CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-371s000

STATISTICAL REVIEW(S)

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
Addendum

NDA/Serial Number:	NDA 22371
Drug Name:	MP03-36 (0.15% azelastine, sweetened)
Indication(s):	MP03-36 is indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis including itchy nose, runny nose, sneezing, nasal congestion for patients 12 years of age and older
Applicant:	MEDA Pharmaceuticals
Date(s):	Submission date: 4/29/2009; Due date: 9/1/2009
Review Priority:	Standard
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Keywords:	NDA review, clinical studies

June 26, 2009

Background

This report, as an addendum to the statistical review completed on 4/9/2009, is prepared to evaluate a clinical study report submitted on 4/2/2009 by MEDA Pharmaceuticals, the sponsor. The latest submission includes one Phase-3 clinical study intended to provide evidence in supporting the effectiveness of the once daily dose of MP03-36 (0.15% azelastine, sweetened) for the treatment of seasonal allergic rhinitis (SAR).

In the earlier submission, the sponsor provided two Phase-3 studies for the once daily dose regimen. Evidence from the two studies showed that MP03-36 once daily was superior to placebo based on the primary efficacy variable, the reflective total nasal symptom score (rTNSS). The superiority was also demonstrated based on the key secondary efficacy variable: instantaneous TNSS. However, the superiority was not shown consistently to be statistically significant at the level of 0.05 (2-sided tests) based on another secondary efficacy variable: instantaneous AM TNSS. This report was intended to find out whether evidence from the new study, MP443, provides add-on evidence for the efficacy.

Statistical Evaluation of Study MP443

Study Designs

This clinical study is a Phase 3 randomized, double-blind, parallel-group, placebo-controlled safety and efficacy studies in patients 12 years of age and older with moderate-to-severe SAR. The study design is identical to the studies submitted in the original submission.

Endpoints

The primary efficacy variable was the change from baseline to the entire 14-day double-blind period in the 12-hour reflective combined (the sum of) AM and PM total nasal symptom scores (TNSS), consisting of runny nose, itchy nose, sneezing, and nasal congestion. The baseline TNSS was defined as the mean TNSS scores over a 7-day placebo run-in period.

Patients entered the individual symptom scores in their diary cards in 12-hour interval both reflectively and instantaneously. Scores for the four individual symptoms were measured on a 4-point scale:

0=no symptoms
1=mild symptoms
2=moderate symptoms
3=severe symptoms

The secondary efficacy variables included:

1. Change from baseline in **instantaneous** TNSS at the end of 24 hours dosing interval for the entire 14-day treatment period.
2. Change from baseline in **instantaneous** TNSS for the entire 14-day treatment period.
3. Change from baseline in 12-hour **reflective** TNSS for the entire 14-day treatment period in **individual** symptom scores.
4. **Daily change** from baseline in 12-hour **reflective** and **instantaneous** TNSS for the entire 14-day treatment period.
5. Change from baseline in 12-hour **reflective** and **instantaneous** TOSS for the entire 14-day treatment period.
6. Change from baseline in 12-hour **reflective** TOSS **individual** symptom scores for the entire 14-day treatment period.
7. Change from baseline to Visit 4 in RQLQ in patients 18 years of age or older.

Analysis Patient Populations

Male and female patients, 12 years of age and older, with a minimum 2-years history of SAR with a positive skin test to a Texas Mountain Cedar pollen were enrolled in the study.

Patients who met the inclusion/exclusion criteria were randomized to one of the two treatment arms: MP03-36 or placebo. The study drug or matching placebo was administered 2 sprays per nostril once daily at AM.

After a 7-day placebo lead-in period, 506 patients were randomized to the treatment groups: 251 in the MP03-36 group and 255 in the placebo group. Among the randomized patients, one patient in the placebo group did not have post-baseline data, therefore was excluded from the analysis. All 506 patients were included for safety evaluation. The number of ITT patients was 505. The following efficacy evaluation includes ITT patients alone.

Table 1 shows that 94% of the ITT patients were per-protocol patients, while the others had major protocol violations.

Table 1 Number of patients by treatment and PP status (MP443)

Grouping By PP Status	Placebo		MP03-36		Total	
	No.	%	No.	%	No.	%
Not PP	16	6.3	14	5.6	30	5.9
PP	238	93.7	237	94.4	475	94.1
Total	254	100.0	251	100.0	505	100.0

Table 2 shows that 95% of the ITT patients completed the study.

Table 2 Number of patients by treatment and completion status (MP443)

Grouping By Completion Status	Placebo		MP03-36		Total	
	No.	%	No.	%	No.	%
Discontinued	14	5.5	13	5.2	27	5.3
Completed	240	94.5	238	94.8	478	94.7
Total	254	100.0	251	100.0	505	100.0

Table 3 Numbers and percentages of ITT patients by treatment and sex/race (MP443)

Grouping By Sex	Placebo		MP03-36		Total	
	No.	%	No.	%	No.	%
Female	150	59.1	157	62.5	307	60.8
Male	104	40.9	94	37.5	198	39.2
Black	29	11.4	28	11.2	57	11.3
White	225	88.6	217	86.5	442	87.5
Other	0	0	6	2.4	6	1.2
Total	254	100.0	251	100.0	505	100.0

Table 4 Analysis of age (MP443)

Treatment	#Patients	Mean	Std	Min	Max
Placebo	254	39	15	12	75
MP03-36	251	38	14	12	74
Overall	505	38	14	12	75

Table 5 shows that the baseline values across the treatments were well balanced.

Table 5 Analysis of baseline values for reflective TNSS, instantaneous TNSS, and instantaneous AM TNSS (MP443)

	Treatment	Count	Mean	Std	Min	Max
TNSS	Placebo	254	18.76	3.30	8.73	24.00
	MP03-36	251	18.48	3.23	8.29	24.00
	Overall	505	18.62	3.27	8.29	24.00
Inst TNSS	Placebo	254	17.63	3.91	7.29	24.00
	MP03-36	251	17.44	3.66	5.86	24.00
	Overall	505	17.53	3.79	5.86	24.00
Inst AM TNSS	Placebo	254	8.93	1.88	4.00	12.00
	MP03-36	251	8.85	1.76	3.75	12.00
	Overall	505	8.89	1.82	3.75	12.00

Statistical Methodology

The efficacy analysis for the SAR study was conducted based on the ITT population data. The primary efficacy variable was the change from baseline to 14 days of treatment period for SAR in reflective AM plus PM TNSS, consisting of runny nose, itchy nose, sneezing and nasal congestion. The baseline TNSS was defined as the mean TNSS scores over the 7-day placebo run-in period. The analysis was performed using ANCOVA including treatment and center as fixed factors and baseline TNSS as a covariate. Note that the sponsor used the repeated measures model. The results were consistent using either model.

Missing data handling

TNSS was set to missing, if any one of the individual symptom score was missing. Missing TNSS were imputed using LOCF.

Efficacy Results

To verify the sponsor's statistical findings, a reanalysis of the sponsor's data was performed. The primary efficacy variable is the change in the sum of 12-hr AM and PM reflective TNSS from baseline to entire 14-day treatment period. For this evaluation, the ANCOVA model included the terms of treatment and center with the baseline TNSS as a covariate. The statistical results can be found in the following tables.

Analysis based on 12-hr AM plus PM reflective TNSS

Superiority of MP03-36 QD to placebo was demonstrated in Table 6.

Table 6 Analysis of change in 12-hr AM plus PM reflective TNSS from baseline to entire 14-day treatment period (MP443)

Treatment	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff. from placebo	95% Confidence interval	P value
MP03_36QD	251	18.48	-3.41	-1.38	-2.05, -0.71	<0.001
Placebo	254	18.76	-2.03			

Analysis based on Instantaneous TNSS

Superiority of MP03-36 QD to placebo was demonstrated in Table 7.

Table 7 Analysis of instantaneous TNSS (Study 433)

Treatment	Comparator	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff	95% Confidence interval	P value
MP03_36QD	Placebo	251	17.43	-3.01	-1.39	-2.04, -0.73	<0.001
Placebo		254	17.63	-1.63			

Analysis based on Instantaneous AM TNSS

Superiority of MP03-36 QD to placebo was demonstrated in Table 8.

Table 8 Analysis of instantaneous AM TNSS (Study 443)

Treatment	Comparator	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff	95% Confidence interval	P value
MP03-66 QD	Placebo	251	8.85	-1.43	-0.61	-0.94, -0.28	<0.001
Placebo		254	8.94	-0.82			

Statistical findings and issues

Statistical findings with respect to instantaneous AM TNSS were not consistent in Studies MP439 and MP440, the two studies that contain information for once daily dosing regimen. The same analysis using data from Study 443 favors MP03-36. For the purpose of comparison, I am listing the results from my previous report for Studies MP439 and MP440, in comparison with Table 8, above.

Table 9 Statistical findings in previous review for Studies MP439 and MP440 based on instantaneous AM TNSS

Treatment	Comparator	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff	95%Confidence interval	P value
MP03-66 QD	Placebo	238	8.10	-1.33	-0.27	-0.64, 0.10	0.147
Placebo		242	8.29	-1.05			
Analysis of instantaneous AM TNSS (Study 439)							
Treatment	**Comparator**	**N**	**LS-mean Baseline**	**LS-mean change from baseline**	**LS-mean diff**	**95%Confidence interval**	**P value**
MP03-66 QD	Placebo	266	8.68	-1.35	-0.70	-1.04, -0.37	<0.001
Placebo		266	8.28	-0.65			
Analysis of instantaneous AM TNSS (Study 440)							

The study designs of three studies were the same. Two of the three studies demonstrated that MP03-36 once daily was statistically significantly superior to placebo based on instantaneous AM TNSS.

Conclusions and Recommendations

Based on the statistical evidence from Study MP443 and that from Studies MP439 and MP440, MP03-06 once daily is recommended for the treatment of **seasonal** allergic rhinitis.

Comments on Proposed Label

I evaluated the CLINICAL STUDIES section of the proposed label dated 4/29/2009. I verified the numbers in Table 10 for Study 5 based on reanalysis of the sponsor's data. The statistics presented for Study 5 are similar to those from my analysis. The conclusions are consistent. The sponsor obtained the statistics based on the repeated measures model, while I used ANCOVA consistently for the evaluation of this application. My results can be found in Table 6 of this review.

(b) (4)

According to my analysis, the results for Study 5 will be:

Study 5		n	LS mean BL	Chg from Base	Diff.		
					LS mean	95% CI	P value
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	251	18.48	-3.41	-1.38	(-2.05,-0.71)	<0.001
	Placebo Vehicle	254	18.76	-2.03			

Source: Table 6

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/s/

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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 22371
Drug Name:	MP03-36 (0.15% azelastine, sweetened)
Indication(s):	MP03-36 is indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis including itchy nose, runny nose, sneezing, nasal congestion for patients 12 years of age and older
Applicant:	MEDA Pharmaceuticals
Date(s):	Submission date: 8/1/2008 Due date: 6/1/2008
Review Priority:	Standard
Biometrics Division:	Biometrics Division 2
Statistical Reviewer:	Ted Guo, Ph.D., Biometrics Division 2
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Keywords:	NDA review, clinical studies

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Executive Summary

Astelin (azelastine hydrochloride) nasal spray was approved (under NDA 20-114) for the treatment of the symptoms of seasonal allergic rhinitis (SAR) including runny nose, itchy nose, sneezing and nasal congestion. Later, the sponsor sought the approval of Astepro, a sweetened formulation of azelastine hydrochloride, which was approved on 10/15/2008 for the treatment of SAR in patients 12 years of age and older. The approved dosage was 0.137 mL solution containing 137 µg of azelastine hydrochloride per spray. For this application, NDA 22-371, dated 8/1/2008, the sponsor proposed to increase the dosage level to 205.5 µg of azelastine hydrochloride in each 0.137 mL spray. In this application, the sponsor submitted four Phase 3 studies to provide evidence for the SAR indication, and two Phase 3 studies for the PAR indication (one was a proof of concept study with small sample size), for patients 12 years of age and older. The proposed dose regimens are: 2 sprays per nostril once or twice daily for SAR and 2 sprays per nostril twice daily for PAR. In addition, the sponsor submitted a 1-year safety and tolerability study including up to 6 months interim report.

The following points summarize the statistical evaluations of the six Phase 3 studies and the 6-month interim data of the 1-year safety and tolerability study:

- **SAR Studies MP433, MP438, MP439, and MP440.**
  The primary efficacy variable was the change from baseline to the entire **14-day** double-blind period in the 12-hour reflective combined (the sum of) AM and PM total nasal symptom scores (TNSS), consisting of runny nose, itchy nose, sneezing, and nasal congestion. Table 1 summarizes the final analysis. My analysis concludes that MP03-36 twice daily (137 µg of azelastine hydrochloride per spray) was shown to be superior to placebo consistently in two studies. MP03-36 once daily (205.5 µg of azelastine hydrochloride per spray) was shown to be superior to placebo in two other studies

Table 1 Statistical reviewer's efficacy findings for SAR indication

Comparison between experimental drug and placebo (N, LS-mean diff, p-value)		SAR Study			
		MP433	MP438	MP439	MP440
MP03-36	Once daily	N=158 Dif=-0.81 P=0.07		N=238 Dif=-0.98 P=0.008	N=266 Dif=-1.41 P<0.001
MP03-36	Twice daily	N=153 Dif=-1.21 P=0.01	N=177 Dif=-2.97 P<0.001		
MP03-33		N=153 Dif=-0.85 P=0.07	N=169 Dif=-2.07 P<0.001		

- **PAR Studies MP434 and MP435**
  The primary efficacy variable was the change from baseline to the entire **28-day** double-blind period in the 12-hour reflective combined (the sum of) AM and PM total nasal symptom scores (TNSS), consisting of runny nose, itchy nose, sneezing, and nasal congestion. Table 2 summarizes the final analysis. My analysis concludes that MP03-36 twice daily was shown to be superior to placebo in one of the two studies with twice daily dose regimen.

Table 2 Statistical reviewer's efficacy findings for PAR indication

Experimental drug superior to placebo		PAR Study	
		MP434	MP435
MP03-36 AM	Once daily		N=53 Dif=-1.19 P=0.3
MP03-36 PM	Once daily		N=50 Dif=-0.88 P=0.42
MP03-36	Twice daily	N=192 Dif=-0.88 P=0.03*	
MP03-33	Twice daily	N=194 Dif=-0.72 P=0.08	

*: The superiority of MP03-36 to placebo (P=0.033, effect size=0.88) was shown based on an ANCOVA of the **mean** change from baseline to the entire 28-day period in the reflective combined TNSS. A repeated-measures analysis performed by the sponsor yielded a p-value of 0.058 and effect size of 0.78.

- The 6-month interim data from the 1-year safety and tolerability study were evaluated. Patients in this study included those who participated in Studies MP434 and MP435 and treated with MP03-36, they also included those newly identified patients who met the inclusion/exclusion criteria. The patients were randomized in a 2:1 ratio to MP03-36 bid or Nasonex qd. This was an open-label study. The focus of the evaluation was on the AE findings. Adverse reactions reported in 2% or more of the total patients are presented in the Table 3.

Table 3 AE findings based on 6-month interim data

AEs presented as MedDRA preferred terms MP03-36: N=465 Nasonex: N=238 Total: N=703	Treatment			
	MP03-36		Nasonex	
	N	%	N	%
(No AE)	182	39.14	110	46.22
Headache	41	8.82	26	10.92
Dysgeusia	61	13.12	2	0.84
Epistaxis	29	6.24	20	8.40
Nasal Discomfort	35	7.53	10	4.20
Upper Respiratory Tract Infection	24	5.16	13	5.46
Nasopharyngitis	20	4.30	8	3.36

AEs presented as MedDRA preferred terms MP03-36: N=465 Nasonex: N=238 Total: N=703	Treatment			
	MP03-36		Nasonex	
	N	%	N	%
Sinusitis	19	4.09	9	3.78
Pharyngolaryngeal Pain	16	3.44	11	4.62
Cough	10	2.15	10	4.20
Fatigue	16	3.44	2	0.84
Somnolence	16	3.44	2	0.84
Sinus Headache	12	2.58	4	1.68
Nasal Congestion	9	1.94	6	2.52
Sneezing	14	3.01	1	0.42
Back Pain	10	2.15	3	1.26
Migraine	8	1.72	3	1.26
Ear Pain	4	0.86	5	2.10

Source: Table 26 in this review.

As the efficacy components, the difference in RQLQ between MP03_36 and Nasonex appeared to be small.

The adverse reactions found in 5% and more of the patients treated with MP03-06 based on the AE data appear on the proposed label except for Upper Respiratory Tract Infection.

In conclusion, I recommend the approval of MP03-06 twice daily for the treatments of SAR and PAR. I also recommend the approval of MP03-06 once daily for the treatment of SAR.

Introduction

Overview

Astelin (azelastine hydrochloride) nasal spray was approved (under NDA 20-114) for the treatment of the symptoms of seasonal allergic rhinitis (SAR) including runny nose, itchy nose, sneezing and nasal congestion. Later, the sponsor sought the approval of Astepro, a sweetened formulation of azelastine hydrochloride, which was approved on 10/15/2008 for the treatment of SAR in patients 12 years of age and older. The approved dosage was 0.137 mL solution containing **137** µg of azelastine hydrochloride per spray.

For this application, NDA 22-371, dated 8/1/2008, the sponsor proposed to increase the dosage level to **205.5** µg of azelastine hydrochloride in each 0.137 mL spray. In this application, the sponsor submitted four Phase 3 studies to provide evidence for the SAR indication, and two Phase 3 studies, one of which was a proof-of-concept study, for the PAR indication, for patients 12 years of age and older.

Scope of Statistical Review

This statistical review includes evaluation of the effectiveness of MP03-36 for the treatment of SAR and PAR in comparisons with placebo and MP03-33 (Astepro, the sweetened azelastine hydrochloride). This review also includes an analysis of the sponsor's AE data to verify the AEs in the proposed label. The statistical evaluation for this report includes:

- Phase 3 studies for SAR: MP433, MP438, MP439, and MP440
- Phase 3 studies for PAR were MP434 and MP435 (a "proof of concept" study)
- 1-year safety and tolerability study MP436 only including 6-month interim data

Data Sources

In this submission, the study reports were submitted in paper and the electronic data were available in the FDA's Electronic Document Room. All the data submitted are either SAS data or a compressed version of SAS data created using SAS CPORT procedure (not a FDA-recommended method) that were converted back to SAS data sets for the statistical evaluation.

Statistical Evaluation

Evaluation of Efficacy

Study Designs and Endpoints

Study Designs

Studies for SAR: MP433, MP438, MP439, and MP440
These clinical studies were Phase 3 randomized, double-blind, parallel-group, placebo-controlled safety and efficacy studies in patients 12 years of age and older with moderate-to-severe SAR. The differences among these studies lie in the treatments included in each study:

Table 4 Treatment arms in the studies for SAR

Study	MP433	MP438	MP439	MP440
Treatment	MP03-33 bid	MP03-33 bid		
	MP03-36 bid	MP03-36 bid		
	MP03-36 qd		MP03-36 qd	MP03-36 qd
	Placebo bid	Placebo bid	Placebo qd	Placebo qd

Studies for PAR: Studies MP434 and MP435
These clinical studies were Phase 3 randomized, double-blind, parallel-group, placebo-controlled safety and efficacy studies in patients 12 years of age and older with moderate-to-severe PAR. The differences among these studies lie in the treatments included in each study,

Table 5 Treatment arms in the studies for PAR

Study	MP434	MP435*	MP436**
Treatment	MP03-33 bid	MP03-36 qd (AM)	
	MP03-36 bid	MP03-36 qd (PM)	
	Placebo bid	Placebo qd (AM or PM)	

***: Study 435** was a proof-of-concept study.
****: Study 436**
This is an on-going 1-year safety and tolerability study. The 6-month interim report is included in this submission. Patients in this study included those who participated in MP434 and MP435 and treated with MP03-36, they also included those newly identified patients who met the inclusion/exclusion criteria. The patients were randomized in a 2:1 ratio to MP03-36 bid or Nasonex qd. This was an open-label study.

Endpoints

Studies for SAR: Studies MP433, MP438, MP439, and MP440

The primary efficacy variable was the change from baseline to the entire 14-day double-blind period in the 12-hour reflective combined (the sum of) AM and PM total nasal symptom scores (TNSS), consisting of runny nose, itchy nose, sneezing, and nasal congestion. The baseline TNSS was defined as the mean TNSS scores over a 7-day placebo run-in period.

Patients entered the individual symptom scores in their diary cards in 12-hour interval both reflectively and instantaneously. Scores for the four individual symptoms were measured on a 4-point scale:

0=no symptoms
1=mild symptoms
2=moderate symptoms
3=severe symptoms

As defined, TNSS ranges from 0 to 24.

The secondary efficacy variables included:

1. Change from baseline in **instantaneous** TNSS for the entire 14-day treatment period. The sponsor either named this endpoint as the key secondary endpoint or put this endpoint on top of the list of the secondary efficacy endpoints.
2. Change from baseline in 12-hour **reflective** TNSS for the entire 14-day treatment period in **individual** symptom scores.
3. Onset of action: Change from baseline in instantaneous TNSS over 4 hours following the initial administration of the study drug. This endpoint was listed as one of the secondary efficacy endpoints in Studies MP433 and MP438.
4. **Daily change** from baseline in 12-hour **reflective** and **instantaneous** TNSS for the entire 14-day treatment period.
5. Change from baseline to Day 14 in RQLQ in patients 18 years of age or older.
6. Other secondary efficacy endpoints associated with secondary symptom complex scores (except for MP433), consisting of postnasal drip, itchy eyes, cough, and headache).

Studies for PAR: Studies MP434 and MP435

The primary efficacy variable was nearly the same as that for the SAR studies **except that the double-blind period was 28 days**.

The secondary efficacy variables included:

1. Change from baseline in **instantaneous** TNSS for the entire 28-day treatment period.
2. Change from baseline in 12-hour **reflective** TNSS for the entire 28-day treatment period in individual symptom scores.
3. Daily change from baseline in 12-hour reflective and instantaneous TNSS for the entire 28-day treatment period.
4. Change from baseline to Day 28 in RQLQ in patients 18 years of age or older.
5. Secondary efficacy endpoints associated with secondary symptom complex scores (SSCS), consisting of postnasal drip, itchy eyes, cough, and headache

Analysis Patient Populations

Male and female patients, 12 years of age and older, with a minimum 2-years history of SAR with a positive skin test to a relevant local fall pollen were enrolled in the study. The eligible patients were randomized to the pre-specified treatment groups. Efficacy analyses were done using the intent-to-treat (ITT) population. The definition of the ITT population was described slightly differently. Studies MP433, MP440, MP434 and MP435 defined the ITT as those **who were randomized and had at least one post baseline observation**. Studies MP438 and MP439 defined the ITT as those **who were randomized and took correct placebo lead-in medication and at least one double-blind medication**. The former definition is commonly used definition. Note that the constraint, “took correct placebo lead-in medication,” in the latter definition for the ITT patients did not actually eliminate any randomized patients from the ITT population.

Table 6-a and -b show the numbers of patients by treatment and PP grouping. Across the treatments, the PP patients accounted for at least 90% of the ITT patients for all the SAR studies; the same percentage was 86% for the two PAR studies.

Table 6-a Number of patients by treatment and PP status (Studies MP433, MP438, MP439, MP440, MP434)

Grouping By PP Status		Placebo		MP03_33BID		MP03_36BID		MP03_36QD		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%
MP433	No	11	7.2	11	7.2	13	8.5	11	7.0	46	7.5
	Yes	142	92.8	142	92.8	140	91.5	147	93.0	571	92.5
	Total	153	100.0	153	100.0	153	100.0	158	100.0	617	100.0
MP438	No	15	8.5	8	4.7	7	4.0			30	5.7
	Yes	162	91.5	161	95.3	170	96.0			493	94.3
	Total	177	100.0	169	100.0	177	100.0			523	100.0
MP439	No	29	12.0					19	8.0	48	10.0
	Yes	213	88.0					219	92.0	432	90.0
	Total	242	100.0					238	100.0	480	100.0
MP440	No	21	7.9					24	9.0	45	8.5
	Yes	245	92.1					242	91.0	487	91.5
	Total	266	100.0					266	100.0	532	100.0
MP434	No	26	13.5	21	10.8	20	10.4			67	11.6
	Yes	166	86.5	173	89.2	172	89.6			511	88.4
	Total	192	100.0	194	100.0	192	100.0			578	100.0

Table 6-b Number of patients by treatment and PP status (StudyMP435)

Grouping By PP Status		MP03_36_AM		Placebo_AM		MP03_36_PM		Placebo_PM		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%
MP435	No	4	7.5	7	30.4	5	10.0	4	14.8	20	13.1
	Yes	49	92.5	16	69.6	45	90.0	23	85.2	133	86.9
	Total	53	100.0	23	100.0	50	100.0	27	100.0	153	100.0

SAS data set used: eff1

Note that the number of patients in MP435 was much smaller than that in NP434. MP435 was a pilot study and not powered to perform significance tests.

Table 7-a and -b show the numbers and percentages of patients discontinued using data from the sponsor's study report.

Table 7-a Numbers and percentages of patients discontinued based on sponsor's report (Studies MP433, MP438, MP439, MP440, MP434)

N and % of patients discontinued	Placebo		MP03_33BID		MP03_36BID		MP03_36QD		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
MP433	6	3.9	5	3.3	9	5.9	4	2.5	24	3.9
MP438	7	3.9	4	2.4	6	3.4			17	3.2
MP439	8	3.3					6	2.5	14	2.9
MP440	18	6.7					19	7.1	37	6.9
MP434	17	8.9	17	8.6	12	6.3			46	7.9

Table 7-b Numbers and percentages of patients discontinued based on sponsor's report (Study MP435)

N and % of patients discontinued	MP03_36_AM		Placebo_AM		MP03_36_PM		Placebo_PM		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
MP435	0	0.0	2	8.3	4	7.7	1	3.7	7	4.5

Patient Distributions of Demographic and Baseline Characteristics

The following tables describe the characteristics of the ITT patients listed for all the studies. Overall, there were twice as many female patients as male patients. More than 70% of the patients were white. The patients across the treatment groups appeared to be evenly distributed.

Table 8-a Numbers and percentages of ITT patients by treatment and sex (Studies MP433, MP438, MP439, MP440, MP434)

Grouping By Sex		Placebo		MP03_33BID		MP03_36BID		MP03_36QD		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%
MP433	Female	95	62.1	96	62.7	93	60.8	97	61.4	381	61.8
	Male	58	37.9	57	37.3	60	39.2	61	38.6	236	38.2
	Total	153	100.0	153	100.0	153	100.0	158	100.0	617	100.0
MP438	Female	116	65.5	111	65.7	107	60.5			334	63.9
	Male	61	34.5	58	34.3	70	39.5			189	36.1
	Total	177	100.0	169	100.0	177	100.0			523	100.0
MP439	Female	162	66.9					154	64.7	316	65.8
	Male	80	33.1					84	35.3	164	34.2
	Total	242	100.0					238	100.0	480	100.0
MP440	Female	171	64.3					175	65.8	346	65.0

Grouping By Sex		Placebo		MP03_33BID		MP03_36BID		MP03_36QD		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%
	Male	95	35.7					91	34.2	186	35.0
	Total	266	100.0					266	100.0	532	100.0
MP434	Female	130	67.7	136	70.1	127	66.1			393	68.0
	Male	62	32.3	58	29.9	65	33.9			185	32.0
	Total	192	100.0	194	100.0	192	100.0			578	100.0

Table 8-b Numbers and percentages of ITT patients by treatment and sex (Study MP435)

Grouping By Sex		MP03_36_AM		Placebo_AM		MP03_36_PM		Placebo_PM		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%
MP435	Female	39	73.6	18	78.3	33	66.0	17	63.0	107	69.9
	Male	14	26.4	5	21.7	17	34.0	10	37.0	46	30.1
	Total	53	100.0	23	100.0	50	100.0	27	100.0	153	100.0

SAS data set used: eff1

Table 9-a Numbers and percentages of ITT patients by treatment and race (Studies MP433, MP438, MP439, MP440, MP434)

Grouping by Study and Race		Placebo		MP03_33BID		MP03_36BID		MP03_36QD		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%
MP433	White	104	68.0	105	68.6	104	68.0	120	75.9	433	70.2
	Black	28	18.3	23	15.0	20	13.1	18	11.4	89	14.4
	Other	21	13.7	25	16.3	29	19.0	20	12.7	95	15.4
	Total	153	100.0	153	100.0	153	100.0	158	100.0	617	100.0
MP438	White	140	79.1	134	79.3	143	80.8			417	79.7
	Black	26	14.7	30	17.8	23	13.0			79	15.1
	Other	11	6.2	5	3.0	11	6.2			27	5.2
	Total	177	100.0	169	100.0	177	100.0			523	100.0
MP439	White	179	74.0					186	78.2	365	76.0
	Black	49	20.2					38	16.0	87	18.1
	Other	14	5.8					14	5.9	28	5.8
	Total	242	100.0					238	100.0	480	100.0
MP440	White	241	90.6					231	86.8	472	88.7
	Black	13	4.9					26	9.8	39	7.3
	Other	12	4.5					9	3.4	21	3.9
	Total	266	100.0					266	100.0	532	100.0
MP434	White	172	89.6	160	82.5	159	82.8			491	84.9

Grouping by Study and Race		Placebo		MP03_33BID		MP03_36BID		MP03_36QD		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%
	Black	11	5.7	28	14.4	26	13.5			65	11.2
	Other	9	4.7	6	3.1	7	3.6			22	3.8
	Total	192	100.0	194	100.0	192	100.0			578	100.0

Table 9-b Numbers and percentages of ITT patients by treatment and race (Study MP435)

Grouping By Race		MP03_36_AM		Placebo_AM		MP03_36_PM		Placebo_PM		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%
MP435	White	44	83.0	19	82.6	45	90.0	22	81.5	130	85.0
	Black	5	9.4	3	13.0	3	6.0	2	7.4	13	8.5
	Other	4	7.5	1	4.3	2	4.0	3	11.1	10	6.5
	Total	53	100.0	23	100.0	50	100.0	27	100.0	153	100.0

SAS data set used: eff1

Table 10-a and -b show that the average age of the patients was around 38 years old. The youngest patient was 12 years of age, and the oldest one was 84 years of age. The patients across the treatment groups appeared to be evenly distributed.

Table 10-a Analysis of age for ITT patients by treatment (Studies MP433, MP438, MP439, MP440, MP434)

Analysis of Age		Placebo	MP03_33BID	MP03_36BID	MP03_36QD	Total
MP433	#Patients	153	153	153	158	617
	Mean	37.0	37.5	38.5	36.2	37.3
	Std.	14.9	14.1	14.7	13.9	14.4
	Min	13	13	13	13	13
	Max	74	83	75	78	83
MP438	#Patients	177	169	177		523
	Mean	36.9	35.4	37.7		36.7
	Std.	14.3	13.7	14.6		14.2
	Min	12	12	12		12
	Max	69	79	76		79
MP439	#Patients	242			238	480
	Mean	35.3			35.5	35.4
	Std.	13.9			13.5	13.7
	Min	12			12	12
	Max	75			78	78

Analysis of Age		Placebo	MP03_33BID	MP03_36BID	MP03_36QD	Total
MP440	#Patients	266			266	532
	Mean	39.5			40.9	40.2
	Std.	14.4			14.5	14.5
	Min	12			12	12
	Max	81			80	81
MP434	#Patients	192	194	192		578
	Mean	38.1	36.9	35.6		36.9
	Std.	15.4	13.1	13.3		14.0
	Min	12	12	12		12
	Max	84	64	71		84

Table 10-b Analysis of age for ITT patients by treatment (Study MP435)

Analysis of Age		MP03_36_AM	Placebo_AM	MP03_36_PM	Placebo_PM	Total
MP435	#Patients	53	23	50	27	153
	Mean	38.5	37.0	40.1	42.0	39.5
	Std.	15.8	15.1	14.2	13.0	14.7
	Min	12	14	12	13	12
	Max	76	62	70	67	76

SAS data set used: eff1

Table 11-a and -b show the analyses of baseline FEV_1. It shows that the baseline FEV_1 values across treatment groups were balanced.

Table 11-a Analysis of baseline FEV_1 (Studies MP433, MP438, MP439, MP440, MP434)

Analysis of Baseline FEV_1		Placebo	MP03_33BID	MP03_36BID	MP03_36QD	Total
MP433	#Patients	153	153	153	158	617
	Mean	18.2	18.0	18.3	18.7	18.3
	Std.	3.0	2.8	2.8	3.0	2.9
MP438	#Patients	177	169	177		523
	Mean	17.9	18.3	17.9		18.0
	Std.	3.3	3.2	3.3		3.3
MP439	#Patients	242			238	480
	Mean	17.7			17.7	17.7
	Std.	3.3			3.5	3.4
MP440	#Patients	266			266	532

Analysis of Baseline FEV_1		Placebo	MP03_33BID	MP03_36BID	MP03_36QD	Total
	Mean	18.0			18.5	18.2
	Std.	3.3			3.3	3.3
MP434	#Patients	192	194	192		578
	Mean	14.8	15.6	15.9		15.5
	Std.	4.0	3.8	3.9		3.9

Table 11-b Analysis of baseline FEV1 (Study MP435)

Analysis of Baseline FEV1		MP03_36_AM	Placebo_AM	MP03_36_PM	Placebo_PM	Total
MP435	#Patients	53	23	50	27	153
	Mean	15.3	16.2	15.3	14.5	15.3
	Std.	4.6	3.3	4.3	3.4	4.1

SAS data set used: eff1

Statistical Methodology

The efficacy analysis for the SAR study was conducted based on the ITT population data. The primary efficacy variable was the change from baseline to 14 days of treatment period for SAR in reflective AM plus PM TNSS, consisting of runny nose, itchy nose, sneezing and nasal congestion. The baseline TNSS was defined as the mean TNSS scores over the 7-day placebo run-in period. The analysis was performed using ANCOVA including treatment and center as fixed factors and baseline TNSS as a covariate. For the PAR studies, the sponsor used the same ANCOVA but the duration was 28 days, instead. I concurred with the sponsor's approach.

Missing data handling

Missing data with respect to TNSS were handled in the following fashion:

1. If a post baseline TNSS was missing, the last non-missing TNSS was carried forward to replace the missing one.
2. Individual nasal symptom scores were not carried forward. The TNSS was calculated using all 4 non-missing individual nasal symptom score at the same time point. If any of the 4 nasal symptom score was missing, the TNSS was set to missing.

Efficacy Results

Analyses of the primary efficacy variable

To verify the sponsor's statistical findings, a reanalysis of the sponsor's data was performed. The primary efficacy variable is the change in the sum of 12-hr AM and PM reflective TNSS from baseline to entire 14-day treatment period. The sponsor used an "ANCOVA model with baseline as a covariate (MP433 and MP438)." However, the sponsor did not clearly detail the terms included in the ANCOVA model. For this report, the ANCOVA model included the terms of treatment and center with the baseline FEV_1 as a covariate. The statistical results can be found in the following tables, in which the LS-mean differences from placebo and the 95% CIs for the differences are demonstrated. The significant findings are indicated with an asterisk next to the p-value. Upon a request from the medical reviewer, comparisons between MP03-36 and MP03-33 were included as well. Table 12 -- Table 16 summarize the analyses for the SAR indication; and Table 17, Table 19, and Table 20 summarize the analyses for the PAR indication.

Analyses for the SAR indication

Table 12 Analysis of change in 12-hr AM plus PM reflective TNSS from baseline to entire 14-day treatment period (MP433)

Treatment	Comparator	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff.	95%Confidence interval	P value
MP03_36QD	Placebo	158	18.61	-3.85	-0.81	-1.72, 0.10	0.08
MP03_36BID	MP03_33BID	153	18.19	-4.25	-0.35	-1.27, 0.57	0.451
	Placebo				-1.21	-2.12, -0.29	0.01*
MP03_33BID	Placebo	153	17.94	-3.89	-0.85	-1.77, 0.06	0.068
Placebo		153	18.08	-3.04			

Table 13 Analysis of change in 12-hr AM plus PM reflective TNSS from baseline to entire 14-day treatment period (MP438)

Treatment	Comparator	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff.	95%Confidence interval	P value
MP03_36BID	MP03_33BID	177	17.72	-5.09	-0.90	-1.82, 0.02	0.055
	Placebo				-2.97	-3.87, -2.06	0.000*
MP03_33BID	Placebo	169	18.18	-4.19	-2.07	-2.99, -1.15	0.000*
Placebo		177	17.73	-2.12			

Table 14 Analysis of change in 12-hr AM plus PM reflective TNSS from baseline to entire 14-day treatment period (MP439)

Treatment	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff. from placebo	95%Confidence interval	P value
MP03_36QD	238	17.40	-3.38	-0.98	-1.71, -0.26	0.008*
Placebo	242	17.38	-2.40			

Table 15 Analysis of change in 12-hr AM plus PM reflective TNSS from baseline to entire 14-day treatment period (MP440)

Treatment	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff. from placebo	95%Confidence interval	P value
MP03_36QD	266	18.48	-3.29	-1.41	-2.06, -0.76	0.000*
Placebo	266	17.98	-1.88			

Table 16 Summary of primary efficacy analyses from the SAR studies

Superior to placebo?		SAR Study			
		MP433	MP438	MP439	MP440
MP03-36	Once daily	No		Yes	Yes
MP03-36	Twice daily	Yes	Yes		
MP03-33	Twice daily	No	Yes		

SAS data set used: EFF1
Program: Ana eff1.sas

The statistical findings for the SAR studies are summarized in the following points:

- MP03-36 bid showed consistently to be statistically significantly superior to placebo in Studies MP433 and MP438.
- MP03-33 bid also showed to be superior to placebo, but failed to reach statistical significance at 2-sided level of 0.05 in Study MP433.
- Superiority of MP03-36 qd to placebo was consistently shown among SAR studies: MP433, MP439 and MP440. However, statistical significance was reached only in Studies MP439 and MP440.
- Difference between MP03-36 bid and MP03-33 bid is not clear as the results are inconsistent among the studies MP433 and MP438.

Overall, accounting for evidence from all these four studies, MP03-36, at bid or qd, demonstrated superiority to placebo in treating SAR.

Analyses for the PAR indication

Table 17 Analysis of change in 12-hr AM plus PM reflective TNSS from baseline to entire 28-day treatment period (MP434)

Treatment	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff. from placebo	95%Confidence interval	P value
MP03_36BID	192	15.75	-4.01	-0.88	-1.69, -0.07	0.0328*
MP03_33BID	194	15.48	-3.84	-0.72	-1.52, 0.09	0.0814
Placebo	192	14.71	-3.13			

Source: D_TNSS.
Total subjects included in the ITT population: 578.

The results shown in Table 17 are slightly different from those of the sponsor. An information inquiry was sent to the sponsor to request its computer program that produced its results. After evaluated the sponsor's data-generating procedures and statistical method (submitted 1/26/09), an explanation for the difference is presented in Table 18. Different ANCOVA models lead to slightly different results.

Table 18 Explanation for the discrepancy between the sponsor's results and the reviewer's results (MP434)

Explanation for the discrepancy

Sponsor's Analysis
Source data set: D_TNSS

```
/*sponsor's model*/
Proc mixed;
    Where 2<= days <=28;
    Class rxgrp invsite pt days;
    Model chgcomr = rxgrp invsite
          days rxgrp*days basecom;
  *repeated/type=uns ub=pt(rxgrp);
    random pt;
    Lsmeans rxgrp /pdiff cl;
quit;
```

Reviewer's Analysis
Source data set: D_TNSS

```
/*reviewer's model*/
proc mixed;
class    rxgrp INVSITE;
model    CHGCOM=rxgrp INVSITE BASE;
lsmeans  rxgrp/cl pdiff;
quit;
```

Sponsor's results:

Treatment	Comparator	LS-mean	P-value	Lower CL	Upper CL
MP03_33BID	MP03_36BID	0.2377	0.5602	-0.5620	1.0374
MP03_33BID	Placebo	-0.5412	0.1855	-1.3426	0.2601
MP03_36BID	Placebo	-0.7789	**0.0577**	-1.5833	0.02545

Reviewer's results:

Treatment	Comparator	LS-mean	P-value	Lower CL	Upper CL
MP03_33BID	MP03_36BID	0.2174	0.5924	-0.5797	1.0144
MP03_33BID	Placebo	-0.6505	0.111	-1.4512	0.1502
MP03_36BID	Placebo	-0.8679	**0.033**	-1.6707	-0.06509

Note that the difference was caused by different statistical models.

Table 19 Analysis of change in 12-hr AM plus PM reflective TNSS from baseline to entire 28-day treatment period (MP435)

Treatment	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff. from placebo	95%Confidence interval	P value
MP03_36_AM	53	15.17	-4.89	-1.19	-3.48, 1.09	0.3001
Placebo_AM	23	15.79	-3.70			
MP03_36_PM	50	15.13	-3.90	-0.88	-3.04, 1.28	0.4167
Placebo_PM	27	14.34	-3.02			

Table 20 Summary of primary efficacy analyses from the PAR studies

Superior to placebo?		PAR Study	
		MP434	MP435
MP03-36 AM	Once daily		No
MP03-36 PM			No
MP03-36	Twice daily	Yes	
MP03-33		No	

SAS data set used: EFF1
Program: Ana eff 435.sas

The statistical findings for the PAR studies are summarized in the following points:

- The statistically significant superiority of MP03-36 bid over placebo in treating PAR was shown in Study MP434.
  The superiority of MP03-36 qd was not shown.

Analyses of secondary efficacy variables

Onset of Action

The "onset of action" was assessed using the change from baseline in instantaneous TNSS over 4 hours following the initial administration of the study drug. This was a secondary efficacy endpoints included in Studies MP433 and MP438. The sponsor did not make any labeling claim regarding the onset of action.

The following points summaries the findings of onset of action by the sponsor.

- In MP433, MP03-06 BID showed a statistically significant improvement compared with placebo at 45 minutes, but no significant improvements were found at 60, 150, and 240 minutes.
- In MP438, MP03-06 BID showed a statistically significant improvement compared with placebo at 30 minutes onward throughout the 4-hour time span.

Based on these findings, the onset of action was not established.

Analysis based on Instantaneous TNSS

The change from baseline for entire 14-day treatment period in instantaneous TNSS was a secondary efficacy variable. I performed analysis of instantaneous TNSS for Studies MP433, MP438, MP439, MP440, and MP434 for future reference purposes. The results are shown below in Table 21 through Table 25.For these analyses, I used ANCOVA including terms of treatment and center with baseline instantaneous TNSS as the covariate. Note that the sponsor used repeated measures analysis for MP438, MP440, and MP434; and ANCOVA for MP433 and MP439.

Table 21 Analysis of instantaneous TNSS (Study 433)

Treatment	Comparator	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff	95%Confidence interval	P value
MP03_36QD	Placebo	158	17.99	-3.35	-0.33	-1.28, 0.62	0.492
MP03_36BID	MP03_33BID	153	17.27	-3.73	0.15	-0.80, 1.11	0.752
MP03_36BID	Placebo	153	17.27	-3.73	-0.71	-1.67, 0.25	0.145
MP03_33BID	Placebo	153	17.09	-3.89	-0.87	-1.82, 0.09	0.075
Placebo		153	17.17	-3.02			

Table 22 Analysis of instantaneous TNSS (Study 438)

Treatment	Comparator	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff	95%Confidence interval	P value
MP03_36	MP03_33	177	16.31	-4.24	-0.80	-1.74, 0.13	0.091
MP03_36	Placebo	177	16.31	-4.24	-2.61	-3.53, -1.69	0.000
MP03_33	Placebo	169	17.11	-3.43	-1.80	-2.74, -0.87	0.000
Placebo		177	16.42	-1.63			

Table 21 and Table 22 indicate that the superiority of MP03-66 BID to placebo was shown for instantaneous TNSS for the SAR indication. However, the statistical significance at 2-sided 0.05 level was only reached in Study 438.

The same analysis was performed for Studies MP439 and MP440 (Table 23 and Table 24). The superiority of MP03-66 QD to placebo was shown for instantaneous TNSS for the SAR indication. The findings are consistent with those reported by the sponsor.

Table 23 Analysis of instantaneous TNSS (Study 439)

Treatment	Comparator	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff	95%Confidence interval	P value
MP03-66 QD	Placebo	238	16.04	-2.90	-0.81	-1.54, -0.09	0.0281
Placebo		242	16.18	-2.09			

Table 24 Analysis of instantaneous TNSS (Study 440)

Treatment	Comparator	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff	95%Confidence interval	P value
MP03-66 QD	Placebo	266	17.06	-2.75	-1.31	-1.97, -0.64	0.000
Placebo		266	16.30	-1.45			

Table 25 shows that the superiority of MP03-66 BID to placebo was demonstrated for the PAR indication in instantaneous TNSS. The findings are consistent with those reported by the sponsor.

Table 25 Analysis of instantaneous TNSS (Study 434)

Treatment	Comparator	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff	95%Confidence interval	P value
MP03_36BID	MP03_33BID	192	14.27	-3.40	-0.07	-0.84, 0.70	0.859
MP03_36BID	Placebo	192	14.27	-3.40	-0.86	-1.64, -0.09	0.03
MP03_33BID	Placebo	194	13.89	-3.33	-0.79	-1.57, -0.02	0.045
Placebo		192	13.27	-2.54			

Evaluation of Safety

Study 436

Safety Analysis

This is an on-going 1-year safety and tolerability study. Submitted now is a 6-month Interim report. Patients in this study included those who participated in MP434 and MP435 and treated with MP03-36, they also included those newly identified patients who met the inclusion/exclusion criteria. The patients were randomized in a 2:1 ratio to MP03-36 bid or Nasonex qd. This was an open-label study. To perform an analysis of AE, the sponsor's data set AE was combined with other data sets submitted: D_EVAL, ENDOFSTUDY, and RANDOMIZATION. AEs reported in 2% or more of the total patients in the same treatment group are presented in Table 26, below. In my observation, the leading adverse reactions were headache, dysgeusia, and epistaxis. For most AEs, the percentages of the patients between the two groups appear comparable, except for dysgeusia for which the percentage in the MP03-36 group was much higher than that in the Nasonex group. However, I would leave the meaningful interpretation of the AEs to the medical reviewer responsible for this NDA submission.

Table 26 Analysis of AEs (Study 436)

AEs presented as MedDRA preferred terms	Treatment			
MP03-36: N=465	MP03-36		Nasonex	
Nasonex: N=238	N	%	N	%
Total: N=703				
(No AE)	182	39.14	110	46.22
Headache	41	8.82	26	10.92
Dysgeusia	61	13.12	2	0.84
Epistaxis	29	6.24	20	8.40
Nasal Discomfort	35	7.53	10	4.20
Upper Respiratory Tract Infection	24	5.16	13	5.46
Nasopharyngitis	20	4.30	8	3.36
Sinusitis	19	4.09	9	3.78
Pharyngolaryngeal Pain	16	3.44	11	4.62
Cough	10	2.15	10	4.20
Fatigue	16	3.44	2	0.84
Somnolence	16	3.44	2	0.84
Sinus Headache	12	2.58	4	1.68
Nasal Congestion	9	1.94	6	2.52
Sneezing	14	3.01	1	0.42
Back Pain	10	2.15	3	1.26
Migraine	8	1.72	3	1.26
Ear Pain	4	0.86	5	2.10

Source: AE, D_EVAL, ENDOFSTUDY, RANDOMIZATION

Efficacy Analysis

The analysis of RQLQ was the efficacy component of this study. Table 27 shows the comparison in total RQLQ between MP03_36 and Nasonex. The p-value was p=0.065.

Table 27 Analysis of RQLQ based on 6-month interim data (MP436)

Treatment	N	LS-mean Baseline	LS-mean change from baseline	LS-mean diff. from placebo	95%Confidence interval	P value
MP03_36	331	2.98	-1.32	0.21	-0.01, 0.43	0.065
Nasonex	198	2.97	-1.53			

SAS data set used: rqlq_ana

Conclusions and Recommendations

Based on the statistical evidence, MP03-06 twice daily is recommended for the treatment of **seasonal** and **perennial** rhinitis. MP03-06 once daily is recommended for the treatment of **seasonal** rhinitis alone.

COMMENTS ON LABELING

Clinical Studies

I evaluated the CLINICAL STUDIES section of the proposed label. I verified the numbers in the following table based on reanalysis of the sponsor's data. With some minor changes, I propose to use the following table.

Table 28 Mean Change from Baseline in Reflective TNSS *
in Adults and Children ⩾ 12 years with Seasonal or Perennial Allergic Rhinitis

Table 2. Mean Change from Baseline in Reflective TNSS * in Adults and Children ≥ 12 years with Seasonal or Perennial Allergic Rhinitis						
Treatment	n	Baseline LS Mean	Change from Baseline	Difference From Placebo		
				LS Mean	95% CI	P value
Seasonal Allergic Rhinitis						
2 Sprays per Nostril Twice Daily for 2 Weeks						
TRADENAME Nasal Spray	177	17.72	-5.09	-2.97	(-3.87, -2.06)	<0.001
Azelastine HCL 0.1% Nasal Spray	169	18.18	-4.19	-2.07	(-2.99, -1.15)	<0.001
Placebo Vehicle	177	17.73	-2.12			
2 Sprays per Nostril Once Daily for 2 weeks						
TRADENAME Nasal Spray	266	18.48	-3.29	-1.41	(-2.06, -0.76)	<0.001
Placebo Vehicle	266	17.98	-1.88			
Perennial Allergic Rhinitis						
2 Sprays per Nostril Twice Daily for 4 Weeks						
TRADENAME Nasal Spray	192	15.75	-4.01	-0.88	(-1.69, -0.07)	0.0328
Azelastine HCL 0.1% Nasal Spray	194	15.48	-3.84	-0.72	(-1.52, 0.09)	0.0814
Placebo Vehicle	192	14.86	-3.33			
*Sum of AM and PM rTNSS for each day (Maximum score=24) and averaged over the 14 or 28 day treatment period						

Adverse Reactions

The 6-month interim data from the 1-year safety and tolerability study were evaluated. The focus of the evaluation was on the AE findings. Adverse reactions reported in 2% or more of the total patients are presented in the following table.

AEs presented as MedDRA preferred terms MP03-36: N=465 Nasonex: N=238 Total: N=703	Treatment			
	MP03-36		Nasonex	
	N	%	N	%
(No AE)	182	39.14	110	46.22
Headache	41	8.82	26	10.92
Dysgeusia	61	13.12	2	0.84
Epistaxis	29	6.24	20	8.40
Nasal Discomfort	35	7.53	10	4.20
Upper Respiratory Tract Infection	24	5.16	13	5.46
Nasopharyngitis	20	4.30	8	3.36
Sinusitis	19	4.09	9	3.78
Pharyngolaryngeal Pain	16	3.44	11	4.62
Cough	10	2.15	10	4.20
Fatigue	16	3.44	2	0.84
Somnolence	16	3.44	2	0.84
Sinus Headache	12	2.58	4	1.68
Nasal Congestion	9	1.94	6	2.52
Sneezing	14	3.01	1	0.42

AEs presented as MedDRA preferred terms MP03-36: N=465 Nasonex: N=238 Total: N=703	Treatment			
	MP03-36		Nasonex	
	N	%	N	%
Back Pain	10	2.15	3	1.26
Migraine	8	1.72	3	1.26
Ear Pain	4	0.86	5	2.10

Source: Table 26 in this review.

The sponsor stated in Section 6 of the proposed label, (b) (4) These AEs were confirmed in my reanalysis of the AE data. It should be noted that the AE, Upper Respiratory Tract Infection occurred in 24 patients in the MP03-36 group, representing 5.16% of the patients in that group; the same AE occurred in 13 patients in the Nasonex group, representing 5.46% of the patients in that group. Therefore, Upper Respiratory Tract Infection should also be included in the label.

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/s/

Ted Guo
4/9/2009 03:23:06 PM
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Stat review

Qian Li
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