CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-203

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 30, 2008
From	Sally Seymour, MD, Medical Team Leader, DPAP
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA# 22-203
Proprietary / Established (USAN) names	[redacted]/azelastine hydrochloride nasal spray, 137mcg
Dosage forms /strength	Nasal spray 0.1%
Proposed Indication(s)	1. Seasonal allergic rhinitis in adults and children 5 years of age and older 2. Vasomotor rhinitis is adults and children 12 years of age and older
Recommended:	Not Approvable

1. Introduction

MedPointe submitted a 505(b)(1) new drug application (NDA# 22-203) on July 30, 2007, for a sweetened azelastine nasal spray for the treatment of symptoms of seasonal allergic rhinitis (SAR) in patients 5 years of age and older and for the treatment of vasomotor rhinitis (VMR) in patients 12 years of age and older. The proposed tradename is [redacted]. The proposed dosing regimen is 1-2 sprays twice daily. An unsweetened azelastine nasal spray is currently approved for the same indications (NDA# 20-114, Medpointe) under the tradename Astelin Nasal Spray, but because of the bitter taste, Medpointe developed the proposed sweetened formulation, which contains the additional excipients, sucralose and sorbitol.

This memo will provide an overview of the application, with a focus on any review issues that warrant discussion, including the lack of support for the following: the VMR indication, SAR indication in children 5 to < 12 years of age, the [redacted] and the [redacted] b(4)
There are no disagreements between primary and secondary viewers to expand upon in this memo. Throughout this document, the sweetened azelastine nasal spray will be referred to as MP03-33.

2. Background

Azelastine hydrochloride is a selective, H_1 antihistamine, and is approved in the US in an ophthalmic solution, Optivar, and in a nasal spray solution, Astelin Nasal Spray. Astelin Nasal Spray was originally approved in the US in November 1996 for the treatment of SAR at a dosage of two sprays per nostril twice daily and in February 2006, as one spray per nostril twice daily. Azelastine hydrochloride nasal spray is approved and marketed for the treatment of symptoms of allergic rhinitis in more than 80 countries worldwide, including most of Europe, and has nonprescription status in many of these countries. The US and the worldwide formulations are similar except for slight differences in the amount of excipients. In most countries, the dosage is one spray per nostril twice daily, but some countries also include the two sprays per nostril twice daily dosage. According to the Applicant there have been no

marketing withdrawals, suspensions, failure to obtain renewal, restrictions on distribution or clinical trial suspensions worldwide.

Astelin Nasal Spray is currently approved for the following indications in the US:

- Seasonal allergic rhinitis (SAR)
  - Children 5 to 11 years - 1 spray per nostril twice daily
  - Adults and children 12 years of age and older -1 or 2 sprays per nostril twice daily
- Vasomotor rhinitis (VMR) in adults and children 12 years of age and older - 2 sprays per nostril twice daily

According to the Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, in vitro tests may be used to document BE for a change in formulation for a nasal spray solution. However, the sweetened and unsweetened formulations are not Q1 (qualitative) and Q2 (quantitative) the same and sucralose is a novel excipient in a nasal spray; therefore, clinical studies were required for this program. The development program for the sweetened azelastine formulation (MP03-33) is based upon comparability with the approved unsweetened azelastine formulation and thus is not a stand alone program. A clinical study comparing the efficacy and safety of MP03-33 and Astelin Nasal Spray and a long term safety trial with MP03-33 were performed. In addition, toxicology studies using the sweetened formulation were required to support the safety of the sweetened formulation. The following is the pertinent regulatory history for the clinical development program for MP03-33:

- May 3, 2005, meeting
  - Sweetened formulation proposed
  - A single SAR study (5 treatment arms) is acceptable to evaluate clinical comparability between the two formulations. Demonstration of clinical comparability is sufficient for approval of the SAR indication in patients 5 years of age and older; however, demonstration of clinical comparability should be convincing. Whether clinical comparability is demonstrated will be a review issue.
  - A single SAR study convincingly demonstrating comparability of the two formulations may be sufficient for carrying over the VMR indication.
  - Study statistically powered to compare active treatment arms vs. placebo is acceptable. A numeric comparison of the two different formulations will be performed. Demonstration of bioequivalence is not expected.
  - For PK program, evaluate BA of new formulation and determine 90% CI of pertinent PK parameters between the new and old formulations. PK information is supportive of safety.
  - 6 month IN toxicology study with sweetened formulation required
  - Pediatric discussion deferred
- September 20, 2005, Special Protocol Assessment for MP430 (comparability study)
  - Study design acceptable
  - Include one and two spray placebo group for blinding
  - b(4)
  - Will need a clinical safety program to support application
- November 30, 2005, Teleconference

- Clarification of need for clinical safety program – long term clinical safety data required because sucralose is novel excipient for IN use
- June 29, 2006, Pre-NDA communication
  - Reminder of tox study requirements
  - Long term safety study of sweetened formulation and placebo for 6 months is acceptable for NDA submission

Of note, the Applicant [redacted] b(4)

3. CMC/Device

MP03-33 is a new formulation of azelastine hydrochloride nasal spray that contains two additional excipients, sucralose and sorbitol. Sucralose is a novel excipient for a nasal spray. b(4)
Sorbitol has been used in other nasal sprays, but the concentration of sorbitol (—) in MP03-33 is higher than other nasal sprays. MP03-33 is a clear, aqueous solution with a pH of 6.4 that contains 0.1% w/v azelastine. MP03-33 contains the same active drug substance, azelastine hydrochloride, as Astelin Nasal Spray. The drug substance is manufactured by MEDA Pharma GmbH & Co. KG, (formerly Viatris GmbH) in Germany. There are no changes in specification of the drug substance. Both products contain 0.1% w/v azelastine and b(4)
deliver 137mcg azelastine/137mL actuation. The excipients are similar between the two products, except as noted above, MP03-33 contains sucralose and sorbitol and does not contain some [redacted] that are present in Astelin Nasal Spray. The drug product is packaged as 30mL fill volume in a —5mL high density polyethylene bottle fitted with a metered spray pump. The 30mL volume is sufficient to provide 200 sprays. The drug product is manufactured by MedPointe Pharmaceuticals in Decatur, Illinois.

The CMC reviewer noted that MP03-33 maintains the current physical, chemical, and spray characteristics using the same container and pump closure system as used in Astelin Nasal Spray. The drug product specifications are almost identical to the specifications for Astelin Nasal Spray.

The cGMP inspection status of all manufacturing and testing facilities was found acceptable in September 2007. The submitted data support that MP03-33 can be stored at room temperature with an expiry of 24 months. There are no outstanding CMC issues and the CMC reviewer, Dr. Martin Haber, recommends Approval.

4. Nonclinical Pharmacology/Toxicology

A full toxicology battery was submitted and previously reviewed under NDA 20-114 for Astelin Nasal Spray. To support the sweetened azelastine nasal spray formulation, the Applicant conducted a 6-month intranasal toxicology study in rats and a 2 month intranasal toxicology study in dogs. These studies were required because sucralose is a novel excipient in a nasal spray and the concentration of sorbitol in MP03-33 is higher than in other approved nasal spray products. The Division's pharmacology/toxicology reviewer, Dr. Luqi Pei, has

reviewed the toxicology studies and determined that MP03-33 and Astelin Nasal Spray have similar toxicity profiles. The main finding is local irritation of the nasal cavity. Dr. Pei recommends Approval of the application.

5. Clinical Pharmacology/Biopharmaceutics

One clinical pharmacology study (MP429) was submitted in this Application to compare the pharmacokinetics of MP03-33 to Astelin Nasal Spray and a higher strength formulation of azelastine nasal spray (~% azelastine) currently under development (MP03-36). In Study MP429, 54 healthy subjects were treated with a single dose of one of the following treatments: 1 spray per nostril of MP03-33, Astelin Nasal Spray, or MP03-36 or 2 sprays per nostril of MP03-33, Astelin Nasal Spray, or MP03-36 to assess comparative bioavailability between the formulations.

The results showed that there was there was slightly lower exposure, based upon Cmax and AUC for azelastine and the major active metabolite (desmethylazelastine) for MP03-33 compared to Astelin Nasal Spray, but all other PK parameters were similar. The lower exposure of azelastine and desmethylazelastine with MP03-33 along with the established systemic safety of Astelin Nasal Spray support the systemic safety of MP03-33. Although not relevant for this application, there was slightly greater than dose proportional pharmacokinetics between MP03-33 (548mcg) and the higher strength formulation, MP03-36 (822mcg). Refer to Dr. Partha Roy's clinical pharmacology review for a detailed review of this study.

6. Clinical Microbiology

Clinical microbiology is not applicable for this NDA.

7. Clinical/Statistical- Efficacy

As discussed in Section 2, the development program for MP03-33 is based upon demonstrating comparability with the approved unsweetened azelastine formulation (Astelin Nasal Spray). This approach was agreed to between the Division and the Applicant and is consistent with the Draft Guidance for Industry: Allergic Rhinitis - Clinical Development Programs for Drug Products. The Applicant submitted two clinical studies to demonstrate comparability of MP03-33 to Astelin Nasal Spray and support the safety and efficacy of MP03-33. Study MP430 is a two-week, safety and efficacy study in patients with seasonal allergic rhinitis (SAR) and Study MP432 is an ongoing 12 month safety study in patients with chronic allergic or nonallergic rhinitis. In addition, the Applicant submitted one PK study (Study MP429) and ——————————————— b(4)

The primary focus of this section is the two week comparability/safety and efficacy study (Study MP430). The ongoing 12 month comparability/safety study (Study MP432) will be discussed in Section 8, Safety. The ——————————————— The table below displays the clinical development program for MP03-33. A detailed review of the clinical studies can be found in Dr. Susan Limb's clinical review with detailed statistical analyses in Ted Guo's statistical review.

Clinical Development Program for [redacted]				
Study	**Design**	**Duration**	**Population**	**Treatment Groups**
MP429	R, OL **Pharmacokinetics**	Single dose	54 healthy subjects	MP03-33 - 1 spray per nostril MP03-33 - 2 sprays per nostril Astelin - 1 spray per nostril Astelin - 2 sprays per nostril MP03-36 (1.5% azelastine) - 1 spray per nostril MP03-36 (1.5% azelastine) - 2 sprays per nostril
MP430 Feb 2006- June 2006 US	MC, R, DB, PC, AC **Comparability, efficacy/safety study**	2 weeks	835 patients with SAR	MP03-33 - 1 spray per nostril BID MP03-33 - 2 sprays per nostril BID Astelin - 1 spray per nostril BID Astelin - 2 sprays per nostril BID Placebo sweetened vehicle - 1 spray per nostril BID Placebo sweetened vehicle - 2 sprays per nostril BID
MP432 July 2006- May 2007 **Ongoing** International	MC, OL, AC **Comparability/ Long-term safety**	12 months	559 NAR & chronic allergic rhinitis	MP03-33 - 2 sprays per nostril BID Astelin - 2 sprays per nostril BID

b(4)

Study MP430 – Two Week Efficacy, Safety, Comparability Study

Study MP430 was a two week, randomized, double-blind, placebo-controlled, active-controlled, parallel group trial of the safety and efficacy of MP03-33 compared to Astelin Nasal Spray in 835 patients 12 years of age and older with SAR. The general design and inclusion/exclusion criteria for Study MP430 are consistent with the Draft Guidance for Industry: Allergic Rhinitis- Clinical Development Programs for Drug Products. In addition, the Applicant submitted a Special Protocol Assessment (SPA) for Study MP430 in September 2005. The general study design was considered acceptable for the proposed comparability approach.

Study MP430 was a 6 arm parallel group trial. Following a one week run in period, eligible patients were randomized to one of the following treatment groups:

- MP03-33 - 1 spray per nostril twice daily
- Astelin Nasal Spray - 1 spray per nostril twice daily
- placebo (sweetened vehicle) - 1 spray per nostril twice daily
- MP03-33 - 2 sprays per nostril twice daily
- Astelin Nasal Spray - 2 spray per nostril twice daily
- placebo (sweetened vehicle) - 2 sprays per nostril twice daily.

Efficacy was assessed by the Total Nasal Symptom Score (TNSS), which included the following symptoms: runny nose, sneezing, itchy nose, and nasal congestion. Patients recorded scores for these symptoms on a 0 to 3 (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms) scale twice daily, in the morning (AM) and evening (PM) in patient diaries. Patients recorded both a 12 hour reflective score (how symptoms were over the previous 12 hours) and an instantaneous score (how symptoms are at the time of evaluation). For the primary efficacy endpoint, the AM and PM reflective TNSS (rTNSS) were summed for each day (maximum score of 24) and then averaged over the 14 day treatment period.

Secondary efficacy variables included onset of action over the 4-hour period following the initial dose of study medication, instantaneous TNSS (iTNSS), individual symptom rTNSS scores, and the change from baseline to Day 14 in Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The RQLQ is a validated instrument for assessing the impact of rhinitis on activities of daily living and overall well-being. It is a 28-item, disease-specific instrument designed to measure the seven domains of functional impairment that are most important to patients with SAR: sleep impairment, non-nasal symptoms (e.g., headache and fatigue), practical problems, nasal symptoms, eye symptoms, activity limitations, and emotional function. There is also an overall quality of life score for the RQLQ that is expressed as the mean of the seven individual domains. Patients are asked to consider their experiences over the previous seven days and to score their degree of impairment on a seven-point scale (0 = not bothered, 6 = extremely bothered). Safety assessments included adverse events and vital signs.

Efficacy analyses were performed on the intent to treat population, defined as all randomized patients who had at least one post-baseline assessment. Baseline was defined as the average of all TNSS scores over the 7 day placebo run-in period. Onset of action was defined as the first timepoint after initiation of treatment when the active drug demonstrated a change greater than placebo from baseline in the iTNSS and was maintained. The iTNSS was measured frequently during the first 4 hours after study medication administration on day one.

The results for the primary endpoint as determined by the Division's statistical reviewer, Dr. Ted Guo are shown in the table below. The numbers differ slightly from the Applicant's numbers, which are likely the result of differences in the model used for analysis; however, the differences do no change the interpretation of the study. For both the Astelin Nasal Spray and MP03-33, the one spray treatment groups were not statistically significant compared to placebo, but both treatment groups were numerically favorable compared to placebo. Both of the two sprays treatment groups were statistically significant compared to placebo. The results for the secondary endpoints were generally consistent with the primary endpoint, i.e. statistically significant compared to placebo for the two spray azelastine treatment groups and numerically favorable for the one spray azelastine treatment groups compared to placebo.

Study MP430 LS Mean Change from Baseline in Reflective TNSS over 2 Weeks*						
Seasonal Allergic Rhinitis						
Treatment	n	Baseline LS Mean	Change from Baseline	Difference from Placebo		
				LS Mean	95% CI	p-value
MP03-33 - 1 spray per nostril BID	139	18.14	-4.20	-0.70	-1.72, 0.32	0.181
Astelin 1 spray per nostril BID	137	18.10	-3.94	-0.44	-1.46, 0.59	0.405
Placebo vehicle 1 spray per nostril BID	137	17.93	-3.51			
MP03-33 - 2 sprays per nostril BID	146	17.95	-5.04	-2.20	-3.21, -1.20	< 0.0001
Astelin 2 sprays per nostril BID	137	18.13	-4.22	-1.39	-2.41, -0.36	0.0079
Placebo vehicle 2 spray per nostril BID	138	18.12	-2.83			
*sum of AM and PM rTNSS for each day and averaged over a 14 day treatment period						

The Applicant asserts that the one spray placebo treatment group had a greater response than the two spray placebo treatment group and compared to placebo in previous studies. To address the issue, the Applicant performed post hoc analyses with the placebo group data pooled for the one and two sprays. In this post hoc analysis, the one spray azelastine treatment groups were statistically significant compared to the pooled placebo treatment group. While the response for the one spray placebo treatment group did affect the results for the one spray azelastine treatment groups, this post hoc analysis is not convincing.

The objective of this study was to show the comparability between MP03-33 and Astelin Nasal Spray. Determination of comparability is worth discussion. As discussed in Section 2, clinical data were necessary for this program since the two formulations are not Q1 (qualitative) and Q2 (quantitative) the same. In the May 3, 2005, meeting with the Applicant, the Division noted that we would compare the dose response curves for the two products using a non-statistical approach (eyeball approach). However, because the one spray treatment groups failed to demonstrate efficacy, there is no dose response to assess comparability. Using a non-statistical approach, the results generally numerically favored MP03-33 compared to Astelin Nasal Spray. Another method of determining comparability outlined in the Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action is by using bioequivalence (BE) criteria using the response curve for the two formulations (90% confidence interval between 80-125%). The Division's statistician performed the BE analysis on the data for the two formulations and the products are not BE. It should be noted that in the May 3, 2005, the Division stated that we did not expect the Applicant to demonstrate bioequivalence between MP03-33 and Astelin Nasal Spray.

Based upon the above discussion, comparability is not convincingly demonstrated. It appears that the addition of the excipients, sucralose and sorbitol have an impact on the formulation and the local delivery of azelastine. That being said, because the data numerically favors MP03-33, with extrapolation from the Astelin Nasal Spray program, there is sufficient data from this single study to support the SAR indication for both one and two sprays per nostril twice daily in patients 12 years of age and older. However, because comparability was not convincingly demonstrated, carry over of other indications and claims should be supported by clinical data. This is consistent with other programs for change in formulation, such as the CFC to HFA albuterol switch programs. In these programs, a comparability approach was sufficient to support the primary indication, treatment of bronchospasm. However, any additional claims, such as exercise induced bronchospasm, required additional studies.

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

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_____ Deliberative Process (b5)

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