ATTACHMENT B

Pharmacology and Toxicology Review #6
by Dr. Luqi Pei completed on February 20, 2007, in IND 69,785.

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND Number:	69,785
Review Number:	6
Sequence No./Date/ Submission Type:	032/ 04-JAN-07/ IT 033/ 16-JAN-07/ PN, IC 034/ 30-JAN-07/ PN, IC
Information to the Sponsor:	None
Sponsor/or Agent:	MedPointe Pharmaceuticals, Somerset, NJ
Manufacturer of the Drug substance:	MedPointe Pharmaceuticals
Reviewer Name:	Luqi Pei, Ph.D.
Division Name:	Pulmonary and Allergy Products
Review Completion Date:	February 20, 2007
Drug:	
Trade Name:	Astelin® Nasal Spray
Generic Name:	Azelastine HCl
Code Name:	MP03-33 (0.1% azelastine) and MP03-36 (0.15% azelastine)
Relevant IND/NDAs:	NDA 20-114, INDs 32,704 and ———
Drug Class:	Antihistamine
Intended clinical population:	Allergic rhinitis (seasonal and perennial)
Route of Administration:	Nasal spray

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Clinical Formulations: Two aqueous nasal sprays of azelastine HCl: MP03-33 and MP03-36. MP03-33 and MP03-36 are two different dosage strengths. Concentrations of azelastine HCl was 0.1% and 0.15% for MP03-33 and MP03-36, respectively. Excipients of the two products are identical: 0.15% sucralose, 0.1% hypromellose ——— % edetate disodium, ——— % sorbitol (b) (4) (—%), (——% sodium citrate, and ——% benzalkonium chloride. Each actuation of both products delivers 0.137 ml of the formulation. The amount of azelastine HCl delivered per actuation is 137 and 206 μg for MP03-33 and MP03-36 respectively.

Proposed Clinical Protocols: This review conducts nonclinical safety evaluations of two protocols of proposed clinical trials. These clinical protocols are numbered MP 434 and MP435, respectively. The following briefly summarizes each protocol. Note the MP03-36 and MP03-33 contains different concentrations of azelastine (i.e., 0.15 and 0.1%, respectively), but use the same vehicle.

Protocol No. MP434: *Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of MP03-36 and MP03-33 in Patients with Perennial Allergic Rhinitis.* Five hundred-forty patients 18 years and older with perennial allergic rhinitis will be 2 sprays of MP03-36, MP33 or placebo per nostril twice daily for 4 weeks. There will be 180 patients in each group. The total daily dose of azelastine will be 1644, 1096, and 0 μg/day for patients in Arms 1, 2 and 3, respectively.

Protocol No. MP435: *Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of MP03-36 in Patients with Perennial Allergic Rhinitis.* Six hundred patients 18 years and older with perennial allergic rhinitis will be 2 sprays of MP03-36 or placebo per nostril once daily for 4 weeks. Patients will be divided into 4 groups (Arms). Patients in Arms 1 and 2 (200 each) will receive 2 sprays of MP03-36/nostril in the morning (Arm 1) or afternoon (Arm 2). As controls, patients in Arms 3 and 4 (100 each) will receive 2 sprays of placebo of MP03-36/nostril AM or PM. The total daily dose of azelastine will be, 822, 822, 0 and 0 μg/day for patients in Arms 1, 2, 3 and 4, respectively.

Previous clinical experience: Two 2-week clinical safety and efficacy trials of MP03-36 and MP03-33 (one each) have been completed. The first trial involved 780 patients while the second 600 patients. Each patient received up to 2 sprays/nostril of MP03-36 or MP03-33, bid for 14 days. Both products were generally well tolerated.

Disclaimer*: Tabular and graphical information are constructed by the reviewer unless cited otherwise.*

Studies submitted and reviewed:

6-month intranasal toxicity study with azelastine and sucralose in Sprague-Dawley rats (Study No. 0460RMS57.001)

Studies submitted and NOT reviewed: None.

Drug History:

This application is developing two new formulations of azelastine. They are named MP03-33 and MP03-36. These products differ only in their azelastine concentrations: 0.1% and 0.15% for MP03-33 and MP03-36, respectively. MP03-33 is to replace Astelin® Nasal Spray, the currently marketed product, while MP03-36 is a new product in development due to its higher than approved azelastine concentration. Consequently, MP03-36 may have enhanced clinical efficacy. Filing dates for the new formulations were 05-MAY-2005 (Serial 000) and 28-JUN-06 (Serial 025) for MP03-33 and MP03-36, respectively.

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The new formulations attempt to remove the bitter after-taste of Astelin® with new excipients: 0 —% sucralose and ' —% sorbitol. The inactive ingredients of MP03-33 and MP03-36 are identical (ref.: the Clinical Formulation section). This reformulation effort differs from others: it not only develops the dosage strength (0.1% azelastine HCl) identical to that of the approved product - Astelin®, but also introduces another unapproved formulation, MP03-36 that contains 0.15% azelastine HCL plus the excipients noted previously.

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The Division and MedPointe have had extensive discussions about regulatory requirements for the development of MP03-33 and MP03-36. A pharmacology/toxicology review completed by Dr. Luqi Pei on August 17, 2006 and minutes of the 08-MAY-2005 meeting and the 08-JUN-2006 telephone conference documented the discussions on MP03-33. The minutes of 29-AUG-2006 meeting documents the discussions on MP03-36. Briefly, clinical trials of either MP03-33 or MP03-36 with the treatment duration longer than 2 weeks need to be supported by adequate nonclinical data. Six-month intranasal toxicity studies with formulations MP03-33 and MP03-36 in rats would be sufficient to support clinical trials with treatment duration exceeding three months. Additional discussions will be held in the future if needed to evaluate the adequacy of a 6-month intranasal toxicity study(ies) that MedPointe recently submitted.

Both MP03-33 and MP03-36 are currently in the phase-3 clinical efficacy trial stage. A phase-3 clinical trial (Protocol MP427) of MP03-33 involving 780 rhinitis patients has been completed. A phase-3 clinical trial (Protocol MP433) of MP03-36 involving 600 rhinitis patients has also been completed. Patients have received up to 2 sprays of MP03-33 or MP03-36/nostril, bid for 14 days. The total daily dose of azelastine will be was up to 1644 , 1092 and 822 μg/day.

The sponsor recently submitted 2 more clinical protocols of MP03-36 and MP03-33 (MP434 and MP435) and a draft report of a 6-month toxicity study in rats (Submission Serial Nos. 032, 033 and 034). Both clinical protocols propose 4-week clinical trials of the to-be-developed products in adult patients with perennial allergic rhinitis. Protocol MP435, submitted on 16-JAN-2007 (Serial No. 033), proposes to study efficacy of MP03-36 once a day only. Protocol MP434, submitted on 31-Jan-2007 (Serial No. 034), proposes to study efficacy of both MP03-36 and MP03-33 twice daily. Serial No. 032 (submitted on 28-DEC-06) is an IT amendment that contains a draft report of a 6-month bridging intranasal toxicity study of MP03-33 and MP03-36 in rats. The current document reviews the animal toxicity study and conducts nonclinical safety evaluations of the newly proposed clinical protocols.

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2.6.6 TOXICOLOGY

2.6.6.1 OVERALL TOXICOLOGY SUMMARY

Local toxicity/irritation potential of MP03-33 and MP03-36 was evaluated in intranasal toxicity studies in the treatment duration up to 6 months in rats and 2 weeks in dogs. MP03-33 and MP03-36 are two reformulation products of the currently marketed Astelin® Nasal Spray. The azelastine concentration is 0.1%, 0.15% and 0.1% for MP03-33, MP03-36 and Astelin®, respectively. MP03-33 and MP03-36 use the same vehicle that differs from Astelin®. The new vehicle contains two ingredients, namely —% sucralose and —% sorbitol. The former represents a novel use of the excipient while the concentration of the latter is higher than the concentration present in approved products. The newly completed 6-month toxicity study, conducted with both to-be-marketed products, evaluates the toxicity of the new vehicle as well as the higher azelastine concentration (0.15%) on the respiratory system. The following summary is based on previously and newly reviewed studies. Table 1 provides an overview of these studies.

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Table 1 Overview of Toxicity Studies of MP03-33 and MP03-36 [a]

Study	Species	Duration (week)	Testing formulation		Group	n/sex /group
			MP03-33	MP03-36		
001	Rat	26	x	x	V [b], Astelin, MP03-33, MP03-36	20
002	Rat	2	x		R, and R + 0.05, 0.10, or 0.15% SUC	10
003	Dog	2	x			3
004	Rat	2		x	V, MP03-36	10
005	Dog	2		x		3
16365	Rat	2	x	x	V, V-SUC, Astelin, MP03-33, MP03-36	10

a, Each animal received the intended treatment at 0.1 ml/nostril, bid.
b, v = the vehicle for MP03-33 and MP03-36, R = MP03-33 minus sucralose, SUC = sucralose

Azelastine

General toxicology:

Azelastine HCl at a concentration of 0.15% is more irritating than 0.1%. Local toxicity/irritation potential of azelastine was evaluated in intranasal toxicity studies in the treatment duration up to 6 months in rats and 2 weeks in dogs (Table 1, above). Azelastine HCl concentrations ranged from 0% - 0.15%. The rats in 0.15% azelastine-treated groups showed increases in the incidence of mucosal inflammation and goblet cell hyperplasia compared to 0.1% group. Also, the incidence in these changes in the 0.15% group was slightly higher than that in the 0.1% group.

Three 2-week intranasal toxicity studies were completed to evaluate the local toxicity of 0.1% and 0.15% azelastine in the new formulations (Studies 16365, 004 and 005). The frequency and volume of treatment was identical for all three studies. In Study 16365, Sprague-Dawley rats (10/sex/group) were treated with the new vehicle in the absence or presence of 0.15% sucralose (Groups 1 and 2), Astelin® (Group 3), MP03-33 (0.1% azelastine, Group 4), or MP03-36 (0.15% azelastine, Group 5) twice daily for 14 days. Rats treated with the vehicle or vehicle plus sucralose (Groups 1 and 2) showed no discernable lesions in the nasal cavity. Rats treated with sucralose in the presence of azelastine (Groups 4 and 5) or those treated with Astelin (group 3) showed microscopic changes in nasal cavity. The changes include hemorrhage (focal or multi-focal), inflammation and hyaline droplets in the respiratory epithelium region and hypertrophy/hyperplasia of the goblet cells. The addition of sucralose appeared to result in increases in goblet cell hyperplasia while the 0.15% azelastine formulation containing sucralose increased the incidence of hemorrhage. The respective incidence (males and females combined due to lack of gender difference) for Groups 1, 2, 3, 4 and 5 was 0/20, 0/20, 1/20, 0/20 and 4/20 for hemorrhage and 0/20, 0/20, 2/20, 8/20 and 8/20 for goblet cell hypertrophy or hyperplasia. The NOAEL for sucralose alone was 0.15% (or 60 $\mu g/cm^2$ on a nasal surface area basis). The NOAEL for azelastine was not identified, nor was it identified for azelastine and sucralose in combination.

The remaining two 2-week intranasal toxicity studies (Studies 0437RM57.004 and 005) evaluated the local toxicity of 0.15% azelastine HCl. One-tenth of 1 ml/nostril of MP03-36 (0.15% azelastine) or the vehicle for MP03-36 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. Both male and female rats and dogs in both vehicle and 0.15% azelastine treated groups showed prevalent abnormalities in the nasal cavity, larynx, and lung. In rats, abnormalities included inflammation, lymphohistiocytic and mixed cell infiltration, and hemorrhage in the lung; mineralization of the submucosa in the nasal cavity; inflammation (acute and subacute), minimal to mild lymphoid infiltration in the submucosa of the trachea. In dogs, the abnormalities included inflammation, lymphohistocytic infiltration, and pigmentation in the lung; inflammation and/or atrophy of mucosa in the larynx; and inflammation of mucosa, degeneration of epithelial cells, and hyperplasia of goblet cells and etc. in the nasal cavity. The results indicate that the addition of 0.15% azelastine to the proposed vehicle did not show any extra incidence or severity of the observations when compared to the vehicle alone.

In the 6-month intranasal toxicity study (Study 0460RM57.001), Sprague-Dawley rats (20/sex/group) were treated with the new vehicle for MP03-33 and MP03-36, (Group 1), Astelin® (Group 2), MP03-33 (0.1% azelastine, Group 4), or MP03-36 (0.15% azelastine, Group 5) twice daily for 26 weeks. Again, prevalent mucosal inflammation and goblet cell hyperplasia were observed all groups. The incidence of these changes was similar between the vehicle, MP03-33 and Astelin® groups. The MP03-36 treated rats, however, showed increases in the severity of subacute or mucosal inflammation in the anterior regions of the nasal cavity. The respective incidence of mild inflammation for the vehicle, Astelin, MP03-33 and MP03-36 was 8/40, 5/40, 6/40 and 12/40 in the Level 1 area and 6/40, 7/40, 8/40 and 15/40 in the Level 2 area. The above data indicate that azelastine at 0.15% is slightly more irritating than at 0.1%.