CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-371s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-371**
SERIAL NUMBER:	**000/ 29-APR-2009 AZ amendment**
DATE RECEIVED BY CENTER:	**April 30, 2009**
PRODUCT:	**Astepro (0.15% Azelastine HCl) Nasal Spray**
INTENDED CLINICAL POPULATION:	**Patients with Seasonal Allergic Rhinitis (age 12 and above)**
SPONSOR:	**Meda Pharmaceuticals**
DOCUMENTS REVIEWED:	**Draft Labeling Proposal**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Products**
PHARM/TOX REVIEWER:	**Luqi Pei, Ph.D.**
PHARM/TOX SUPERVISOR:	**Timothy Robison, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Colette Jackson**

Date of review submission to Division File System (DFS): June 24, 2009

REVIEW OF 29-APR-09 AMENDMENT

A nonclinical review of the 29-APR-09 amendment (stamp date 30-APR-09) is not needed. The amendment consisted of two parts: additional clinical data and a newly proposed draft labeling. The amendment contained no nonclinical data. The lack of any new data renders a nonclinical review unnecessary.

Neither there is a need for a review of the draft labeling proposal based on the following considerations. Dr. Luqi Pei previously completed a review of the nonclinical sections of a proposed draft labeling on April 20, 2009. The review contained annotated recommendations of the 10-APR-09 proposal. The nonclinical sections of the 10-ARP-09 and 29-APR-09 proposals were identical so that an additional review is not necessary. Please refer to Dr. Pei's review dated April 20, 2009 for detailed labeling recommendations.

Luqi Pei, Ph.D.
Senior Pharmacologist

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/s/

Luqi Pei
6/24/2009 07:59:20 AM
PHARMACOLOGIST

Timothy Robison
6/24/2009 09:38:23 AM
PHARMACOLOGIST
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-371**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**August 1, 2008**
	April 10, 2009
PRODUCT:	**0.15% Azelastine HCl Nasal Spray**
INTENDED CLINICAL POPULATION:	**Patients with Seasonal Allergic Rhinitis (age 12 and above)**
SPONSOR:	**Meda Pharmaceuticals**
DOCUMENTS REVIEWED:	**Vol. C1 – C13**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Products**
PHARM/TOX REVIEWER:	**Luqi Pei, Ph.D.**
PHARM/TOX SUPERVISOR:	**Timothy Robison, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Colette Jackson**

Date of review submission to Division File System (DFS): April 20, 2009

LABELING REVIEW

The nonclinical sections of the proposed draft labeling submitted on April 10, 2009 are generally acceptable except for the product names and dose ratios between animals and humans. The draft listed both strengths (0.1% and 0.15%) of Astepro Nasal Spray and presented dose ratios of each individual drug product in the nonclinical sections. This approach resulted in significant lengthening of the labeling without any significant additional value. The review recommends editing the draft by deleting product strengths and presenting only the most conservative dose ratios as previously discussed in the original Pharmacology and Toxicology Review completed Dr. Luqi Pei on March 16, 2009.

Meda have submitted at least 4 versions of proposed labeling so far. These submissions were dated August 1 and December 22, 2008; and February 20, and April 10, 2009. Dr. Pei completed a review of the nonclinical sections of the first three submissions on March 16, 2009 in the original pharmacology and toxicology review as alluded to earlier. Labeling comments of the review were based on the February 20, 2009 submission. The comments were not conveyed to Meda due to a need for major high-level redrafting by other disciplines. The contents and text of the nonclinical sections of the proposed draft labeling of the 10-APR-2009, however, were identical to the 20-FEB-2009 except for the product names. The respective 0.1% and 0.15% azelastine products were referred as Astepro Nasal Spray and (b) (4) in the 20-FEB-09 submission and Astepro Nasal Spray 0.1% and Astepro Nasal Spray 0.15% in the 10-APR-2009 submission. Consequently, all nonclinical labeling comments in the pharmacology and toxicity review completed by Dr. Pei on March 19, 2009 are still applicable.

The review also finds it necessary to remove any reference to pediatric (children) populations in the nonclinical section of the labeling. Azelastine (0.1%) has been marketed for adults and children 12 years of age and older since its initial approval on November 1, 1996 (Astelin Nasal Spray, NDA 20-114). A reformulation product of azelastine (Astepro Nasal Spray, 0.1%) was also approved recently approved (NDA 22-203, approval date of 15-OCT-2008). The current application proposes a higher dosage strength of the Astepro Nasal Spray. The patient population of the all three azelastine dosage strengths is identical. The nonclinical labeling sections of the approved labeling states animal-to-human dose ratios for both adults and children. The inclusion of "children" in the nonclinical sections of Astelin and Astepro nasal spray lebeling apparently deviates from other products indicated for the same population. A survey among nonclinical reviewers of the Division found that no other DPAP products in their nonclinical sections have a pediatric population spelled out unless the drug is indicated for patients 11 years of age or younger. Generally, subjects >12 and <18 years of age have been referred to as adolescents. In other instances, all subjects >12 years of age are pooled together. More recent practice is to use "the maximum recommended human use" to cover all populations. The review, therefore, concludes that the term "maximum recommended human dose" be used in the nonclinical sections of the labeling and the reference to

"children" be removed.[1] Table 1 (below) presents a comparison between the approved and suggested labeling of the same dosage strength of the Azelastine product (0.1%) for a mouse carcinogenicity study.

Table 1 Example of Approved and Suggested Labeling

Approved	Suggested
(b) (4)	

As discussed in the original review, revisions are recommended to make the labeling more legible. These revisions included omitting the reference to any specific product and using the most conservative dose ratios (i.e., animal to human dose ratios were calculated using the maximum recommended daily intranasal dose obtained with the clinical 0.15% dosage strength). Table 2 presents a comparison of the proposed and suggested versions of the animal carcinogenicity section of the labeling.

Table 2 Example of Proposed and Suggested Labeling

Proposed	Suggested
(b) (4)	

[1] The removal of children from the nonclinical sections of the product labeling was considered, although not documented, previously during the review of Astepro Nasal Spray labeling. It was decided to let it go given the historic perspective of the product: a) the term "children" was there since the approval in 1996, b) a major review of labeling was forthcoming because the Azelastine 0.15% application was expected to be filed soon.

SUGGESTED LABELING:

The following section is the suggested nonclinical sections of labeling. Edits (colors) were made to the proposal submitted on April 10, 2009. The strike outs indicate deletion while underline indicates addition. The animal-to-human dose ratio was based on the 0.15% only. As indicated in the original review, revisions to dose-ratios are recommended so that the ratios would comply with the rounding the Agency's rule. Table 3 presents dose ratios in the proposed and suggested labeling.

Table 3 Animal-to- Human Dose Ratios for MP03-36 Labeling

Section No.	Description	Species	mg/kg [a]	Km	mg/m^2	Animal-to-Human Ratio [b] Calculated	Suggested [c]	Proposed [d]
(b) (4)								

a. Oral doses in animals.
b. Based on a human dose of 1.22 mg/m^2. This value was calculated from a maximum recommended daily dose of 2 sprays per nostril twice a day in a 50-kg patient. Each spray of MP03-36 contains 205.5-µg azelastine. The total daily dose of azelastine is 1.644 mg/day or 0.0329 mg/kg/day. A conversion factor of 37 was used to derive the dose of 1.22 mg/m^2 on a surface area basis.
c. Rounded to the nearest integer, 5s and 10s for single, double and triple-digit numbers, respectively. These numbers are used in the newly suggested labeling.
d. Numbers proposed by the sponsor in the 22-DEC-08 submission.

8 USE IN SPECIFIC POPULATIONS

2 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

(b) (4)

[redacted]

Luqi Pei, Ph.D.
Senior Pharmacologist

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/s/

Luqi Pei
4/20/2009 02:02:19 PM
PHARMACOLOGIST

Timothy Robison
4/20/2009 03:34:25 PM
PHARMACOLOGIST
I concur

INTEROFFICE MEMO

TO: NDA 22-371 (0.15% Azelastine HCl Nasal Spray)
#000 dated August 1, 2008

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Senior Pharmacology/Toxicology Reviewer
Division of Pulmonary and Allergy Products

DATE: March 26, 2009

I concur with Dr. Luqi Pei's Review dated March 16, 2009. The 0.15% Azelastine HCl Nasal Spray is the third azelastine nasal spray product intended for allergic rhinitis. Two previously approved and currently marketed azelastine products are Astelin (NDA 20-114) and Astepro (NDA 22-203) with the approval dates of November 1, 1996 and October 15, 2008, respectively. The applicant completed a bridging toxicology program comparing the toxicity profile of 0.15% Azelastine HCl Nasal Spray to the two approved azelastine products (i.e., Astepro® and Astelin® nasal sprays). Intranasal toxicity studies up to 6 months in rats determined that the 3 products possess similar toxicity profiles: slightly irritant to the nasal mucosa. Please see Dr. Pei's review for additional details.

The toxicological characterization of azelastine was completed in the development of Astelin® Nasal Spray (NDA 20-114), the first approved and currently marketed azelastine product.

The nonclinical sections of the proposed draft labeling submitted on February 20, 2009 were generally acceptable except for the drug names and dose ratios between animals and humans. To improve the readability of the labeling and be consistent with similar products, Dr. Pei's review recommended omitting the reference to any specific product and using the most conservative dose ratios (i.e., animal to human dose ratios were calculated using the maximum recommended daily intranasal dose obtained with the clinical 0.15% dosage strength).

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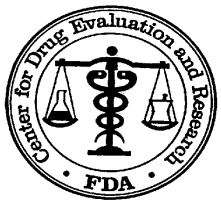
/s/

Timothy Robison
3/26/2009 09:44:26 AM
PHARMACOLOGIST



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PUBLIC HEALTH SERVICE
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CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-371**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**August 1, 2008**
PRODUCT:	**0.15% Azelastine HCl Nasal Spray**
INTENDED CLINICAL POPULATION:	**Patients with Seasonal Allergic Rhinitis (age 12 and above)**
SPONSOR:	**Meda Pharmaceuticals**
DOCUMENTS REVIEWED:	**Vol. C1 – C13**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Products**
PHARM/TOX REVIEWER:	**Luqi Pei, Ph.D.**
PHARM/TOX SUPERVISOR:	**Timothy Robison, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Colette Jackson**

Date of review submission to Division File System (DFS): March 16, 2009

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

This review recommends an approval of the MP-03-36[1] (0.15% azelastine HCl) application from the nonclinical perspective. The applicant completed a bridging toxicology program comparing the toxicity profile of MP03-36 (the to-be-marketed product) to two approved and currently marketed azelastine products (Astepro® and Astelin® nasal sprays). The azelastine concentration is 0.15%, 0.10% and 0.10% for MP03-36, Astepro and Astelin, respectively. The vehicle of MP03-36 and Astepro is identical while Astelin uses a slightly different vehicle. The bridging program consisted of intranasal toxicity studies up to 6 months in treatment duration in rats. Results of the studies indicated that the 3 products possessed similar toxicity profiles. The available nonclinical data is considered adequate to support the registration of MP03-36.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

The review recommends deleting trade names and revising dose ratios between animals and humans in nonclinical sections of the proposed product labeling. The remaining portions of the proposed labeling were identical to that of Astepro (Approval date of October 15, 2008) and were acceptable. Only necessary edits were references to drug names and dose ratios between animals and humans. The recommended changes shortened the labeling and improved its readability. Please see the Suggested Labeling section (Page 12) for the recommended edits of the labeling proposed on February 20, 2009.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

MP03-36, Astepro®, Astelin® nasal sprays possess similar toxicity profiles. MP03-36 is the be-be-marketed product. Astepro and Astelin are two approved and currently marketed azelastine products. The azelastine concentration is 0.15%, 0.1% and 0.1% for MP03-36, Astepro and Astelin, respectively. MP03-36 and Astepro use the same vehicle. The intranasal toxicity studies up to 6 months in rats

[1] The application also refers the product as (b) (4). Internal discussions indicated that the Agency would most likely reject these names and recommend Astepro® 0.15% Nasal Spray. The marketed product Astepro® Nasal Spray will probably be renamed as Astepro 0.1% nasal spray. Due to the uncertainty of the product name, the review continues to use MP03-36, a name used in the IND phase and previous reviews.

revealed that the 3 products possess similar toxicity profiles: slightly irritant to the nasal mucosa.

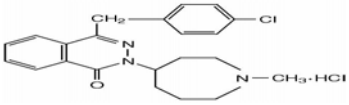
B. Pharmacologic activity
No new data was submitted. Azelastine hydrochloride exhibits histamine H_1 - receptor antagonist activity in isolated tissues, animal models, and humans.

C. Nonclinical safety issues relevant to clinical use

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA Number:	22-371
Review Number :	1
Sequence number/date/submission type:	000/ August 1, 2008/ N
Information to the Sponsor:	Yes (x), No ( )
Sponsor/or Agent:	Meda Pharmaceuticals, Somerset, NJ
Manufacturer for Drug Substance:	Meda Pharmaceuticals, Somerset, NJ
Reviewer Name:	Luqi Pei, Ph.D.
Division Name:	Pulmonary and Allergy Products
Review Completion Date:	March 16, 2009
Drug:	
Trade Name:	Astepro 0.15% Nasal Spray
Generic Name:	0.15% Azelastine HCl Nasal Spray
Code Name:	MP03-36, (b) (4)
Chemical Name:	(±)-1-(2H)-phthalazine, 4-[(4-chlorophenyl]methyl-2-2(hexahydrol-1-methyl-1H-azepin-4-yl)-, mono-hydrochloride
CAS Register Number:	N/A
Molecular Form and Weight:	$C_{22}H_{24}ClN_3O \cdot HCl$, 418.4
Structure:	
Relevant IND/NDAs/DMFs:	NDAs 20-114 and 22-203; INDs 32,704 and 69,785
Drug Class:	Antihistamine
Intended clinical population:	Seasonal allergic rhinitis in patients 12 years and older
Route of Administration:	Nasal spray

Clinical Formulation: An aqueous nasal spray consists of 0.15% azelastine, (b) (4) sucralose, (b) (4) hypromellose (b) (4) edetate disodium, (b) (4) sorbitol solution (b) (4) sodium citrate, (b) (4) benzalkonium chloride and purified water. Each actuation of a device delivers 0.137 ml of the formulation and 206 µg of azelastine HCl.

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

Studies reviewed within this submission: None.

Studies not reviewed within this submission:

14-day Nasal Irritation Procedure in Rats (Study No. 0437RMS57.004)
14-day Intra-nasal toxicity study in dogs (Study No. 0437RMS57.005)
14-day Nasal Irritation Procedure in Rats (Study No. 16365)
6-month intranasal toxicity study with azelastine and sucralose in Sprague-Dawley rats (Study No. 0460RMS57.001)

The above studies were not reviewed because Dr. Luqi Pei had reviewed them on November 29, 1996 and February 20, 2007 in IND 69785.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

No new data were submitted to this NDA. Azelastine hydrochloride, a phthalazinone derivative and the active ingredient of the application, exhibits histamine H_1 -receptor antagonist activity in isolated tissues, animal models, and humans. Histamine has been known to play an important role in allergic rhinitis. The Agency has approved two nasal products of azelastine, Astelin and Astepro (NDAs 20-114 and 22-203). Both products are currently marketed for the indication of allergic rhinitis.

2.6.2.2 Primary pharmacodynamics

Not applicable because no data was submitted.

2.6.2.3 Secondary pharmacodynamics

Not applicable because no data was submitted.

2.6.2.4 Safety pharmacology

Not applicable because no data was submitted.

2.6.2.5 Pharmacodynamic drug interactions

Not applicable because no data was submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable because no data was submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Not applicable because no data was submitted.

2.6.4.2 Methods of Analysis

Not applicable because no data was submitted.

2.6.4.3 Absorption

Not applicable because no data was submitted.

2.6.4.4 Distribution

Not applicable because no data was submitted.

2.6.4.5 Metabolism

Not applicable because no data was submitted.

2.6.4.6 Excretion

Not applicable because no data was submitted.

2.6.4.7 Pharmacokinetic drug interactions

Not applicable because no data was submitted.

2.6.4.8 Other Pharmacokinetic Studies

Not applicable because no data was submitted.

2.6.4.9 Discussion and Conclusions

Not applicable because no data was submitted.

2.6.4.10 Tables and figures to include comparative TK summary

Not applicable because no data was submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable because no data was submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

MP03-36 possesses a similar toxicity profile to Astepro® Nasal Spray (MP03-33), a recently approved and currently marketed azelastine product (NDA 22-203). MP03-36 and MP03-33 are also referred to as sweetened formulations. They contain the same vehicle but different azelastine concentrations: 0.15% and 0.1%, respectively. Intranasal toxicity studies up to 6

months in rats and 2 weeks in dogs showed that the two products possessed comparable toxicity profiles although MP03-36 was slightly more irritating to the nasal mucosa than MP03-33.

The toxicological characterization of azelastine has been completed in the development of Astelin® Nasal Spray (NDA 20-114), the first approved and currently marketed azelastine product. The characterization included studies of general, reproductive and genetic toxicology and carcinogenicity. Findings of the studies are described in the labeling of the Astelin and Astepro® nasal sprays. Briefly, azelastine is non-genotoxic and non-carcinogenic. Azelastine adversely affects the fetal development when given to female rats and rabbits during pregnancy.

The nonclinical development of both MP03-33 and MP03-36 were bridging toxicology programs, based on discussions with the Division on August 29, 2006. The agreed programs consisted of intranasal toxicity studies up to 6 months in rats and 2 weeks in dogs. Table 1 (below) provides an overview of toxicity studies completed during the development of the MP03-36. All studies had been previously submitted and reviewed by the Division in IND 69,785. The studies showed that intranasally administered MP03-36, MP03-33 and Astelin Nasal Sprays possess comparable toxicity profiles. The following summary is based on the Pharmacology and Toxicology Review Nos. 5, 6 and 7 by Dr. Luqi Pei completed on 11/29/06, 2/20/07 and 3/27/07 in IND 69,785, respectively, and the original nonclinical review of NDA 22-203 completed on March 26, 2008.

Table 1 Overview of Intranasal Toxicity Studies of (b) (4)

Study	Species	Duration (week)	Testing formulation [a]		Group	n/sex /group
			Astepro	MP03-36		
460RMS57.001	Rat	26	X	x	V [b], Astelin, MP03-36, MP03-33	20
437RMS57.004	Rat	2		x	V, MP03-36	10
437RMS57.005	Dog	2		x		3
16365	Rat	2	X	x	V, V - SUC, Astelin, MP03-33, MP03-36	10

a, MP03-33 was referred also as Astepro in NDA 22-203.
b, V = the vehicle for MP03-36 and MP03-33; SUC = sucralose.

Three 2-week intranasal toxicity studies were completed to evaluate the local toxicity of 0.1% and 0.15% azelastine (Studies 16365, 437RMS57s.004 and 005). The frequency and volume of treatment was identical for all three studies: 0.1 ml/nostril, twice daily. In Study 16365, Sprague-Dawley rats (10/sex/group) were treated with the vehicle (Group 1), vehicle without sucralose (Group 2), Astelin® (Group 3), MP03-33 (Group 4), or MP03-36 (Group 5) twice daily for 14 days. Groups 1 and 2 rats showed no discernable lesions in the nasal cavity. Azelastine treated rats (Groups 3 – 5) showed microscopic changes in nasal cavity. The changes included hemorrhage (focal or multi-focal), inflammation and hyaline droplets in the respiratory epithelium region and hypertrophy/hyperplasia of the goblet cells. The respective incidences (males and females combined due to lack of gender difference) for Groups 1, 2, 3, 4 and 5 were 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 azelastine was not identified.

Studies 437RMS57s.004 and 005 compared the toxicity of MP03-36 against the vehicle. 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 rats and dogs in both vehicle and 0.15% azelastine treated groups showed prevalent abnormalities in the nasal cavity, larynx, and lung but there were no remarkable differences in incidence or severity of these abnormalities between the groups. 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.

Study 0460RM57.001 was a 6-month intranasal toxicity studying rats. 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 in all groups. The incidence of these changes was similar between the vehicle, Astepro 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, Astepro 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% was slightly more irritating than at 0.1%.

2.6.6.2 Single-dose toxicity

Not applicable because no data was submitted.

2.6.6.3 Repeat-dose toxicity

Not applicable because no new data were submitted.

2.6.6.4 Genetic toxicology

Not applicable because no data was submitted.

2.6.6.5 Carcinogenicity

Not applicable because no data was submitted.

2.6.6.6 Reproductive and developmental toxicology

Not applicable because no data was submitted.

2.6.6.7 Local tolerance

Not applicable because no data was submitted.

2.6.6.8 Special toxicology studies

Not applicable because no data was submitted.

2.6.6.9 Discussions and Conclusion

None.

2.6.6.10 Tables and Figures

Not applicable because no data was submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable because no data was submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The applicant has submitted adequate nonclinical safety data to support registration of Astepro 0.15% nasal spays (MP03-36), a new dosage of azelastine nasal sprays. There are currently two azelastine nasal spray products on the market: Astepro (MP03-33) and Astelin. Both contain 0.1% azelastine HCl. The sponsor submitted intranasal toxicity studies up to 6 months in treatment-duration in rats to compare the toxicity profiles of these products in rats. The studies showed that these products possessed similar toxicity profiles, although azelastine at a concentration of 0.15% is slightly more irritating to the nasal mucosa than 0.10%. The available nonclinical data is considered supportive of the intended use of MP03-36.

MP03-36 is the third azelastine nasal spray product intended for allergic rhinitis. Two previously approved and currently marketed azelastine products are Astelin (NDA 20-114) and Astepro (NDA 22-203) with the approval dates November 1, 1996 and October 15, 2008, respectively. MP03-36 and Astepro use the same vehicle, which differs slightly from that used for Astelin. Specifically, the vehicle for MP03-36 and Astepro added sucralose (b) (4) and sorbitol (b) (4), but eliminated (b) (4) Since sucralose and sorbitol as excipients have been qualified

previously in NDA 22-203, the current review deals with the increased concentration of azelastine only.

The applicant conducted a bridging toxicology program that consisted of intranasal studies with the treatment duration up to 6 months in rats and 2-week in dogs as discussed in the 29-AUG-2006 meeting. Briefly, lack of pre-neoplastic findings in 6-month intranasal toxicity studies with the formulation would be sufficient to support registration of the product. Dr. Pei completed a review of the study on February 20, 2007 (Review #6 in IND 69785). The review concluded that no pre-neoplastic findings were observed.

The 6-month intranasal toxicity study (Study 0460RM57.001) compared the toxicity of MP03-36, Astepro and Astelin. 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 in all groups. The incidence of these changes was similar between the vehicle, Astepro 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 data indicated that azelastine at 0.15% was slightly more irritating than at 0.1%.

Unresolved toxicology issues (if any): None.

Recommendations:

Approval of MP03-36 is recommended from the nonclinical discipline.

LABELING REVIEW

The nonclinical sections of the proposed draft labeling submitted on February 20, 2009 are generally acceptable except for the drug names and dose ratios between animals and humans. Meda had submitted at least three versions of labeling (submission dates of 01-AUG-08, 22-DEC-08 and 20-FEB-09). The nonclinical sections of the 01-AUG-08 (original) and 22-DEC-08 submissions were essentially the same and they were specific to the 0.15% dosage strength only. The 20-FEB-09 submission attempted to harmonize the labeling for the 0.1% and 0.15% dosage strength. As a result, the proposed labeling listed dose ratios for each product. For example, the dose ratios in the carcinogenicity section were revised to:

(b) (4)

The high lights indicate edits to the 22-DEC-08 version. The revisions made the sentence more complex and confusing. To improve the sentence and be consistent with similar products, the review recommends omitting the reference to any specific product and using the most conservative dose ratios (i.e., animal to human dose ratios were calculated using the

maximum recommended daily intranasal dose obtained with the clinical 0.15% dosage strength). The newly suggested sentence would read as:

(b) (4)

The text portion describing the nonclinical findings of the proposed labeling was identical to that of Astepro® Nasal Sprays. There was no need to change them because there was no new data. The current labeling review simply revised the dose ratios between animals and humans and eliminated references to individual product. Table 2 (below) summarizes the dose ratios and the parameters used to derive the animal-to-human ratios of azelastine in Astepro 0.15%, or MP03-36. The sponsor's calculations reasonably estimated the animal-to-human ratios under the expected use. Revisions, however, are recommended so that the ratios would comply with the rounding the Agency's rule. The following text is the suggested edits to the proposed labeling. The underline and strikeouts indicate addition and deletion respectively.

Table 2 Animal-to- Human Dose Ratios for MP03-36 Labeling

Section No.	Description	Species	mg/kg [a]	Km	mg/m^2	Animal-to-Human Ratio [b]		
						Calculated	Suggested [c]	Proposed [d]

(b) (4)

a. Oral doses in animals.
b. Based on a human dose of 1.22 mg/m^2. This value was calculated from a maximum recommended daily dose of 2 sprays per nostril twice a day in a 50-kg patient. Each spray of MP03-36 contains 205.5-µg azelastine. The total daily dose of azelastine is 1.644 mg/day or 0.0329 mg/kg/day. A conversion factor of 37 was used to derive the dose of 1.22 mg/m^2 on a surface area basis.
c. Rounded to the nearest integer, 5s and 10s for single, double and triple-digit numbers, respectively. These numbers are used in the newly suggested labeling.
d. Numbers proposed by the sponsor in the 22-DEC-08 submission.

Suggested labeling:

The following section is the suggested nonclinical sections of labeling. Edits (red color) were made to the proposal submitted on February 20, 2009. The strike outs indicate deletion while underline indicates addition. Justifications for the recommended edits can be found in the previous section (i.e., Labeling Review, p 11).

8 USE IN SPECIFIC POPULATIONS

(b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

adults on a mg/m^2 basis) caused abortion, delayed ossification and decreased fetal weight; however, these doses also resulted in severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose of 0.3 mg/kg (approximately 3times ~~(for ASTEPRO ES Nasal Spray) and 5 times (for ASTEPRO Nasal Spray)~~ the MRDID in adults on a mg/m^2 basis).

Luqi Pei, Ph.D.
Senior Pharmacologist

Appendix:
1. Pharmacology review No. 7 IND 69,785
2. Pharmacology review No. 6 IND 69,785
3. Pharmacology review No. 3 IND 69,785

(b) (4)

Review Number: 7
Sequence No./Date/ Submission Type: 032/ 04-JAN-07/ IT
037/ 12-MAR-07/ IT
Information to the Sponsor: None
Sponsor/or Agent: MedPointe Pharmaceuticals, Somerset, NJ

Reviewer Name: Luqi Pei, Ph.D.
Division Name: Pulmonary and Allergy Products
Review Completion Date: March 28, 2007

Drug:
Trade Name: Astelin® Nasal Spray
Code Name: MP03-33 (0.1% azelastine) and MP03-36 (0.15% azelastine)

Relevant IND/NDAs: NDA 20-114, INDs 32,704 and (b) (4)

Drug Class: Antihistamine

Intended clinical population: Allergic rhinitis (seasonal and perennial)

Route of Administration: Nasal spray

Studies submitted and Not reviewed:
6-month intranasal toxicity study with azelastine and sucralose in Sprague-Dawley rats (Study No. 0460RMS57.001)

A detailed review of the study is not necessary. Dr. Luqi Pei previously completed a review of a draft report of the study (Serial 032, submitted on January 4, 2007) on February 20, 2007 (Review #6). There were no changes between the final and draft reports regarding the scientific sections of the study. Only changes were additions of signature and quality assurance sections (certificates of analysis and compliance). The lack of significant changes between the final and draft report renders it unnecessary to review the final report.

Internal recommendations: None.

External Recommendation: None.

Luqi Pei, Ph.D.
Senior Pharmacologist

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Luqi Pei
3/27/2007 08:44:48 AM
PHARMACOLOGIST/TOXICOLOGIST

Timothy McGovern
3/27/2007 10:10:02 AM
PHARMACOLOGIST/TOXICOLOGIST
I concur.

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 (b) (4)
Drug Class:	Antihistamine
Intended clinical population:	Allergic rhinitis (seasonal and perennial)
Route of Administration:	Nasal spray

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: (b) (4) sucralose, (b) (4) hypromellose (b) (4) edetate disodium, (b) (4) sorbitol solution (b) (4) sodium citrate, and (b) (4) 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.

The new formulations attempt to remove the bitter after-taste of Astelin® with new excipients: (b) (4) sucralose and (b) (4) 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.

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 (b) (4) sucralose and (b) (4) 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.

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%.

Sucralose and sorbitol

General toxicology:

Sucralose at a concentration of 0.15% and sorbitol at 6.45% 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.

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 (b) (4) sorbitol, (b) (4) hypromellose (b) (4) edetate disodium, (b) (4) sodium citrate and (b) (4) benzalkonium chloride.
b. Astelin® contains the following as excipients: (b) (4) benzalkonium chloride, edetate disodium, hypromellose, (b) (4). 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 /Crl: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:	(b) (4) sucralose, (b) (4) hypromellose (b) (4) edetate disodium, (b) (4) sorbitol solution (b) (4) sodium citrate, (b) (4) 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] (mean)
		minimal	mild	moderate	Overall	
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 to replace 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 (b) (4) and sorbitol (b) (4)) because of the novel 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%, 0.15% and 6.45% 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.

However, most of the above studies, especially the 6-month toxicity study in rats, have minor deficiencies in design study. 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 (b) (4) sucralose and (b) (4) 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; (b) (4) and 0% in sucralose; and (b) (4) and 0% 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®.

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Luqi Pei
2/20/2007 01:03:46 PM
PHARMACOLOGIST

Timothy McGovern
2/20/2007 02:07:45 PM
PHARMACOLOGIST
I concur.

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND Number:	69,785
Review Number:	5
Sequence No./Date/ Submission Type:	021/ 28-JUN-06/IT, PN, PI, IM 025/ 25-AUG-06/ IT, PI, PC 029/ 21-SEP-06 / IT
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:	November 29 2006
Drug:	
Trade Name:	Astelin® Nasal Spray
Generic Name:	0.1% and 0.15% 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 (b) (4)
Drug Class:	Antihistamine
Intended clinical population:	Seasonal allergic rhinitis
Route of Administration:	Nasal spray

Clinical Formulations: Aqueous nasal sprays of azelastine HCl: MP03-33 and MP03-36, 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: (b) (4) sucralose, (b) (4) hypromellose (b) (4) edetate disodium, (b) (4) sorbitol solution (b) (4) sodium citrate, and (b) (4) 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:

Protocol No. MP427: *Randomized Nasal Sensory Evaluation of Perceived Taste of an Investigational Formulation of Azelastine Hydrochloride Solution Compared to Astelin® Nasal Spray*. Twelve healthy subjects 18 years and older will be using one (and only once through the study) of the following three treatments per nostril/day: 1 spray of MP03-36, 2 sprays of MP03-36 and 2 Astelin® nasal sprays. Each subject will use formulations in a non-sequential order. The purpose of the study is to compare the perceived taste between the higher concentration of azelastine HCl and Astelin®.

Protocol No. MP433: *Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of MP03-36 in Patients with Seasonal Allergic Rhinitis.* Six hundred patients 18 years and older with seasonal allergic rhinitis will be one of the following four treatments daily for 14 days: 2 sprays of MP03-36/nostril, bid (Arm 1); 2 sprays of MP03-36/nostril AM only (Arm 2); 2 Astelin® nasal sprays, bid (Arm 3); or the vehicle for MP03-36, bid (Arm 4). Participants in Arm 3 will also use 2 sprays/nostril of the vehicle in the afternoon to keep the frequency of treatments among group constant. The total daily dose of azelastine will be 1644, 822, 1096 and 0 µg/day for Arms 1, 2, 3 and 4, respectively.

Previous clinical experience: No previous human nasal experience of MP03-36, the study formulation, is available. There is, however, sufficient clinical experience of the ingredients of the formulation. Azelastine is the active ingredient of both MP03-36 and Astelin® Nasal Spray. The latter is an approved and currently marketed drug. MP03-36 and Astelin® differ in their azelastine concentrations and excipients. The azelastine concentration is 0.10% and 0.15% for Astelin® and MP03-36, respectively. The inactive ingredients of MP03-36 is different from Astelin®, but is identical to another formulation, MP03-33 that is currently in phase 3 clinical trial involving 780 rhinitis patients.

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

Studies submitted and reviewed:

14-day intranasal toxicity study with azelastine and sucralose in Sprague-Dawley rats (Study No. 0437RMS57.004)

14-day intranasal toxicity study with azelastine and sucralose in beagle Dogs (Study No. 0437RMS57.005)

Studies submitted and NOT reviewed: None.

Drug History:

This IND is developing two new formulations of azelastine, namely MP03-33 and MP03-36. The difference between these formulations is their azelastine concentrations: 0.1% and 0.15% for MP03-33 and MP03-36, respectively. MP03-33 will replace Astelin® Nasal Spray while MP03-36 is a proposed new product with the potential for 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. Both formulations are currently in phase-3 clinical development.

The new formulations attempt to remove the bitter after-taste of Astelin® with new excipients: (b) (4) sucralose and (b) (4) 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.

A phase-3 clinical trial (Protocol MP430) of MP03-33 (0.1% AZ with sucralose and sorbitol) is currently ongoing. Dr. Luqi Pei completed safety evaluations of the MP03-33 formulation

in pharmacology and toxicology reviews with completion dates of June 8, 2004 (Review #1), November 4, 2005 (Review #2), and August 17, 2006 (Review #3). Protocol MP430 involves 780 rhinitis patients.

A phase-3 clinical trial involving 600 rhinitis patients (Protocol MP433) of MP03-36 is also currently ongoing. A phase-1 clinical trial of MP03-36 (taste screen trial) was completed. On June 28, 2006, MedPointe submitted a clinical protocol of MP03-36 to study 0.15% azelastine HCl (Protocol MP427). The protocol proposes a taste-screening study to determine whether the new excipients will be able to mask the bitter taste of the higher concentration of azelastine. Twelve healthy subjects 18 years and older will be using each of the following three treatments once only in three days: 1 spray/nostril of 0.15% azelastine HCl, 2 sprays/nostril of 0.15% azelastine HCl and 2 sprays/nostril of the marketed Astelin® nasal spray. Each subject will use the formulations in a non-sequential order. The protocol was allowed to proceed.

The Division and MedPointe have had extensive discussions about regulatory requirements for the development of both MP03-33 and MP03-36. The discussion on MP03-33 has been documented in detailed in a pharmacology/toxicology review by Dr. Luqi Pei with the completion date of August 17, 2006 and minutes of the 08-MAY-2005 meeting and the 08-JUN-2006 telephone conference. Discussions about the regulatory requirement for MP03-36 were held on August 29, 2006 meeting. 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 to evaluate the adequacy of a 6-month intranasal toxicity study(ies) that MedPointe is conducting.

The current review evaluates two 14-day intranasal toxicity studies of MP03-36 in rats and dogs. It also evaluates nonclinically the safety of clinical protocol MP 427 submitted on June 28, 2006.

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2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Local toxicity/irritation potential of 0.15% azelastine HCl was evaluated in two 14-day intranasal toxicity studies in rats and dogs (Studies 0437RM57.004 and 005). One-tenth of 1 ml/nostril of MP03-36 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. The vehicle consisted of (b) (4) sucralose, (b) (4) hypromellose (b) (4) edetate disodium, (b) (4) sorbitol, (b) (4) sodium citrate, (b) (4) benzalkonium chloride and water. All animals were sacrificed on the day after the last treatment. The respiratory system was examined microscopically.

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. Such results indicate that the 0.15% azelastine can be regarded as the NOAEL. Such a conclusion, however, contradicts previous studies that showed 0.10% azelastine was slightly irritating to the nasal cavity in the same species. Also, it is unknown whether these abnormalities observed in these studies reflect irritant effects of the vehicle or a background incidence of studies since a negative control was not included.

2.6.6.3 Repeat-Dose Toxicity

Study Title: 14-day intranasal toxicity study with azelastine and sucralose in Sprague-Dawley rats (Study No. 0437RMS57.004)

Key findings: Intranasal instillation of a vehicle in the presence or absence of 0.15% azelastine HCl resulted in similar effects in the respiratory system in rats. Prevalent abnormalities in the nasal cavity, larynx, and lung were observed in both groups. These 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. The sponsor concludes that the NOAEL for nasal administration of azelastine is 0.15%. The conclusion, however, contradicts previous observations that 0.1% azelastine was slightly irritating. Also, it is unknown whether the

prevalent abnormalities were attributed to the vehicle effect or spontaneous background incidence, due to the lack of appropriate control (e.g., saline).

Study number:	0437RM57.004
Volume #, and page #:	Draft report: Vol. C13.1, p 88 ; Final report: C16.3. p 1.
Report Date:	April 28, 2006
Conducting laboratories and location:	(b) (4)
Date of study initiation:	February 14, 2006
Study completion date:	March 3, 2006
GLP compliance:	Yes, with a signed page
QA reports:	Yes, with a signed page
Drug, lot #, radio-label, and % purity:	Batches 03-36-01C Purity: azelastine 95 – 105%,

Methods

Sprague-Dawley rats (10/sex/group) were treated with a vehicle in the absence or presence of 0.15% azelastine HCl. The vehicle consists of (b) (4) sucralose, (b) (4) hypromellose (b) (4) edetate disodium, (b) (4) sorbitol solution (b) (4) sodium citrate, and (b) (4) benzalkonium chloride. Each nostril was instilled with 0.1 ml solution twice a day. The rats were sacrificed on day 15. The respiratory system was examined microscopically. Of note, no standard negative (e.g., saline) or positive (approved azelastine formulation) control group was included.

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 /Crl:CD(SD)
#/sex/group (main study):	10
Age:	Approximately 8 weeks
Weight (mean):	M: 248 - 280 g; F: 185 - 215 g
Route, formulation, volume and infusion rate:	Nasal instillation, solution, 1 ml/nostril, twice daily, 6 hrs between doses
Sampling times:	See below
Vehicle:	(b) (4) sucralose, (b) (4) hypromellose (b) (4) edetate disodium, (b) (4) sorbitol solution (b) (4) sodium citrate, (b) (4) 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: None.

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: Prevalent abnormalities (incidences up to 7-9 out of 10) were observed in the vehicle and drug-treatment groups in both sexes (Table 2). These abnormalities included inflammation, lymphohistiocytic and mixed cell infiltration, and hemorrhage in the lung; mineralization of submucosa in the nasal cavity; minimal to mild lymphoid infiltration in the submucosa of the trachea. Addition of 0.15% azelastine, however, did not increase significantly the incidence of these abnormalities when compared to the vehicle only treatment group.

Table 2. Notable Microscopic Findings in Rats (n = 10/group)

Findings	Male		Female	
	Vehicle	Azela-stine	Vehicle	Azela-stine
Lung: mineralization, vascular (minimal)	9	5	8	2
Inflammation: subacute, mixed, alveolar (min. – mild)	7	5	7	3
Infiltration: lymphohistiocytic, perivascular (min. – mild)	7	5	4	7
Mixed. Perivascular (min. – mild)	6	7	6	6
Hemorrhage, alveolus (minimal –mild)	5	5	5	3
Nasal Cavity				
Inflammation/Subacute: Lymphoid, olfactory epithelial, focal, (min)	1	0	0	0
Lymphoid, nasolacrimal duct, focal, bilateral (min-mild)	0	3	2	2
Lymphoid, nasolacrimal duct, focal, unilateral (min-mild)	4	0	3	2
Subacute/mixed/mucosa: Focal, (min)	0	0	0	4
Multi-focal, (min - mild)	4	5	2	0
Subacute/mixed/nasolacrimal duct: bilateral, (min - mild)	0	0	1	1
Unilateral, (min)	1	1	1	2
Acute, mucosa, multi-focal, minimal	5	6	8	7
Metaplasia/Olfactory epithelium: focal (minimal)	1	1	1	1
Multi-focal (minimal)	2	0	0	0
Squamous: focal, minimal	0	0	0	6
Multi-focal, minimal - mild	2	4	1	0
Mineralization: Submocusa, multilateral (minimal)	8	4	5	2
Olfactory epithelium: focal (minimal)	1	0	1	0
Multi-focal (minimal)	1	0	0	0
Hyperplasia: Olfactory epithelium, focal (minimal)	1	0	0	0
Degeneration: Olfactory epithelium, focal (minimal)	1	2	0	0
Erosion: Olfactory epithelium, unilateral, multi-focal (minimal)	1	0	0	0
Focal (minimal)	1	0	0	0
Trachea: Infiltration: lymphoid, submucosa, diffuse (minimal)	0	0	1	0
Infiltration/lymphoid/ submucosa: focal (minimal - mild)	0	3	0	0
Multi-focal (minimal - mild)	6	3	5	3
Attenuation: epithelium, focal (minimal)	0	0	1	0
Inflammation: subacute, mixed, mucosa, focal (minimal)	0	0	1	0

Study Title: 14-Day Intranasal Toxicity Study with Azelastine and Sucralose in Beagle Dogs (Study 0437RM57.005)

Key findings: Daily intranasal instillation of the vehicle in the presence or absence of 0.15% azelastine HCl for 14 days resulted in similar effects as noted in the respiratory system in rats. Treatment with vehicle alone resulted in 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. Addition of 0.15% azelastine HCl to the vehicle did not result in any additional significant adverse effect on the nasal cavity when compared to the vehicle alone. However, the effect of the vehicle cannot be fully evaluated because the study lacked an appropriate control (e.g., negative such as saline or positive like approved azelastine formulation).

Study number:	0437RM57.005
Volume #, and page #:	Darft report: Vol. C13.2, p 1 Final report: C16.4. p 1.
Report Date:	April 25, 2006
Conducting laboratories and location:	(b) (4)
Date of study initiation:	February 8, 2006
study completion date:	March 2, 2006
GLP compliance:	Yes, with a signed page
QA reports:	Yes, with? a signed page
Drug, lot #, radio-label, and % purity:	Batches 03-36-01C for azelastine HCl; 03-33-02C for vehicle; Purity: 99.7%

Methods:

Beagle dogs (3/sex/group) were treated with a vehicle in the absence (Group 1) or presence (Group 2) of 0.15% azelastine HCl. The vehicle consisted of (b) (4) sucralose, (b) (4) hypromellose (b) (4) edetate disodium, (b) (4) sorbitol, (b) (4) sodium citrate, and (b) (4) benzalkonium chloride. Each nostril was instilled with 0.1 ml solution twice a day for 14 days. The dogs were sacrificed on day 15. The respiratory system was examined microscopically. Of note, the study design did not include an appropriate negative (e.g., saline) or positive (approved azelastine formulation) control group.

Doses:	0 or 0.15% (i.e., 2.7 mg/kg on a body weight basis and 60 µg/cm^2 on a nasal surface area basis)
Species/strain:	Dogs /Beagle
#/sex/group (main study):	3
Age:	Approximately 11 months
Weight:	Male: 8.5 – 9.5 kg; Female: 7.1 – 9.0 kg
House:	Individually housed
Route, formulation:	Nasal instillation, 1 ml/nostril
Treatment duration:	Twice a day for 14 days, 6 hours between doses on the same day
Reference:	0.1% azelastine with other excipients

Observations and times:

Clinical signs:	Twice daily
Body Weight:	Weekly
Food consumption:	daily
Ophthalmoscopy	Not assessed
EKG:	Not assessed
Hematology:	Not assessed
Clinical chemistry:	Not assessed
Urinalysis:	Not assessed
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, and uterus

Histology: Respiratory system only in all animals: nasal cavity, nasopharynx, larynx, trachea, lung with main stem bronchus, tracheobronchial lymph nodes.

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

Peer review: yes ( ), no (x)

Results:

Mortality: None

Clinical signs: No drug-related findings were noted

Body weights: No drug-related findings were noted

Gross pathology: No drug-related findings were noted

Organ weights: No drug-related findings were noted

Histopathology: Prevalent incidences (up to 3 of 3) of abnormalities were observed in the vehicle and drug-treatment groups in both sexes (Table 3). After administration of the vehicle alone, these abnormalities included inflammation, lymphohistiocytic 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 addition of 0.15% azelastine to the vehicle formulation, however, did not increase significantly the incidence of these abnormalities.

Table 3. Notable Microscopic Findings in Dogs (n = 3/group)

Findings	Male		Female	
	Vehicle	Azela-stine	Vehicle	Azela-stine
Lung: / Inflammation: subacute, bronchiole/ multi-focal (minimal)	2	3	3	3
/Subacute/ mixed, alveolar (minimal)	2	3	3	3
Infiltration: lymphohistiocytic, perivascular (minimal)	2	3	1	3
Pigmentation/ black /perivascular / multi-focal (minimal)	2	3	1	2
Larynx: Inflammation/Subacute/mixed: mucosa: Focal (min - mild)	3	3	2	0
Submucosa: multi-focal (minimal – mild)	1	2	1	0
Degeneration: muscle (?)/multi-focal (minimal)	3	1	1	0
Submucosa/ glands / multi-focal (min. – mild)	1	2	1	0
Respiratory epithelium/ multi-focal (minimal – mild)	3	3	2	0
Atrophy/ submucosa/ glands /multi-focal (minimal – mild)	1	2	1	0
Metaplasia/ squamous/ respiratory epithelium (minimal)	2	1	1	0
Mucosa associated lymphoid tissue	0	0	0	3
Nasal Cavity:				
Inflammation/ subacute/ lymphoplasmatic/ mucosa/multi-focal (min)	2	1	2	3
/ mixed/ mucosa/ diffuse (minimal - mild)	1	1	1	1
/ mixed/ nasolacrimal duct/ mucosa (minimal - mild)	3	3	3	3
Degeneration/ single cell/epithelium/vascular/ multi-focal (minimal)	1	3	1	0
Cystic/ respiratory epithelium/multi-focal (minimal)	0	0	0	2
Infiltration /follicular/mucosa/multi-focal (min – mild)	3	3	3	3
Hyperplasia /goblet cell/multi-focal (min – mild)	3	3	3	2
Edema/ mucosa/ multi-focal (minimal)	2	0	1	0
Necrosis/ single cell/ respiratory/ multi-focal	0	0	2	0

2.6.6.9 Discussion and Conclusions

The irritation/toxicity potential of 0.15% azelastine in a vehicle containing (b) (4) sucralose and other excipients to the respiratory tract was evaluated in two 14-day intranasal toxicity studies in rats and dogs (Studies 0437RM57.004 and 005). The vehicle consisted of (b) (4) sucralose, (b) (4) hypromellose (b) (4) edentate disodium, (b) (4) sorbitol, (b) (4) sodium citrate, and (b) (4) benzalkonium chloride. One-tenth of one milliliter of the vehicle or vehicle plus 0.15% azelastine HCl was instilled into the nasal cavity twice a day for 14 days in each species. Sample sizes were 10 and 3/sex/dose in rats and dogs, respectively. Results showed high incidences of abnormalities in both vehicle and azelastine treated groups in both species. Addition of 0.15% azelastine to the vehicle did not produce any significant increases in the incidence or severity of any abnormalities.

Abnormalities observed in rats included inflammation, lymphohistocytic and mixed cell infiltration, and hemorrhage in the lung; mineralization of submucosa in the nasal cavity; minimal to mild lymphoid infiltration in the submucosa of the trachea. Abnormalities observed in dogs 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 in the nasal cavity.

The results of the studies indicate that the addition of 0.15% azelastine does not enhance the irritation potential of the vehicle to the respiratory tract in either rats or dogs though rather prevalent abnormalities were observed in the vehicle alone group. The results suggest that

the NOAEL for azelastine might be 0.15% in both rats and dogs. Such a conclusion, however, contradicts a previously established finding that the NOAEL for nasal azelastine is below 0.1% (see review #3). Furthermore, each study employed only two groups: the vehicle and azelastine treated groups. While the abnormalities could also be background findings, the review cannot refute a conclusion that that the lesions could be vehicle-related because of the lack of an appropriate control such as saline, given that the vehicle contains novel excipients. The review, therefore, does not make any conclusion on the NOAEL of azelastine.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

The available nonclinical data of the application are supportive of the safety of the proposed clinical trials of MP03-36 (0.15% azelastine). The application proposed to study the safety and tolerability of up to 14-day intranasal use of MP03-36 in healthy volunteers and rhinitis patients. Pivotal toxicity studies supporting the safety of these trials are two 14-day intranasal toxicity studies of MP03-36 in rats and dogs. These studies showed that the addition of 0.15 azelastine HCl to the vehicle for MP03-36 did not result in any significant increase in adverse effects. Previous safety reviews found the proposed use of the vehicle reasonably safe. The available nonclinical data are considered adequate to support the safety of MP03-36. The proposed trials, therefore, are considered reasonably safe from the preclinical perspective.

The recent submissions (Serial Nos. 021 and 025) contain two clinical protocols of MP03-36. Protocol MP427 is a taste-screening study in healthy volunteers. Twelve subjects 18 years and older will be using each of the following three treatments once in three days: 1 spray/nostril of 0.15% azelastine HCl, 2 sprays/nostril of 0.15% azelastine HCl and 2 sprays/nostril of the marketed Astelin® nasal spray. Each subject will be administered the treatment in a non-sequential order. The purpose of the study is to compare the perceived taste between the higher concentration/reformulation of azelastine HCl and Astelin®.

Protocol MP433 proposes to study the safety and efficacy of MP03-36 in patients with seasonal allergic rhinitis. Six-hundred patients 18 years and older will receive one of the following four treatments daily for 14 days: 2 sprays of MP03-36/nostril, bid (Arm 1); 2 sprays of MP03-36/nostril AM only (Arm 2); 2 Astelin® nasal sprays, bid (Arm 3); or the vehicle for MP03-36, bid (Arm 4). Participants in Arm 3 will also use 2 sprays/nostril of the vehicle in the afternoon to keep the frequency of treatments among group constant. The total daily dose of azelastine will be 1644, 822, 1096 and 0 μg/day for Arms 1, 2, 3 and 4, respectively.

The nonclinical data supporting the safety of the proposed trials are two 14-day intranasal toxicity studies of MP03-36 in rats and dogs (Studies 0437RMS57.004 and 0437RMS57.005). One-tenth of 1 ml/nostril of MP03-36 or its vehicle 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. The respiratory system was examined microscopically at the end of the treatment. Results showed that the addition of 0.15% azelastine HCl to the vehicle

containing (b) (4) sucralose and other excipients did not increase the incidence of abnormalities compared to the vehicle group though rather prevalent abnormalities were observed in the vehicle alone group. The results did not reveal any significant signal for safety concern about the proposed use of the higher concentration (0.15%) of azelastine. Such data is considered sufficient to support the proposed use of the 0.15% azelastine.

The available data support the safety of the excipients in MP03-36. MP03-36 contains (b) (4) sucralose and (b) (4) sorbitol as excipients. The toxicity studies 0437RMS57.004 and 0437RMS57.005 are insufficient to evaluate the effect of these excipients on the respiratory tract due to their lack of appropriate controls. A previous review (Review #3) in the application completed by Dr. Luqi Pei on August 17, 2006, however, has concluded it safe to use these excipients at the proposed concentration and duration of treatment. Thus, there is no safety concern about the proposed use of the excipients. Overall, the available nonclinical data are considered sufficient to support the safety of the proposed use of the new formulation of azelastine, MP03-36.

Internal recommendations

The available nonclinical data of the application support the safety of the proposed clinical trials. It is recommended that the trials be allowed to proceed.

External Recommendation: None.

Luqi Pei, Ph.D.
Pharmacologist/toxicologist

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/s/

Luqi Pei
11/29/2006 07:50:02 AM
PHARMACOLOGIST

Timothy McGovern
11/29/2006 08:35:11 AM
PHARMACOLOGIST
I concur.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Luqi Pei
3/16/2009 10:01:29 AM
PHARMACOLOGIST

Timothy Robison
3/16/2009 10:43:47 AM
PHARMACOLOGIST
I concur

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

NDA 21-Day Pharmacology Fileability Check List

Reviewer: Luqi Pei, Ph.D.

NDA No: 22-371
Drug Name: TRADENAME, Azelastine 0.15%, MP03-36
Date of submission: August 1, 2008 (stamp date)
Date of 45-day file-ability meeting: September 10, 2008
Information to the Sponsor: None.
Date of check list: September 16, 2008

(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	( )	( )	(x)
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 azelastine 0.15% will differ. The difference will be handled during labeling review.

(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
9/17/2008 02:28:49 PM
PHARMACOLOGIST