Sucralose and sorbitol

General toxicology:

Sucralose at a concentration of —% and sorbitol at — % are not irritating to the nasal cavity. Four intranasal toxicity studies were conducted to evaluate the effect of sucralose and sorbitol on the respiratory system in rats and dogs. The treatment duration was up to 6 months in rats and 2 weeks in dogs. The respiratory system was examined microscopically at the end of treatment. The presence of sucralose at concentrations ranging from 0.05% to 0.15% did not increase the irritating potential of azelastine. b(4)

In addition to the 6-month intranasal toxicity study (Study 0460RM57.001) and the 2-week studies in rats (Studies 16365 and 0437RM57.004) and dogs (Study 0437RM57.005), which are described earlier in the Azelastine section, the sponsor also conducted two 2-week intranasal toxicity studies in rats and dogs (one each) to evaluate the effect of sucralose on the respiratory system. Sprague-Dawley rats (10/sex/group) and beagle dogs (3/sex/group) were instilled intra-nasally 0.1 ml/nostril of MP03-33 containing 0% (G1), 0..05% (G2), 0.1% (G3), or 0.15% sucralose twice daily for 14 days (Studies 0437RM57.002 and 003). Low incidence of inflammation and goblet cell hyperplasia were observed in all groups. The presence or absence of sucralose at concentrations up to 0.15% did not affect incidence of these changes. The above data indicate that sucralose at concentrations up to 0.15% is not irritating to the nasal cavity.

2.6.6.3 REPEAT-DOSE TOXICITY

Study Title: A 6-Month Intranasal Toxicity Study with Azelastine and Sucralose in Sprague-Dawley Rats (Study No. 0460RMS57.001, draft)

Key findings: Azelastine at 0.15% was slightly more irritating to the anterior nasal mucosa than at 0.1%. MP03-36 (0.15% azelastine) was instilled to the rat nose (0.1 ml/nostril, Bid) for 6-month. Compared to its vehicle, MP03-33 (0.1%azelatine and same vehicle for MP03-36), or Astelin® Nasal Spray (marketed product), the MP03-36 treated rats showed increases in the severity of subacute or mucosal inflammation in the anterior regions of the nasal cavity.

Study number:	0460RM57.001
Volume #, and page #:	Draft report: Vol. C23.1, p 3;
Report Date:	December 18, 2006
Conducting laboratories and location:	— b(4)
Date of study initiation:	Jan 24, 2006
Study completion date:	August 4, 2006
GLP compliance:	Yes, without a signed page

QA reports:	Yes, without a signed page
Drug, lot #, radio-label, and % purity:	Batches 03-33-02c Purity: azelastine 100%,

Methods

Sprague-Dawley rats (20/sex/group) were instilled 0.1 ml/nostril of the following formulations twice daily for 6 moths: the vehicle for MP-03-33 and MP03-36, Astelin® Nasal Spray, MP-03-33, or MP03-36. Table 1 presents the major ingredients of each testing material. The respiratory system was examined microscopically at the end of the treatment.

Table 2 Formulations of the 6-Month Intranasal Toxicity Study in Rats

Groups	I	II	III	IV
Treatment	Vehicle [a]	Astelin [b]	MP03-33	MP03-36
Azelastine	-	0.1%	0.1%	0.15%
Sucralose	0.15%	-	0.15%	0.15%

a. The vehicle for MP03-33 and MP03-36 also contains — % sorbitol, —% hypromellose, —— % edetate disodium, — % sodium citrate and — % benzalkonium chloride.
b. Astelin® contains the following as excipients: 0.125% benzalkonium chloride, edetate disodium, hypromellose, citric acid, dibasic sodium phosphate, sodium chloride. The concentrations of these excipients, except for benzalkonium chloride are not given.

Doses:	0 or 0.15% azelastine (i.e., 1.5 mg/kg body weight, 2.4 μg/cm^2 nasal surface area)
Species/strain:	Rats —:CD(SD)
#/sex/group (main study):	20
Age:	Approximately 9 weeks
Weight (mean):	M: 265 - 325 g; F: 195-241 g
Route, formulation, volume and infusion rate:	Nasal instillation, solution, 1 ml/nostril, twice daily, 6 hrs between doses
Sampling times:	See below
Vehicle:	— % sucralose, — % hypromellose —— % edetate disodium, — % sorbitol (b) (4) —— % sodium citrate, — % benzalkonium chloride and purified water

Observations and times:

Mortality:	Twice daily
Clinical signs:	Once daily
Body Weights:	Weekly (days 1, 8 and 14)
Food consumption:	Weekly
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, tracheobronchial lymph nodes, thymus, thyroid/parathyroid, and uterus

Histology: Respiratory system (nasal cavity, naso-pharynx, larynx, trachea, lung with main stem bronchus, tracheobronchial lymph nodes) and liver.

Adequate Battery: yes (x), no ( ) — as agreed during the May 8, 2005 End-of-Phase 2 meeting

Peer review: yes ( ), no (x)

Results:

Mortality: No drug-related findings were noted. Three rats died or were sacrificed due to moribund conditions during the study. These rats were distributed in Groups 1 (#7501, male and #7586, female) and 4 (#7645, female). These events occurred on days 14 (G1 female), 107 (G1 male) and 122 (G4 female). The cause of death was mononuclear leukemia (G1 male), sepsis and oral trauma. These mortalities were not considered treatment-related.

Clinical signs: No drug-related findings were noted.

Body weights: No drug-related findings were noted.

Food consumption: No drug-related findings were noted.

Gross pathology: No drug-related findings were noted.

Organ weights: No drug-related findings were noted.

Histopathology: Rats treated with MP03-36 showed noticeable increases in the severity of mucosal inflammation in the anterior area of the nasal cavity (Levels 1 and 2). Table 2 presents the incidence and severity of the inflammation. The table listed the incidence as male and females combined because of the lack of apparent differences in responses between sexes. The inflammation was rather prevalent in all groups. Also every rat showed some degree of inflammation. The incidence and severity of the inflammation was generally similar across all groups, except the MP03-36 group which showed increases in the incidence of mild inflammation. The respective incidence 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.

Table 3 Inflammation in the Nasal Cavity (N= 40/group)

		Incidence				Severity [a]
Location	Group	minimal	mild	moderate	Overall	(mean)
Level 1	G1	25	8	2	35	1.34
	G2	31	5	2	38	1.24
	G3	32	6	2	40	1.25
	G4	23	**12**	2	37	1.43
Level 2	G1	33	6	0	39	1.15
	G2	32	7	0	39	1.18
	G3	32	8	0	40	1.20
	G4	25	**15**	0	40	1.38
Level 3	G1	21	16	0	37	1.43
	G2	19	18	0	37	1.49

	G3	25	12	0	37	1.32
	G4	22	15	0	37	1.41
Level 4	G1	21	7	0	28	1.25
	G2	30	1	0	31	1.03
	G3	20	8	0	28	1.29
	G4	31	4	0	35	1.11

a. Severity was scored as 0, 1, 2, and 3 for the degrees of none, minimal, mild and moderate, respectively.

The MP03-33 treated rats showed an increase in the incidence of goblet cell hyperplasia in the Level 4 area (Table 4). The review does not consider the observation a treatment-related finding based on the following: 1) there were no similar findings in the other 3 areas of the nasal cavity, and 2) there was no dose-response relationship between the incidence of hyperplasia and azelastine concentrations. The only difference in treatment between Groups 3 and 4 were the azelastine concentrations: 0.1% vs 0.15% for Groups 3 and 4, respectively.

Table 4 Goblet Cell Hyperplasia in the Nasal Cavity (N= 40/group)

Location	Groups	Incidence				Severity [a]
		minimal	mild	moderate	Overall	(mean)
Level 1	G1	16	19	4	39	1.69
	G2	14	18	5	37	1.76
	G3	9	23	7	39	1.95
	G4	8	25	5	38	1.92
Level 2	G1	13	3	0	16	1.19
	G2	15	0	0	15	1.00
	G3	23	3	0	26	1.12
	G4	20	2	0	22	1.09
Level 3	G1	7	0	0	7	1.00
	G2	19	0	0	19	1.00
	G3	14	2	0	16	1.13
	G4	11	0	0	11	1.00
Level 4	G1	7	0	0	7	1.00
	G2	6	1	0	7	1.14
	G3	14	2	0	16	1.13
	G4	8	0	0	8	1.00

a. Severity was scored as 0, 1, 2, and 3 for the degrees of none, minimal, mild and moderate, respectively.

2.6.6.9 DISCUSSION AND CONCLUSIONS

The nonclinical safety evaluation of the application concentrates on local effects (the respiratory system) of the active and inactive ingredients of the to-be-developed reformulation products: MP03-33 and MP03-36. These products are ——— the currently marketed Astelin® Nasal Spray. The azelastine concentrations are 0.1%, 0.15% and 0.1% for MP03-33, MP03-36 and Astelin®, respectively. The active ingredient is of safety concern because MP03-36 contains higher azelastine concentration than Astelin®. The inactive ingredients of interest are sucralose (— %) and sorbitol (— %) because of the novel

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intranasal use of the former and the higher concentration compared to the amount present in approved products of the latter. The sponsor conducted intranasal toxicity studies up to 6 months in rats and 2 weeks in dogs in treatment to support the clinical development and approval of the new formulations. These studies identified clinically monitorable responses in the nasal cavity in rats and dogs: mild inflammation. These studies are considered nonclinically sufficient to support the registration of the two reformulation product if no additional safety concerns arise during their development.

The sponsor recently completed additional toxicity studies using one or both of the to-be-developed products in rats and dogs. The route of administration was intranasal instillation. The treatment duration was up to 6 months in rats and 2 weeks in dogs. The tested concentration for compounds of interest was up to 0.15%, —% and — % for azelastine, sucralose and sorbitol, respectively. Reference articles were Astelin® or the vehicle for MP03-33 and MP03-36. Each animal received 0.1 ml/nostril of the testing, twice daily for the scheduled duration. Toxicological evaluations of the studies concentrated on the respiratory system because the systemic toxicity of each compound of interest has been fully characterized previously. Results showed that MP03-33 and Astelin® had no significant differences in their effects on the respiratory system. MP03-36, however, was slightly more irritating to the anterior area of the nasal cavity. The MP03-36 treated rats showed a slight increase in the severity of inflammation, when compared with the vehicle, Astelin® or MP03-33 treated rats. The total incidence of the inflammation, however, was very similar among the group. b(4)

However, most of the above studies, especially the 6-month toxicity study in rats, have minor deficiencies in the study design. The most significant one is probably the lack of proper references (i.e., saline) to fully evaluate the effect of the vehicle components, namely sucralose and sorbitol. The 6-month toxicity rat study that offers a sole opportunity to evaluate local effects of these ingredients after a chronic use is an example. The study consists of 4-treatment groups: Astelin®, the vehicle of MP03-33 and MP03-36, MP03-33, and MP03-36. All treatments but Astelin® contain sucralose and sorbitol. The study compares the local effect of the vehicle against Astelin® that contains 0.1% azelastine and is known to be slightly irritating to the nasal mucosa in animals. This comparison may underestimate the irritation potential of the vehicle, if any. This concern, however, may be mostly alleviated by the lack of difference in responses between the Astelin® and MP03-33. The design deficiency, therefore, is considered minor and the review will not pursue it any further.

Overall, the recently completed toxicity studies in animals have adequately evaluated the local effect of sucralose and sorbitol. No additional toxicity studies are needed for the future clinical development and registration of nasal products containing up to —% sucralose and —% sorbitol unless new safety concerns arise in the future.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

The available nonclinical data of the application support the safety of 2 newly proposed clinical protocols (MP434 and MP435). These protocols propose to treat patients of perennial allergic rhinitis with MP03-36 or MP03-33 nasal sprays for four weeks. Nonclinical data support the protocols were intranasal toxicity studies of both formulations with the treatment duration up to 6 months in rats and 2 weeks in dogs. These studies showed that: i) Astelin® (the currently marketed product) and MP03-33 possess similar safety profiles, and ii) MP03-36 was slightly more irritating to the nasal mucosa than Astelin® and MP03-33 in rats. The nasal irritation is of no significant safety concern as the Division considers it a monitorable response of nasal MDIs. Thus, the available nonclinical data of the application are considered supportive of the proposed clinical trial.

The sponsor proposes to study the safety and efficacy of MP03-36 and MP03-33 on perennial allergic rhinitis. Detailed proposals can be found in Protocols MP434 and 435. Briefly, Protocol MP434, submitted on 31-Jan-2007 (Serial No. 034), will study both MP03-36 and MP03-33. Adult patients will receive 2 sprays/nostril of MP03-36, MP03-33, or vehicle twice daily for 4 weeks. Protocol MP435, submitted on 16-JAN-2007 (Serial No. 033), will study MP03-36 only. Adult patients will receive 2 sprays/nostril of MP03-36 or vehicle once a day for 4 weeks. The total daily azelastine dose will be 1644, 1096, 822 and 0 µg/day, respectively. The number of patients involved will be 540 and 600 for Protocols MP434 and 435, respectively. Table 5 presents differences in study design between these two protocols.

Table 5 Overview of Clinical Study Protocols

Protocol No.	Frequency	Treatment		
		MP03-33	MP03-36	Placebo
MP434 [a]	bid	x	x	x
MP435 [b]	qd, AM		x	x
	qd, PM		x	x

a. Each arm will have 180 patients.

b. The number of patients will be 200 and 100 for the MP03-36 and placebo groups.

The nonclinical safety evaluations of these clinical protocols concentrate on local effects (the respiratory system) of the active and inactive ingredients of the to-be-developed reformulation products: MP03-33 and MP03-36. The focus was attributed to our knowledge of individual ingredient toxicity and formulation features. From toxicological perspective, there are no safety concerns about the systemic toxicity of any ingredients of the formulations for the intended use, but the local effect of some ingredients, however, is not well known. For example, sucralose is not included as an excipient in any approved intranasal products, neither has its effect on the respiratory system from intranasal route of administration been studied. Similarly, azelastine at a concentration of 0.15% has not been approved in any products or studied in the laboratory.

From the formulation perspective, MP03-33 and MP03-36 have the 3 following features: 1) MP03-33 and Astelin® contain the same azelastine concentration but different inactive ingredients, 2) MP03-33 and MP03-36 differ only in their azelastine concentrations, 3) MP03-36 and Astelin® differ not only in azelastine concentrations but also in the inactive ingredients. Specifically, the respective concentrations in MP03-33, MP03-36 and Astelin® is 0.1%, 0.15% and 0.1% in azelastine; [redacted] in sucralose; and [redacted] and [redacted] in sorbitol. Additional formulation information can be found in the Clinical Formulation section on Page 1 of the review. Consequently, sucralose and sorbitol in both MP03-33 and MP03-36 are of interest because of the novel intranasal use or a higher concentration than that found in approved products. For MP03-36, the active ingredient is also of interest because it contains a higher concentration of azelastine than Astelin®. b(4)

The sponsor conducted intranasal toxicity studies up to 6 months in rats and 2 weeks in dogs to support the clinical development and approval of the new formulations. Pivotal nonclinical data supporting the safety of the newly proposed trials are a 6-month intranasal toxicity study of MP03-33 and MP03-36 in rats (Study 0460RMS57.001). As indicated earlier in the review, 0.1 ml/nostril of MP03-36, MP03-33, the vehicle or Astelin® Nasal Spray was instilled into the nasal cavity twice daily for 6 months. The respiratory system was examined microscopically at the end of the treatment. Rather prevalent mucosal inflammation (35/40 – 40/40) and goblet cell hyperplasia (37/40 – 39/40) were observed in all groups. The MP03-36 treated group, however, showed an increase in the severity of inflammation in the anterior nasal cavity. The respective incidence of mild mucosal inflammation for the vehicle of MP03-36 and MP03-36, Astelin®, MP03-33 and MP03-36 groups was 8/40, 5/40, 6/40 and 12/40 in the Level 1 section and 6/40, 7/40, 8/40 and 15/40 in the Level 2 section. The results indicate that 0.15% azelastine was slightly more irritating than the 0.1% azelastine formulation.

Dr. Luqi Pei completed reviews of 2-week intranasal toxicity studies in rats and dogs on August 17 (Review #3) and November 29, 2006 (Review #5). These reviews did not identify significant safety concerns about up to sprays/nostril of the products twice daily for 14 days in humans.

The Division determined previously that the proposed dosing schedule of MP03-33 or MP03-36 for up to 14 days was safe. Please refer to the pharmacology and toxicology review by for additional information. The newly collected data showed that the local effect of MP03-33 is similar to that of Astelin®. MP03-36 is slightly more irritating to the nasal mucosa in rats than the approved Astelin formulation, but the irritation effect is a clinically monitorable effect. Any safety concern about this effect can be adequately addressed clinically as indicated in Dr. Susan Limb's clinical review completed on February 5, 2007. The review considers the available nonclinical data supportive of the safety of the proposed clinical protocols.

Internal recommendations

The available nonclinical data of the application support the safety of the proposed clinical trials of MP03-36 and MP03-33 (Protocols MP434 and MP435). It is recommended that the trials be allowed to proceed.

The completed nonclinical studies of the application are considered sufficient to support future developments and registrations of both MP03-33 and MP03-36. No additional toxicity studies of either product is needed if no safety concerns arise during the future clinical development.

External Recommendation: None.

Luqi Pei, Ph.D.
Senior Pharmacologist

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/s/

Luqi Pei
3/26/2008 02:46:56 PM
PHARMACOLOGIST

Timothy McGovern
3/27/2008 07:59:18 AM
PHARMACOLOGIST
I concur.

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

NDA 21-Day Pharmacology Fileability Check List

Reviewer: Luqi Pei, Ph.D.

b(4)

NDA No: 22-203
Drug Name: [redacted], MP03-33
Date of submission: July 30, 2007 (stamp date)
Date of 45-day file-ability meeting: September 6, 2007
Information to the Sponsor: None.
Date of check list: September 12, 2007

(1) On its face, is the pharmacology/toxicology section of the NDA organized in a manner to allow substantive review? Yes.

(2) On its face, is the pharmacology/toxicology section of the NDA legible for review? Yes.

(3) Are final reports of all required and requested preclinical studies submitted in this NDA? Final reports of all toxicology study reports are submitted.

	Yes	No	NA
Pharmacology	( )	( )	(x)
ADME	( )	( )	(x)
Toxiciology (duration, route of administration and species specified)			
acute	( )	( )	(x)
subchronic and chronic studies	( )	( )	( )
reproductive studies	( )	( )	(x)
carcinogenicity studies	( )	( )	(x)
mutagenicity studies	( )	( )	(x)
special studies	( )	( )	(x)
others *	(x)	( )	( )

* The application is a reformation of the current marketed product, Astelin. A 6-month bridging study of the to-be-marketed formulation in rats, the most appropriate species had been completed and its report was submitted.

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, are repeating or bridging the studies necessary? No.

If no, state why not: The to-be-marketed formulation and the formulation used in toxicity studies are identical. Bridging toxicity studies, therefore, is not necessary.

If yes, has the applicant made an appropriate effort to repeat the studies using the 'to be marketed' product, to bridge the studies or to explain why such repetition or

bridging should not be required?

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) appropriate (including human dose multiples expressed in either mg/m^2 or comparative systemic exposure levels) and in accordance with 201.57?

Yes. The label does follow the new product labeling recommendations (PLR). Dose ratios between animals and humans in preclinical sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) are appropriate as they are expressed in either mg/m^2. The text of these nonclinical sections is identical to what has been approved for Astelin®. These ratios for Astelin and (b) (4) ™ are identical. There is no new, relevant additional data to warrant any deviations from the approved labeling.

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion? Yes.

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route? Yes.

If not, has the applicant submitted a rationale to justify the alternative route? Yes/No

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? Yes.

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? N/A.

(10) Are there any outstanding preclinical issues? No.

If yes, identify those below

(11) From a preclinical perspective, is this NDA fileable? Yes.

If no, state below why it is not.

If yes, should any additional information/data be requested? No.

If yes, identify those below.

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/s/

Luqi Pei
9/12/2007 10:31:41 AM
PHARMACOLOGIST

Timothy McGovern
9/12/2007 03:15:25 PM
PHARMACOLOGIST
I concur.