebo was to be made using contrasts.

In order to adjust for multiplicity in dose and endpoints, a gate-keeping strategy was pre-specified. Each of the following comparisons were to be conducted in the following order using a two-sided α=0.05. Each analysis was to be considered confirmatory only if the preceding analyses were statistically significant.

- Comparison of 12-hour combined AM+PM rTNSS between MP03-36 and placebo
- Comparison of 12-hour combined AM+PM rTNSS between MP03-33 and placebo
- Comparison of 12-hour combined AM+PM rTOSS between MP03-36 and placebo
- Comparison of 12-hour combined AM+PM rTOSS between MP03-33 and placebo

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

As described in Table 1, 489 subjects were randomized in a 1:1:1 ratio stratified by age group (6 to <9 years of age versus 9 to <12 years of age) to receive MP03-36, MP03-33, and placebo. Two MP03-36 and one placebo subject are not included in the ITT group since they did not report any post-baseline efficacy data. Early study discontinuation was fairly infrequent and relatively balanced across treatment groups and therefore is not expected to have substantially impacted the primary or key secondary efficacy analyses.

Subject disposition within each age category was also examined. No substantial differences in the disposition of subjects within each age group from that of the overall group were identified (data not shown).

Table 1: Subject Disposition (ITT)

	MP03-36	MP03-33	Placebo
All Randomized n (%)	161 (100%)	166 (100%)	162 (100%)
Intent-to-Treat Population* n (%)	159 (99%)	166 (100%)	161 (99%)
Early Study Discontinuation n (%)	13 (8%)	10 (6%)	16 (10%)
Adverse Event	2		6
Treatment Failure	1		2
Protocol Violation	1	3	3
Non-Compliance		1	
Subject Withdrew Consent	1	2	1
Lost to Follow-up	3	1	
Administrative Problems	3	3	4
Other	2		

*ITT is protocol defined as all subjects who were randomized with at least one post-baseline efficacy observation

Subject demographics and baseline characteristics for the ITT group are presented in Table 2. As would be expected since study treatment was randomly assigned, the three treatment groups were comparable with regard to demographic and baseline clinical characteristics.

Subject demographics and baseline characteristics within each age category were also examined. Demographics and baseline characteristics of subjects within each age group were found to be consistent with that of the overall group (data not shown).

Table 2: Subject Demographics* (ITT)

		MP03-36 (N=159)	MP03-33 (N=166)	Placebo (N=161)
Age	**Mean**	9	9	9
	Range	6 to 11	6 to 12	6 to 12
	6 to <9 [n (%)]	68 (43%)	72 (43%)	71 (44%)
	9 to <12 [n (%)]	91 (57%)	94 (57%)	90 (56%)
Gender [n (%)]	**Male**	86 (54%)	101 (61%)	93 (58%)
	Female	73 (46%)	65 (39%)	68 (42%)
Race [n (%)]	**White**	131 (82%)	129 (78%)	119 (74%)
	Black	17 (11%)	25 (15%)	20 (12%)
	Asian	4 (3%)	3 (2%)	9 (6%)
	Native Hawaiian or Other Pacific Islander	1 (1%)	0 (0%)	1 (1%)
	American Indian or Alaska Native	0 (0%)	1 (1%)	1 (1%)
	Other	6 (4%)	8 (5%)	11 (7%)
Baseline rTNSS	**Mean**	17	17	16
	Standard dev.	3.4	3.4	3.1
Baseline rTOSS	**Mean**	7	7	7
	Standard dev.	4.9	4.9	4.8
Duration of PAR History (yrs)	**Mean**	5	6	5
	Range	1 to 11	1 to 11	1 to 11
SAR Skin Test Result [n (%)]	**Positive**	77 (48%)	83 (50%)	92 (57%)
	Negative	43 (27%)	43 (26%)	37 (23%)
	Not Done	39 (25%)	40 (24%)	32 (20%)

*Small amount (<2%) of missing data for certain endpoints ignored in calculations.

3.2.4 Results and Conclusions

The pre-specified primary efficacy analysis, as provided by the sponsor is shown in Table 3. An additional FDA analysis of the primary efficacy endpoint conducted using slightly different statistical methodology that is more typical in this type of setting is also provided in the later portion of Table 3.

The analysis conducted by FDA requires an assumption that the covariance matrices for the day-to-day response are the same for all treatment groups. This is a commonly applied assumption in estimating the treatment effect in this type of setting. The methods used to produce the pre-specified primary efficacy analysis include a correction that allows the covariance matrix for the day-to-day response to be different for each treatment group. This was pre-specified by the sponsor and appears to be an appropriate assumption in this case in that in this study, the observed covariance matrices for the day-to-day response were different between treatment groups.

The qualitative conclusion and the magnitude of the treatment effect size in the comparison of MP03-36 and placebo are consistent between statistical approaches. That is the change from baseline in 12-hour rTNSS in the MP03-36 group is statistically significantly and approximately one unit lower than that of placebo. The 95% confidence interval suggests that this difference could be as large as 1.7 and as small as 0.3 units.

The magnitudes of the estimated treatment effect for comparison of MP03-33 and placebo are similar (i.e., slightly less than one) for both statistical approaches; however, the qualitative conclusions regarding statistical significance are not consistent as the FDA analysis produce a p-value larger than 0.05 while the methods that are corrected for unequal covariance matrices produce a p-value smaller than 0.05. The pre-specified model represents a better fit to the observed data (as evidence by a likelihood ratio test comparing the two approaches, $p<0.0001$). In addition, the statistical assumptions required for the use of the pre-specified model are less restrictive than those of the more traditional FDA approach. Therefore, from a statistical perspective, the correction allowing the covariance in day-to-day response to vary is acceptable and a statistically significant benefit of MP03-33 over placebo in terms of the change from baseline in 12-hour rTNSS has been demonstrated. The 95% confidence interval for the difference between MP03-33 and placebo using the pre-specified approach suggest that the treatment effect could be as large as 1.6 and as small as 0.2 units.

Table 3: Primary Efficacy Analysis: Change from Baseline in 12-Hour Reflective TNSS over the 28-Day Treatement Period: AM and PM Combined (ITT)

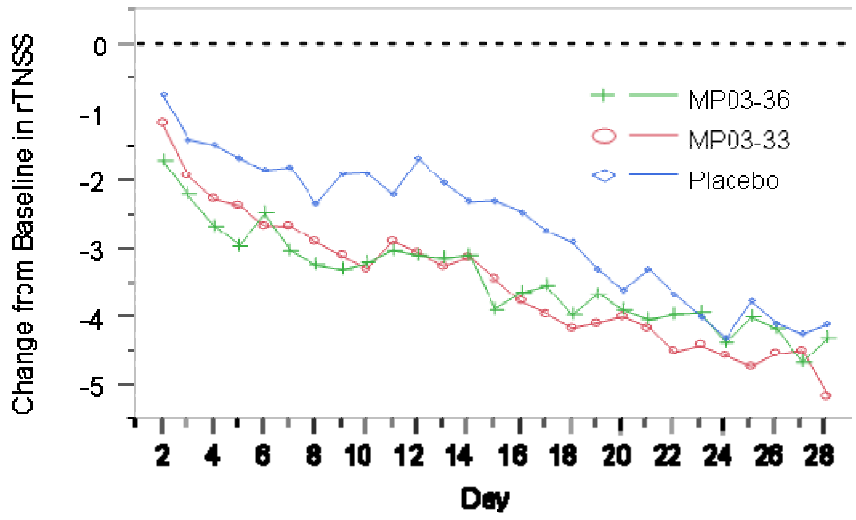
	Pre-Specified Analysis [1]			**FDA Sensitivity Analysis** [2]		
	MP03-36 N=159	**MP03-33 N=166**	**Placebo N=161**	**MP03-36 N=159**	**MP03-33 N=166**	**Placebo N=161**
LS Mean Chg from Baseline	-3.4	-3.4	-2.5	-3.7	-3.4	-2.7
Comparison to Placebo						
Treatment Difference	-1.0	-0.9	NA	-1.0	-0.7	NA
95% Confidence Interval	(-1.7, -0.3)	(-1.6, -0.2)		(-1.7, -0.3)	(-1.4, 0.06)	
p-value	0.005	0.015		0.007	0.07	

1. Source: Adapted from Clinical Study Report Table 17, page 63.
Correction to statistical methods to allow different covariance matrix in day-to-day response for each treatment group applied.
Mixed model for repeated measures with study day, treatment group, age category (6 to less than 9 years versus 9 to 12 years), pooled site, and baseline. Unstructured covariance matrix allowed to differ between treatment groups. Mivque0 option utilized to aid in convergence.
Degrees of freedom estimated by Satterthwaite approximation.

2. Source: FDA analysis.
Requirement that the covariance matrix for day-to-day response be the same for each treatment group is applied.
Mixed model for repeated measures with study day, treatment group, age category (6 to less than 9 years versus 9 to 12 years), pooled site, and baseline. Unstructured covariance matrix utilized. Mivque0 option utilized to aid in convergence. Degrees of freedom estimated by Satterthwaite approximation.

For descriptive purposes, the mean (ignoring missing data) change from baseline in the rTNSS for each treatment group during the 28-day treatment period is shown in Figure 1.

Figure 1: Change from Baseline in 12-Hour Reflective TNSS over the 28-Day Treatment Period: AM and PM Combined (ITT) [1]



1. FDA analyses

Results of the analysis of individual symptoms from the rTNSS using the same statistical methods as were pre-specified for the primary efficacy analysis (i.e., those that do not require equal covariance matrices in the day-to-day responses in all treatment groups) are shown in Table 4. No single symptom appeared to be overly-influential in the results of the rTNSS score. In addition, no reversals in any individual symptoms were noted.

Table 4: Change from Baseline Individual Symptoms of the 12-Hour Reflective TNSS over the 28-Day Treatement Period: AM and PM Combined (ITT) [1]

	MP03-36 N=159	MP03-33 N=166	Placebo N=161
Change from Baseline in Combined Itch Score			
LS Mean Chg from Baseline	-0.8	-0.8	-0.7
Comparison to Placebo			
Treatment Difference	-0.2	-0.2	NA
95% Confidence Interval	(-0.4, 0.04)	(-0.5, 0.001)	
p-value	0.1	0.052	
Change from Baseline in Combined Congestion Score			
LS Mean Chg from Baseline	-0.9	-1.0	-0.7
Comparison to Placebo			
Treatment Difference	-0.1	-0.2	NA
95% Confidence Interval	(-0.3, 0.08)	(-0.4, 0.00)	
p-value	0.2	0.05	
Change from Baseline in Combined Runny Nose Score			
LS Mean Chg from Baseline	-1.1	-1.0	-0.8
Comparison to Placebo			
Treatment Difference	-0.2	-0.2	NA
95% Confidence Interval	(-0.4, 0.1)	(-0.4, 0.1)	
p-value	0.1	0.1	
Change from Baseline in Combined Sneezing Score			
LS Mean Chg from Baseline	-0.6	-0.6	-0.4
Comparison to Placebo			
Treatment Difference	-0.2	-0.2	NA
95% Confidence Interval	(-0.4, 0.1)	(-0.4, 0.04)	
p-value	0.1	0.1	

1. Source: Adapted from Appendix to Clinical Study Report Tables 14.2.4.1 thru 14.2.4.4, pages 377 thru 380.
Correction to statistical methods to allow different covariances in day-to-day response for each treatment group applied.
Mixed model for repeated measures with study day, treatment group, age category (6 to less than 9 years versus 9 to 12 years), pooled site, and baseline. Unstructured covariance matrix allowed to differ between treatment groups. Mivque0 option utilized to aid in convergence.
Degrees of freedom estimated by Satterthwaite approximation.

Statistical significance for the comparison of each treatment group to placebo for both MP03-36 and MP03-33 was achieved for the primary efficacy endpoint, therefore, according to the pre-specified hierarchical plan used to control the overall type I error, hypothesis testing of the key secondary efficacy endpoint may be conducted in the pre-specified order, the MP03-36 to placebo comparison first followed by the MP03-33 to placebo comparison only if the former is significant. The results for the key secondary efficacy endpoint, the change from baseline in 12-hour reflective TOSS over the 28-day treatement period, as provided by the sponsor are shown in Table 5. These results are produced with equivalent methods as the primary efficacy analysis including the adjustment to allow the unstructured covariance matrix for day-to-day response to vary across treatment groups. No significant difference between either MP03-36 and placebo or MP03-33 and placebo in the key secondary efficacy endpoint, the change from baseline in 12-hour reflective TOSS over the 28-day treatment period, was identified.

Table 5: Key Secondary Efficacy Analysis: Change from Baseline in 12-Hour Reflective TOSS over the 28-Day Treatment Period: AM and PM Combined (ITT) [1]

	MP03-36 N=157	MP03-33 N=164	Placebo N=160
LS Mean Chg from Baseline	-1.6	-1.7	-1.3
Comparison to Placebo			
Treatment Difference	-0.3	-0.4	NA
95% Confidence Interval	(-0.7, 0.2)	(-0.9, 0.1)	
p-value	0.2	0.2	

1. Source: Adapted from Appendix to Clinical Study Report Tables 14.2.8.2, page 410.
Correction to statistical methods to allow different covariances in day-to-day response for each treatment group applied. Mixed model for repeated measures with study day, treatment group, age category (6 to less than 9 years versus 9 to 12 years), pooled site, and baseline. Unstructured covariance matrix allowed to differ between treatment groups. Mivque0 option utilized to aid in convergence. Degrees of freedom estimated by Satterthwaite approximation.

3.3 Evaluation of Safety

The reader is referred to the medical review of this application for an evaluation of the safety of MP03-36 and MP03-33 in pediatric patients ages 6 to <12.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

No statistically significant differences in the treatment effect in terms of the primary efficacy endpoint across age, gender, or race categories were identified (p=0.1, p=0.9, and p=0.3, respectively for the subgroup-by-treatment interaction). Nevertheless because the study was stratified by age and because of the clinical interest in the efficacy of each age category, the primary efficacy analysis is presented by age group in Table 6.

Although the pre-specified analysis for these subgroup analyses called for use of a compound symmetry covariance matrix, this was not applied in this case. For consistency with the primary efficacy endpoint and because the compound symmetry assumption is more restrictive than is probably appropriate for the observed data, these results are produced with equivalent methods as the primary efficacy analysis including the adjustment to allow the unstructured covariance matrix for day-to-day response to vary across treatment groups.

Table 6: Change from Baseline in the 12-Hour Reflective TNSS over the 28-Day Treatment Period: AM and PM Combined (ITT) by Age

	MP03-36 N=159	MP03-33 N=166	Placebo N=161
Ages 6 to less than 9 Years			
Sample Size	68	72	71
LS Mean Chg from Baseline	-4.4	-4.3	-2.9
Comparison to Placebo			
Treatment Difference	-1.5	-1.4	NA
95% Confidence Interval	(-8.7, 5.7)	(-8.2, 5.3)	
p-value	0.2	0.2	
Ages 9 to 12 Years			
Sample Size	91	94	90
LS Mean Chg from Baseline	-2.5	-2.5	-2.1
Comparison to Placebo			
Treatment Difference	-0.4	-0.4	NA
95% Confidence Interval	(-5.6, 4.8)	(-6.4, 5.7)	
p-value	0.5	0.6	

1. Source: FDA analyses.
Correction to statistical methods to allow different covariances in day-to-day response for each treatment group applied.
Mixed model for repeated measures with study day, treatment group, age category (6 to less than 9 years versus 9 to 12 years), pooled site, and baseline. Unstructured covariance matrix allowed to differ between treatment groups. Mivque0 option utilized to aid in convergence.
Degrees of freedom estimated by Satterthwaite approximation.

4.2 Other Special/Subgroup Populations

The treatment effect for the primary efficacy endpoint was not statistically significantly different in seasonal allergic rhinitis (SAR) positive and SAR negative subjects (p=0.2 for the SAR-by-treatment interaction). Nevertheless, because of the clinical interest in this factor, analysis of the primary efficacy endpoint in SAR positive and SAR negative subgroups are presented in Table 7.

Although the pre-specified analysis for these subgroup analyses called for use of a compound symmetry covariance matrix, this was not applied in this case. For consistency with the primary efficacy endpoint and because the compound symmetry assumption is more restrictive than is probably appropriate for the observed data, these results are produced with equivalent methods as the primary efficacy analysis including the adjustment to allow the unstructured covariance matrix for day-to-day response to vary across treatment groups.

Table 7: Change from Baseline Individual Symptoms of the 12-Hour Reflective TNSS over the 28-Day Treatement Period: AM and PM Combined (ITT) by SAR Positive / Negative

	MP03-36 N=159	MP03-33 N=166	Placebo N=161
SAR Positive			
Sample Size	77	83	92
LS Mean Chg from Baseline	-2.5	-3.9	-2.8
Comparison to Placebo			
Treatment Difference	0.4	-1.0	NA
95% Confidence Interval	(-4.7, 5.5)	(-6.5, 4.5)	
p-value	0.5	0.3	
SAR Negative			
Sample Size	43	43	37
LS Mean Chg from Baseline	-3.6	-1.9	-1.0
Comparison to Placebo			
Treatment Difference	-2.6	-0.9	NA
95% Confidence Interval	(-10.9, 5.7)	(-9.3, 7.6)	
p-value	0.2	0.4	

1. Source: FDA analyses.
Correction to statistical methods to allow different covariances in day-to-day response for each treatment group applied.
Mixed model for repeated measures with study day, treatment group, age category (6 to less than 9 years versus 9 to 12 years), pooled site, and baseline. Unstructured covariance matrix allowed to differ between treatment groups. Mivque0 option utilized to aid in convergence.
Degrees of freedom estimated by Satterthwaite approximation.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During the course of this review, the following statistical issues were identified and are described in the context of the referenced section.

- Use of an unstructured covariance matrix that was allowed to vary across treatment groups for the primary efficacy analysis (section 3.2.4)
- Differing estimates of the treatment effect resulting from the use of the unstructured covariance matrix versus the pre-specified compound symmetry covariance matrix in the subgroup analyses (section 4)

5.2 Collective Evidence

Since a single phase 3 study was submitted in support of this application, no assessment of collective evidence across is studies is provided in this review and the reader is referred to section 5.3 for the conclusions and recommendations resulting from the review of study MP441.

5.3 Conclusions and Recommendations

Study MP441 demonstrates a statistically significant effect on the primary efficacy endpoint, the change from baseline in the 12-hour reflective TNSS (AM and PM combined) over the 28-day

treatment period, for both MP03-36 and MP03-33 relative to placebo. The magnitude of the benefit of MP03-36 over placebo is estimated to be 1.0 unit with a 95% confidence interval from 0.3 to 1.7. The magnitude of the benefit of MP03-33 over placebo is estimated to be 0.9 units with a 95% confidence interval from 0.2 to 1.6. Analysis of individual symptoms from the rTNSS indicated that no single symptom appeared to be overly-influential in these primary efficacy results. In addition, no reversals in any individual component of the rTNSS score were noted.

No significant difference between either MP03-36 and placebo or MP03-33 and placebo in the key secondary efficacy endpoint, the change from baseline in 12-hour reflective TOSS (AM and PM combined) over the 28-day treatment period, was identified.

No statistically significant differences in the treatment effect in terms of the primary efficacy endpoint across age, gender, race (white/other), or seasonal allergic rhinitis classification (positive/negative) categories were identified.

5.4 Labeling Recommendations (as applicable)

The following text (in regular font) is proposed by the sponsor to be inserted in section 14 of the product label to describe the results of study MP441. FDA statistical recommendations for labeling are indicated by strike out. (b) (4)

(b) (4)

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

/s/

RUTHANNA C DAVI
06/09/2013

JOAN K BUENCONSEJO
06/10/2013
I concur.