

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-203

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

SECONDARY STATISTICAL REVIEW

NDA/Serial Number: 22-203

Drug Name: Sweetened formulation of Azelastine hydrochloride 137 mcg nasal spray (Proposed trade name: _____)

Indication(s): Proposed for the treatment of seasonal allergic rhinitis and vasomotor rhinitis in patients 5 years of age and older

Applicant: MedPointe Pharmaceuticals

Date(s): Submitted: July 30th, 2007

Review Priority: Standard

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Introduction

This NDA contains information of a revised formulation of azelastine hydrochloride (HCL) 137 mcg nasal spray, named MP03-33, submitted by MidPointe pharmaceuticals. This new formulation contained sucralose and sorbitol and intended to enhance the palatability of the original formulation -- Astelin®, with which complains of bitter taste was reported. Astelin® was first approved in US under NDA 20-114 for the indication of seasonal allergic rhinitis (SAR) in patients 12 years of age and older for two sprays per nostril BID in 1996, later in patients 5-11 years of age for one spray per nostril BID in 2000, and one spray per nostril BID in patients 12 years of age and older in 2006. The indication for vasomotor rhinitis was approved in patients 12 years of age and older for two sprays per nostril BID in 2000. MidPointe sought for the approval of MP03-33 for all the indications and dosing regimens that were approved for Astelin®.

In this submission, the sponsor submitted the following five studies:

- Study MP429 was a randomized, open-label, single center, parallel group study to determine the bioavailability of three intranasal formulations of azelastine HCl in healthy volunteers.
- Study MP430 was a randomized, double-blind, placebo controlled, and multi-center study to evaluate the safety and efficacy of MP03-33 in patients with SAR.

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- Study MP432 was a randomized, open-label, active controlled study to evaluate the safety of MP03-33 in patients with chronic allergic and nonallergic rhinitis.

- Study _____ . This study was not conducted by MidPointe.

Among the five studies, Studies MP429, MP430, and MP432 were required studies for the evaluation of the new formulation.

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The primary statistical reviewer of this submission was Dr. Ted Guo, who provided detailed evaluation of Studies MP430 and _____. The two studies were identified for review because Study MP430 provided efficacy information for MP03-33 and _____

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_____. However, information on this study was not submitted at filing stage and was submitted later during the review of the NDA. As the statistical reviewers did not receive notification of the submission of the study in a timely manner, this study was not covered in the primary statistical review.

This secondary statistical review documented findings, statistical concerns and issues arose during the review.

SAR indication

Design of Study MP430

The efficacy evaluation of MP03-33 and comparability assessment between MP03-33 and Astelin® was conducted in Study MP430. This was a randomized, double-blind, placebo vehicle controlled, parallel group, and multi-center study. Patients 12 years of age and older with a minimum of 2-year history of SAR and positive skin tests to a relevant seasonal allergen were randomized to MP03-33 one or two sprays per nostril, Astelin® one or two sprays per nostril, and placebo one or two sprays per nostril. The treatment was administered twice daily. The period of double-blind treatments was 2 weeks, which was followed by a 1-week placebo run-in period. The nasal symptoms, including runny nose, itchy nose, nasal congestion, and sneezing, were assessed twice daily in the morning (AM) and evening (PM) reflectively. Instantaneous symptom assessments were measured at 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes the first day after the administration the study drugs. Each individual symptom was rated on a scale of 0-3, with 0 as no symptom and 3 as the worst symptom. The rhinitis quality of life questionnaire (RQLQ) was also assessed at baseline and Day 14 of the treatment period.

The sum of the AM and PM total nasal symptom score (AM+PM TNSS) was used for the efficacy assessment. The primary endpoint was defined as the average change from baseline in the AM+PM TNSS over the 2-week treatment period. There were two key secondary efficacy endpoints:

- Onset of action: change from baseline in instantaneous TNSS compared to placebo over the 4-hour period following the initial administration of study drug;
- Change from baseline in RQLQ at Day 14.

The primary analyses were conducted in an intent-to-treat (ITT) patient population which included all patients who were randomized and had at least one post baseline assessment. Missing TNSS values in the ITT patient population were imputed using the last observation carried forward method. Analysis of covariance model was used in the primary statistical review including baseline, treatment and center as covariates for analyses of the primary efficacy variable, RQLQ, as well as the analyses for the onset of action.

Study MP430 randomized 835 patients, of which 139, 137, and 137 were in MP03-33, Astelin®, and vehicle one spray treatment groups, respectively, and 146, 138, and 138 in MP03-33, Astelin®, and vehicle two spray treatment groups, respectively. All patients except one of the randomized patients in the Astelin® 2 spray group were included in the ITT population.

Primary efficacy analyses of Study MP430:

The primary efficacy analyses from the primary statistical review are summarized in Table 1. As shown in Table 1, the symptom reductions in the MP03-33 and Astelin® 2 spray treatments were statistically significantly greater than the symptom reduction seen in the placebo 2 spray treatment. The statistically significant treatment difference was not observed in the 1 spray treatment groups. In both 1 and 2 spray treatments, MP03-33 showed numerically larger symptom reductions than Astelin®, which may indicate that MP03-33 was no worse than Astelin® in treating the symptoms of SAR. However, as there was a concern of possible

unblinding the identity of the treatments due to the difference in taste of the study medications, such observations may not be robust.

Table 1: Mean change from baseline in reflective AM+PM TNSS averaged over 14 days of treatment from Study MP430.

Treatment	N	Baseline	Change from baseline	Difference from placebo		
				Estimate	95% CI	p-value
One spray						
MP03-33	139	18.1	-4.2	-0.7	-1.7, 0.3	0.181
Astelin®	137	18.1	-3.9	-0.4	-1.5, 0.6	0.405
Placebo	137	17.9	-3.5			
Two sprays						
MP03-33	146	18.0	-5.0	-2.2	-3.2, -1.2	<0.001
Astelin®	137	18.1	-4.2	-1.4	-2.4, -0.4	0.008
Placebo	138	18.1	-2.8			

Source: Dr. Ted Guo's primary statistical review.

Onset of action from Study MP430:

Based on Dr. Guo's analyses, the results of onset action showed that the onset time of MP03-33 1 spray was at 15 minutes after the initiation of treatment and that of MP03-33 2 sprays was at 30 minutes.

The onset time of Astelin® 1 spray was not established over the 4-hour period assessed in the study. The onset time of Astelin® 2 sprays was 45 minutes.

RQLQ from Study MP430:

The analyses of RQLQ performed by Dr. Guo included only patients who had RQLQ assessment at Day 14. The analysis results are summarized in Table 2. As shown in Table 2, only the MP03-33 2 spray treatment showed a difference in magnitude that was larger than the minimum important clinical difference which was defined as '—'. b(4)

Table 2: Analyses of RQLQ from Study MP430.

Treatment	N	Baseline	Change from baseline	Difference from placebo		
				Estimate	95% CI	p-value
One spray						
MP03-33	138	3.5	-1.0	-0.1	-0.4, 0.2	0.580
Astelin®	135	3.8	-1.2	-0.3	-0.6, 0.0	0.083
Placebo	136	3.6	-0.9			
Two sprays						
MP03-33	143	3.7	-1.4	-0.6	-0.9, -0.3	<0.001
Astelin®	136	3.7	-1.2	-0.3	-0.6, -0.0	0.042
Placebo	137	3.7	-0.9			

Source: Dr. Ted Guo's primary statistical review.

Vasomotor rhinitis indication:

No study was available for this indication.

Statistical issues

Blinding

Due to differences in taste of the three treatments used in Study MP430, blinding could be broken by recognizing the taste of the treatment received. The protocol did not take any measures to disguise the taste differences among the treatments.

Establishing comparability between MP03-33 and Astelin®

One of the objective of Study MP430 was to evaluate the comparability of MP03-33 and Astelin® . However, the study protocol did not specify any criteria to establish the equivalence between MP03-33 and Astelin®.

Data handling in the primary statistical review

In Study MP430, the primary statistical reviewer noticed irregular data in TNSS in two patients. Patient 01-036 who had only TNSS symptom score on Day 1 and missing for the rest of the treatment period. Patient 19-044 had symptom scores of 0 from Day 2 to the end of the treatment period. By the definition of ITT patient population, the two patients should be included in the ITT population for the primary efficacy analysis. In the primary reviewer's analyses, missing data for Patient 01-036 was carried forward to the entire study period; the symptom scores of 0 for Patient 19-044 were used for Day 2 to Day 14 in the calculation of the average change from baseline in TNSS over the 14-day treatment period.

Conclusion

Based on Study MP430, MP03-33 2 sprays per nostril administered twice daily showed to be efficacious in treating symptoms of SAR in patients 12 years of age and older when compared

with placebo 2 sprays. The treatments with MP03-33 1 spray and Astelin® 1 spray did not show statistically significant improvements in SAR symptoms compared with placebo 1 spray.

Study MP430 showed that, numerically, MP03-33 was no worse than Astelin® with both 1 and 2 sprays. However, it was not clear how robust the study results were if the treatment identities can be determined by taste.

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In Study MP430, only the MP03-33 2 spray treatment showed an improvement in RQLQ that was larger in magnitude than the required MID. This observation was not replicated.

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Qian Li
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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 22203

Drug Name: _____, (MP03-33 azelastine nasal spray)

Indication(s): _____ is indicated for the treatment of the symptoms of seasonal allergic rhinitis including itchy nose, runny nose, sneezing, nasal congestion for patients 12 years of age and older

Applicant: MedPointe

Date(s): Applicant's submission date: 7/30/07

Review Priority: Standard

Biometrics Division: Biometrics Division 2

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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. The recommended dose regimens are: 1 or 2 sprays per nostril bid for patients 12 years of age and older and 1 spray per nostril bid for patients 5-11 years of age. Because of reported bitter taste and nasal burning with Astelin nasal spray, the sponsor developed a new formulation MP03-33 (——— of azelastine hydrochloride nasal spray to improve the adherent use of the product. The sponsor submitted Study 430 to support the efficacy evaluation of MP03-33 and ' ———

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The study results showed that MP03-33 administered 2 sprays per nostril bid were statistically superior to placebo. ———

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—————. However, MP03-33 administered 1 spray per nostril bid did not show statistical superiority to placebo. Taking evidence from previous clinical trials into consideration, the approvability of MP03-33 at 1 spray per nostril bid is considered to be a regulatory decision.

The most frequent AEs reported in this NDA included dysgeusia, headache, epistaxis, nasal discomfort, fatigue, pharyngolaryngeal pain, and somnolence, most of which have been included in the proposed label.

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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. The recommended dose regimens are 1 or 2 sprays per nostril bid for patients 12 years of age and older and 1 spray per nostril bid for patients 5-11 years of age. Because of reported bitter taste and nasal burning with Astelin nasal spray, the sponsor developed a new formulation, MP03-33, of azelastine

hydrochloride nasal spray to improve the adherent use of the product. With this purpose, the sponsor conducted Study 430 and submitted the study report to seek approval of the safety and efficacy claims of the new formulation, MP03-33 of Astelin nasal spray. —

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Scope of Statistical Review

This statistical review includes (1) evaluation of the effectiveness of MP03-33 in comparisons with placebo and Astelin as well the onset time of MP03-33, and (2) an analysis of the AE data to evaluate the safety findings.

Data Sources

The sponsor submitted its study report in paper and its data in electronic format to the FDA's Electronic Document Room. All the data were submitted in SAS v.5 transport format and were converted to SAS data set for statistical evaluations.

Statistical Evaluation

Study 430

Evaluation of Efficacy

Study Designs and Endpoints

Study 430 was a randomized, double-blind, parallel-group, placebo-controlled clinical study to compare MP03-33 at 1 or 2 sprays per nostril with Astelin 1 or 2 sprays per nostril, and placebo 1 or 2 sprays given twice daily (bid) in patients aged 12 years and older with moderate-to-severe SAR. There were a total of 6 treatment groups. A computer-generated randomization code was used to assign patients to the treatment groups.

The primary efficacy variable was the change from baseline to the 14-day double-blind period in reflective 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.