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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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.

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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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