

Studies submitted and reviewed:

- 14-day Nasal Irritation Procedure in Rats (Study No. 0437RMS57.002)
- 14-day Intra-nasal toxicity study in dogs (Study No. 0437RMS57.003)
- 14-day Nasal Irritation Procedure in Rats (Study No. 16365)

Studies submitted and NOT reviewed: None.

Drug History:

This IND is currently in a phase-3 clinical development stage. A protocol for a phase-3 clinical trial (Protocol MP430) involving approximately 780 male and female patients 12 years and older is ongoing. Protocol MP430 was initially submitted as a special clinical protocol assessment request on September 21, 2005. The Division issued a letter responding to the request on November 4, 2005. As a part of the assessment of the protocol, the Division and MedPointe agreed that two 2-week intranasal toxicity studies would be submitted prior to initiation of the proposed clinical study. MedPointe submitted the above studies on February 13, 2006 and resubmitted Protocol MP430 on March 06, 2006. Protocol MP430 is now ongoing since MedPointe has fulfilled their commitment.

MedPointe is reformulating its currently marketed Astelin[®] Nasal Spray (azelastine HCl). This program attempts to rid the marketed product of an unfavorable (bitter) after-taste. The IND was opened with an oral taste screen study to aid the selection of a formulation for clinical development. The study has been completed. Based on the results of the taste screen study, MedPointe chose its to-be-developed formulation in April 2005. The new formulation is recently code-named MP03-33 (Serial No. 016, submission date of March 3, 2006). MP03-33 uses sucralose and sorbitol as sweetening agents to mask the bitter flavor. It discards citric acid (—%), dibasic sodium phosphate (—%) and sodium chloride (—%).

MP03-33 now consists of the following: 0.1% azelastine HCl, —% sucralose, —% hypromellose 2 —, —% edetate disodium, —% sorbitol, (b) (4) (—% sodium citrate, —% benzalkonium chloride and purified water. Each actuation delivers 0.137 ml of the formulation which contains 137 mcg of azelastine HCl, — μg sucralose and — μg sorbitol. Table 1 above provides the amount of other excipients released by each actuation.

Nonclinical concerns with MP03-33 development are potential toxicities associated with the new formulation and the unapproved inhalation use of excipients in the formulation. The unapproved excipients are sucralose and sorbitol. As indicated in the original pharmacology and toxicology review by Dr. Luqi Pei with the completion date of June 8, 2004, sucralose is not included as an excipient in any approved nasal spray products; the proposed sorbitol concentration is 2.3 times the highest concentration present in currently marketed products. The nonclinical program of MP03-33 needs to evaluate the safety of the new formulation (short-term) and the long-term use of sucralose.

MedPointe and the Division have had extensive discussions about the nonclinical requirement for the development and registration of the new formulation. These discussions were documented in the minutes of an End-of-Phase-2 meeting held on May 8, 2005 and a follow-up telephone conference held on June 8, 2005. The EOP2 meeting discussed overall

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requirements for registration of the product and timing for submitting animal toxicity studies. The Division informed MedPointe that 1) 14-day intranasal toxicity studies of the new formulation in 2 species which include at least one non-rodent species are needed to support clinical trials of 2-weeks duration, 2) intranasal toxicity studies of sucralose or the formulation up to 6 months in treatment duration are needed to support longer duration trials or for NDA filing.

The June 8, 2005, telephone conference continued the discussion on the nonclinical requirement for the 2-week, phase 3 clinical trials. MedPointe attempted to use a previously completed 2-week intranasal toxicity study of a different sucralose-containing formulation in rats (Study No. 16365) to support their clinical trials. The Division conducted a preliminary review of the study report. The review concluded that sucralose, although non-irritating by itself, may enhance the irritation associated with azelastine. The finding prompted the Division to reject MedPointe's argument that Study 16365 was adequate to support the safety of 2-week clinical trial. The Division informed MedPointe that 2-week intranasal toxicity studies of the to-be-developed formulation in two species are needed to support to support clinical trials of 2-weeks in duration. MedPointe initiated 14-day intranasal toxicity studies of the new formulation in rats and dogs in early September 2005.

On September 21, 2005 (Serial No. 003), MedPointe filed a Special Clinical Protocol Assessment Request. The request proposed a 2-week, phase-3 clinical protocol that involves approximately 630 rhinitis patients. Each patient would be treated with Astelin[®] or the new formulation for 14 days (Protocol MP430). The request acknowledged that MedPointe lacked the necessary nonclinical support for the protocol. On November 4, 2005, the Division issued a letter which acknowledged MedPointe's agreement that the study would not be initiated without submitting two 14-day intranasal toxicity studies of the new formulation or sucralose. This action was based on nonclinical deficiencies identified in a pharmacology and toxicology review (Review #2) by Dr. Luqi Pei with the completion date of November 4, 2005. Of note, the review recommends that the protocol be put on clinical hold and proposes comments to be sent to the sponsor. The review team later decided to accept the sponsor's commitment to provide the supporting toxicology studies and did not place the protocol on clinical hold.

MedPointe recently completed two 14-day intranasal toxicity studies of the new formulation in rats and dogs, and submitted their reports on February 16, 2006 (Serial No. 015). MedPointe also resubmitted Protocol 430 on March 3, 2006 (Serial No. 016). The resubmitted Protocol MP430 differs slightly from its original. The differences were apparently the results of a revision that incorporated the clinical comments from the medical team during the previously review. A notable difference is a name change for the new formulation that is now referred as MP03-33. These revisions do not impact on the nonclinical safety of the protocol.

MedPointe recently submitted another 14-day intranasal toxicity study of a different candidate formulation in rats (Study 16365, discussed briefly above). Two versions of the study report have been submitted. The first version was submitted in INDs 69,785 and 32,704 on February 18 and 21, 2005, respectively. As indicated in the minutes of a meeting between the Division and MedPointe held on May 3, 2005, the report lacked necessary

description of the testing formulation. On June 2, 2005, MedPointe submitted an amended report that supplied the formulation information.

This review evaluates the two 14-day intranasal toxicity studies of MP03-33 in rats and dogs, prerequisites for the initiation of clinical trials of MP03-33. The review also evaluates the final report of a 14-day study with a different formulation (Study 16365). Finally, the review reevaluates the safety of clinical Protocol MP 430.

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2.6.6 TOXICOLOGY

2.6.6.1 Brief Summary

Repeat dose toxicity

Two 14-day intranasal toxicity studies of a new formulation of azelastine HCl (MP03-33) in rats and dogs were completed to evaluate the irritation potential of sucralose to the respiratory tract (Studies 0437RM57.002 and 003). One-tenth of 1 ml/nostril of MP03-33 was instilled into the nasal cavity of Sprague-Dawley rats (10/sex/group) and beagle dogs (3/sex/group) twice a day for 14 days. Sucralose concentrations were 0, 0.05%, 0.1% and 0.15% respectively. The control (or reference) solution contained 0.1% azelastine, 0.1% hypromellose, 0.1% edetate disodium, 0.1% sorbitol, 0.1% sodium citrate, and 0.1% benzalkonium chloride. The respective total daily doses of azelastine/sucralose of the control, low, mid and high-dose groups, based on nasal surface area, were 40/0, 40/20, 40/40 and 40/60 $\mu\text{g}/\text{cm}^2$ in rats and 1.8/0, 1.8/0.9, 1.8/1.8 and 1.8/2.7 cm^2 in dogs. The results showed that the addition of sucralose at concentrations up to 0.15% to the azelastine formulation did not induce further irritation to the respiratory tract in rats or dogs. Also, based on the nasal surface area comparisons, the sucralose NOAEL was 60 and 2.7 $\mu\text{g}/\text{cm}^2$ in rats and dogs, respectively. The NOAEL for azelastine was not established in rats or dogs, but the studies were not designed to do so.

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Another 14-day intranasal toxicity study with a different formulation was completed in rats by a different laboratory (Study 16365). Sprague-Dawley rats (10/sex/group) were treated with 0.1 ml/nostril of Astelin® Nasal Spray solution, a vehicle, the vehicle plus 0.15% sucralose, or the vehicle plus 0.15% sucralose and azelastine HCl (0.1% or 0.15%) twice a day for 14 days. The vehicle consisted of 0.1% hypromellose, 0.1% edetate disodium, and 0.1% benzalkonium chloride. This study showed that: 1) neither sucralose with the vehicle nor a vehicle without sucralose or azelastine was irritating to the nasal cavity, 2) Astelin®, the marketed formulation, was irritating to the nasal cavity, 3) sucralose appeared to enhance the irritation potential of azelastine and 4) a formulation with 0.15% azelastine and sucralose induced an increased incidence of hemorrhage in the nasal cavity. This study is not used for safety evaluation because it employed a not to-be-developed formulation though it does provide information related to the approved Astelin formulation.

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2.6.6.3 Repeat-Dose Toxicity

Study Title: 14-Day Intranasal Toxicity Study with Azelastine and Sucralose in Sprague-Dawley Rats (Study 0437RM57.002)

Key findings: Intranasal administration of sucralose does not significantly affect the local toxicity of azelastine in rats. Sprague-Dawley rats (10/sex/group) were treated with a vehicle (reference, group 1) containing 0.1% azelastine and other excipients in the absence of sucralose for 14 days. Additional groups (Groups 2 – 4) were treated with the vehicle in presence of sucralose. The reference group consisted of 0.1% azelastine, 0.1% hypromellose, 0.1% edetate disodium, 0.1% sorbitol, 0.1% sodium citrate, and

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0.1% benzalkonium chloride. Formulations for groups 2 - 4 contained the components listed above and 0.05%, 0.1% and 0.15% sucralose for the low, mid and high concentrations of sucralose, respectively. Each nostril was instilled with 0.1 ml solution twice a day. The total daily administered doses of azelastine/sucralose, based on nasal surface area, were 40/0, 40/20, 40/40 and 40/60 $\mu\text{g}/\text{cm}^2$ for the control, low, mid and high dose groups, respectively. The respiratory system was examined microscopically. Low incidences of abnormalities were observed in the reference group in both sexes. The incidence was reflective of the local irritation associated with azelastine (reference: Study 16365, reviewed below). Addition of sucralose up to 0.15% in concentration did not significantly increase the incidence of these abnormalities. The sucralose NOAEL for local toxicity was 60 $\mu\text{g}/\text{cm}^2$ in rats, based on the nasal surface area. The NOAEL for azelastine was not established but the study was not designed to do so.

Study number:	0437RM57.002
Volume #, and page #:	Vol. C7.1, p 2 in IND 69785
Report Date:	February 3, 2006
Conducting laboratories and location:	_____
Date of study initiation:	September 12, 2005
study completion date:	September 30, 2005
GLP compliance:	Yes, with a signed page
QA reports:	Yes, with a signed page
Drug, lot #, radio-label, and % purity:	Batches 03-32-02C, 03-37-01C, 03-33-02C and Lot 0000002635 (Astelin [®] , 0.1% azelastine HCl), Purity: azelastine 99.6%, Sucralose: not available.

Methods

Sprague-Dawley rats (10/sex/group) were treated with an azelastine-containing vehicle (reference) in the absence or presence of sucralose twice a day for 14 days. The reference (Group 1) consisted of 0.1% azelastine, 0.1% hypromellose, 0.1% edetate disodium, 0.1% sorbitol, 0.1% sodium citrate, and 0.1% benzalkonium chloride. Additional groups (Groups 2 - 4) were treated with the reference plus varying concentrations of sucralose. Sucralose concentrations for the treated groups were 0.05%, 0.1% and 0.15% for Groups 2, 3 and 4, respectively. Each nostril was instilled with 0.1 ml solution twice a day with 6 hrs between doses. The total daily azelastine dose was 40 $\mu\text{g}/\text{cm}^2$ based on nasal surface area or 1.6 mg/kg based on body weight in each group including the reference group. The respective total daily dose of sucralose in the low mid, and high dose groups was 20, 40 and 60 $\mu\text{g}/\text{cm}^2$ on a nasal surface area basis and 0.8, 1.6 and 2.4 mg/kg on a body weight basis.

Doses:

Groups	1	2	3	4
Treatment	Reference	Reference + 0.05% sucralose	Reference + 0.10% sucralose	Reference + 0.15% sucralose
Sucralose /azelastine dose ^a				
mg/kg (based on body weight)	0/1.6	0.8/1.6	1.6/1.6	2.4/1.6
µg/cm ² (based on a nasal surface area)	0/40	20/40	40/40	60/40
mg/ml (based on concentration)	0/1.0	0.5/1.0	1.0/1.0	1.5/1.0

a. The doses were calculated from the following parameters: daily instillation volume of 0.4 ml (0.1 ml/nostril, twice a day), nasal surface area of 10 cm²/rat, body weight of 0.25 kg/rat, azelastine concentration of 1 mg/ml and sucralose concentrations of 0.5, 1 and 1.5 mg/ml.

Species/strain: Rats / — :CD(SD)
 #/sex/group (main study): 10
 Age: Approximately 9 weeks
 Weight (mean): M: 262 - 312 g; F: 197 - 232 g
 Route, formulation, volume and infusion rate: Nasal instillation, solution, , 1 ml/nostril, twice daily, 6 hrs between doses
 Sampling times: See below
 Unique study design: NA

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Observations and times:

Clinical signs: Once daily
Body Weights: Weekly
Food consumption: Not assessed
Ophthalmoscopy: Not assessed
EKG: Not assessed
Hematology: Not assessed
Clinical chemistry: Not assessed
Urinalysis: Not assessed
Gross Pathology: End of treatment (24 hrs after the last treatment)
Organ weights: Adrenal glands, brain, heart, kidneys, liver, lungs with trachea, gonads, pancreas, pituitary gland, prostate, spleen, and thymus, thyroid/parathyroid, uterus
Histology: Respiratory system only: nasal cavity, nasopharynx, larynx, trachea, lung with mainstem bronchus, tracheobronchial lymph nodes.
 Adequate Battery: yes (x), no () — as agreed during the May 8, 2005 End-of-Phase 2 meeting. The minutes states: "The studies should be designed to adequately evaluate the toxicity profile of sucralose and the sweetened formulation in the respiratory tract."
 Peer review: yes (), no (x)

Results:

Mortality: None