CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-371s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-371
Type:	505 (b) (1)
Brand Name (proposed):	Astepro
Generic Name:	Sweetened Azelastine Hydrochloride 0.15%
Indication:	Seasonal and perennial allergic rhinitis for adults and children ≥12 yrs
Dosage Form:	Nasal Spray
Strength:	205.5 mcg / 0.137 mL per spray
Route of Administration:	Nasal spray
Dosing Regimen (proposed):	1 or 2 sprays per nostril once or twice daily
Applicant:	MedPointe (MEDA) Pharmaceuticals
OCP Division:	Division of Clinical Pharmacology 2
Clinical Division:	Division of Pulmonary and Allergy Drug Products
Submission Date:	August 1, 2008
Reviewer:	Ying Fan, Ph.D.
Team Leader:	Sally Choe, Ph. D.

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed the Clinical Pharmacology information submitted under NDA 22-371 on August 1, 2008 and finds it acceptable provided that a satisfactory agreement is reached between the applicant and the Agency regarding the proposed new language to be included in the package insert.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The sponsor submitted a 505(b) (1) application for a sweetened formulation of azelastine hydrochloride nasal spray with a proposed brand name of Astepro. An unsweetened formulation of 0.1% w/v azelastine hydrochloride nasal spray, Astelin® was approved under NDA 20-114 and is currently marketed. Due to a distinctive bitter taste that limits marketing of Astelin® and patient compliance, the sponsor developed a sweetened intranasal azelastine formulation, Astepro, containing two additional excipients, sucralose and sorbitol. Astepro was approved on October 15, 2008 under NDA 22-203 for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older. This Astepro has the strength of 0.1% w/v azelastine hydrochloride and the recommended dose is 2 sprays per nostril once or twice daily for seasonal allergic rhinitis (SAR) and 2 sprays per nostril twice daily for perennial allergic rhinitis (PAR). In order to demonstrate improved efficacy over the marketed Astelin® Nasal Spray formulation and support once daily administration, the sponsor proposed a higher strength azelastine formulation (0.15% w/v azelastine) for relief of symptoms associated with allergic rhinitis (seasonal and perennial) in patients 12 years of age and older in current submission.

The current clinical submission comprises of seven Phase 3 efficacy/safety trials (4 Phase 3 trials for SAR and 3 Phase 3 trials for PAR). Specifically, for clinical pharmacology, the sponsor has re-submitted two studies: relative bioavailability (BA) study (Study MP429) and multiple dose pharmacokinetics (PK) study (Study 25) which have been submitted and reviewed in NDA 22-203 and NDA 20-114 previously. In relative BA study, the sponsor compared commercial formulation of 0.1% Astelin® (total dose: 548 mcg), approved formulation of 0.1% Astepro (total dose: 548 mcg), and proposed higher strength formulation of 0.15% Astepro (total dose: 822 mcg). The results indicate that

the pharmacokinetics parameters, CL, $T_{1/2}$, and T_{max} for azelastine and its major active metabolite, desmethylazelastine are comparable among the three treatments. The dose normalized C_{max} and $AUC_{0\text{-}inf}$ of the proposed higher strength formulation of 0.15% Astepro are similar to the commercial formulation of 0.1% Astelin (Table 1).

Table 1. Mean ± SD dose normalized AUC, C_{max}, T_{max}, $T_{1/2}$ and CL of azelastine and desmethylazelastine following 2 sprays of 0.1% Astelin® (548 mcg), 0.1% Astepro (548 mcg) and 0.15% Astepro (dose: 822 mcg) solution per nostril

PK parameters	Azelastine			Desmethylazelastine		
	Astelin® (marketed)	Astepro (approved 0.1%)	Astepro (proposed 0.15%)	Astelin® (marketed)	Astepro (approved 0.1%)	Astepro (proposed 0.15%)
$AUC_{0\text{-}inf}$ ** (pg hr/ml/µg)	11.17 ± 4.33	9.35 ± 2.82	11.32 ± 4.81	4.77 ± 1.42	3.89 ± 1.11	4.65 ± 1.44
C_{max} ** (pg/ml/µg)	0.43 ± 0.16	0.36 ± 0.12	0.50 ± 0.19	0.04 ± 0.01	0.04 ± 0.02	0.05 ± 0.02
T_{max} (hr)*	4.0 (0.25-6.0)	3.0 (0.5 – 4.0)	4.0 (0.25-6.0)	24 (24-72)	24 (12 – 96)	24 (24-48)
$T_{1/2}$ (hr)	24 ± 6.0	22 ± 7.5	25 ± 8.7	60 ± 22	52 ± 21	57 ± 23
CL/F (mL/min/kg)	25 ± 18	26 ± 9.5	26 ± 15	53 ± 24	61 ± 16	57 ± 23

* median (range)
** dose-normalized

The multiple dose PK study was a double-blind, placebo-controlled, randomized, parallel study to determine the tolerability and safety of 0.1% azelastine hydrochloride nasal spray solution when administered for 29 consecutive days. This study was resubmitted to evaluate the dose proportionality and time-independent PK of azelastine. Azelastine hydrochloride nasal spray was administered in metered-dose spray pump designed to deliver one, two, or three sprays (0.14 mg, 0.28 mg, or 0.42 mg respectively) per nostril of azelastine hydrochloride nasal spray. When these multiple dose PK data was re-evaluated by this reviewer, azelastine hydrochloride did not demonstrate either dose proportionality or time-independent PK due to the large variability of the data leading to inconsistent results in these analyses.

2 QUESTION BASED REVIEW

2.1 General Attributes

What is the regulatory history of Astepro?

The sponsor submitted a 505(b) (1) application for a sweetened formulation of azelastine hydrochloride nasal spray with a proposed brand name of Astepro. An unsweetened formulation (Astelin®) is currently marketed. Due to a distinctive bitter taste that limits marketing of Astelin® and patient compliance, the sponsor developed a sweetened intranasal azelastine formulation (Astepro, NDA 22-203), containing two additional excipients, sucralose and sorbitol. Astepro (NDA 22-203) was approved on October 15, 2008 for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older. In order to demonstrate improved efficacy over the marketed Astelin® Nasal Spray formulation and support once daily administration, the sponsor proposed a higher strength azelastine formulation (0.15% w/v astelastine) for relief of symptoms associated with allergic rhinitis (seasonal and perennial) in patients 12 years of age and older.

The proposed new formulation contains 205.5 mcg of azelastine hydrochloride per spray and has a higher concentration (0.15%) than that of the previously approved Astelin® Nasal Spray (NDA 20-114) and Astepro Nasal Spray (NDA 22-203) which contain 0.1% azelastine hydrochloride (137 mcg per spray). This represents a total daily dose ranging from 822 mcg to 1,644 mcg (two sprays per nostril once or twice daily for seasonal allergic rhinitis and 2 sprays per nostril twice daily for perennial allergic rhinitis) for Astepro 0.15% w/v Nasal Spray compared to a total daily dose ranging from 548 mcg to 1,096 mcg (one or two spray per nostril twice daily for seasonal allergic rhinitis in adults and children 12 years and older and one spray per nostril for children 5-11 years old, and two spray per nostril twice daily for vasomotor rhinitis in adults and children 12 years and older) for Astelin® Nasal Spray and Astepro 0.1% w/v Nasal Spray.

This higher concentration 0.15% azelastine hydrochloride formulation was developed to demonstrate improved efficacy over the marketed Astelin® Nasal Spray formulation and support once daily administration. In Astelin® Nasal Spray clinical trials, a distinctive bitter taste, which is associated with the active ingredient, azelastine hydrochloride, has been reported as an adverse effect in approximately 15% to 20% of subjects. Thus, in an effort to develop a formulation containing a higher concentration of azelastine hydrochloride that also has a reduced incidence of bitter taste, this new azelastine hydrochloride 0.15% w/v formulation (also referred to as formulation MP03-36) was developed. Like approved Astepro (NDA22-203), this new sweetened formulation vehicle contains the taste masking agent sucralose (b) (4) with sorbitol.

2.2 General Clinical Pharmacology

2.2.1 What is known about the pharmacokinetics of 0.15% Astepro?

The sponsor evaluated single-dose pharmacokinetics of azelastine in an open-label, single-center, randomized, parallel group relative bioavailability study in which 18 healthy male subjects ages 18-50 years were treated with one of three intranasal formulations (2 sprays per nostril) of azelastine hydrochloride: (1) 0.1% Astelin® (total dose: 548 mcg), (2) 0.1% Astepro (total dose: 548 mcg) and (3) proposed 0.15% Astepro (total dose: 822 mcg).

The pharmacokinetic results of azelastine and its major active metabolite, desmethylazelastine from 0.1% Astelin®, 0.1% Astepro, and 0.15% Astepro are presented in Figure 1, Figure 2 and Table 2. Azelastine was found to be absorbed into the systemic circulation with a median T_{max} of 4 hours following single dose 0.15% Astepro intranasal administration. The mean azelastine peak plasma concentration (Cmax) is 409 pg/ml and the mean extent of systemic exposure (AUC0-inf) is 9312 pg.hr/ml. The mean terminal half-life values of azelastine and desmethylazelastine after single dose of 0.15% Astepro were calculated to be 25 hrs and 57 hrs, respectively.

Figure 1. Mean azelastine plasma concentration vs. time profiles for 2 sprays of 0.1% Astelin® (548 mcg), 0.1% Astepro (548 mcg) and 0.15% Astepro (dose: 822 mcg) solution per nostril

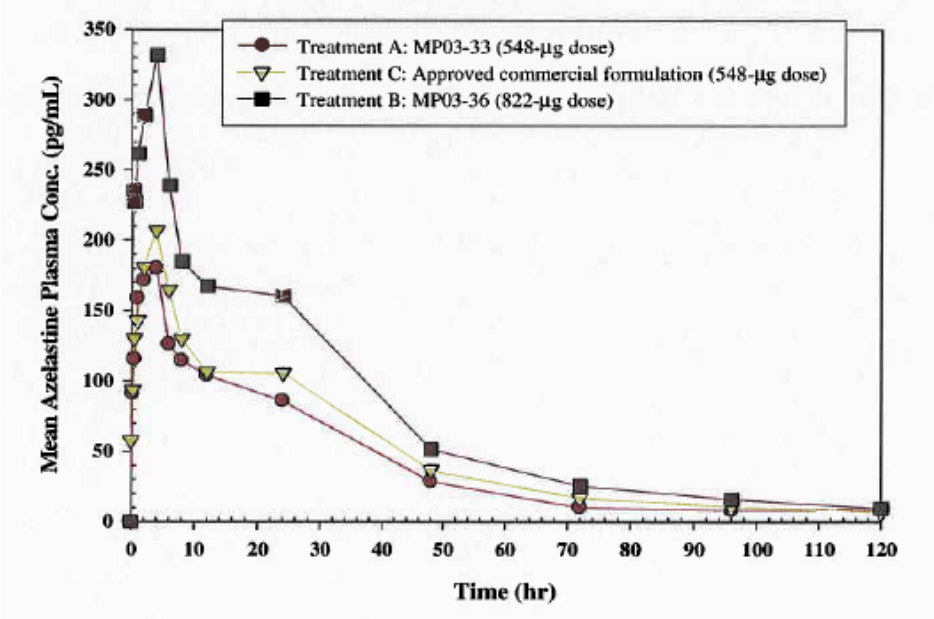


Figure 2. Mean desmthyazelastine plasma concentration vs. time profiles for 2 sprays of 0.1% Astelin® (548 mcg), 0.1% Astepro (548 mcg) and 0.15% Astepro (dose: 822 mcg) solution per nostril

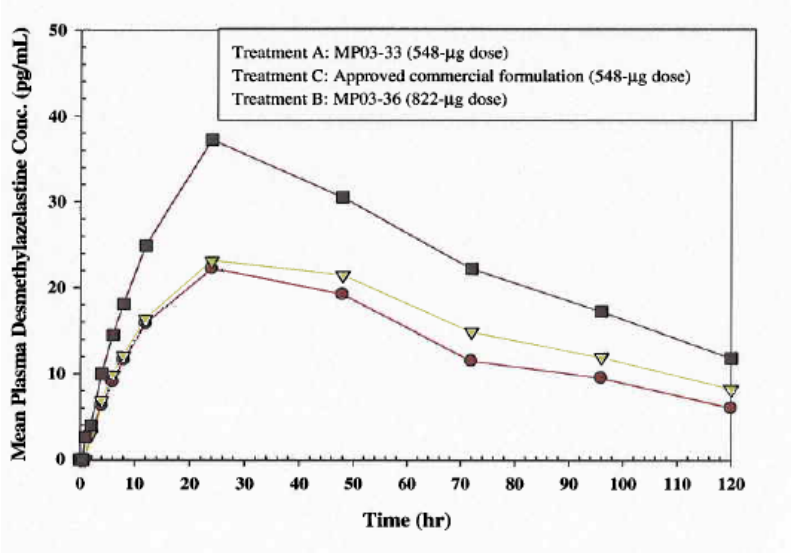


Table 2. Mean ± SD pharmacokinetic parameters of azelastine and desmethylazelastine following 2 sprays of 0.1% Astelin® (548 mcg), 0.1% Astepro (548 mcg) and 0.15% Astepro (dose: 822 mcg) solution per nostril

PK parameters	Azelastine			Desmethylazelastine		
	Astelin® (marketed)	Astepro (approved 0.1%)	Astepro (proposed 0.15%)	Astelin® (marketed)	Astepro (approved 0.1%)	Astepro (proposed 0.15%)
AUC_{0-t} (pg.hr/mL)	5903 ± 2264	4917 ± 1394	8941 ± 3749	1873 ± 553	1634 ± 603	2780 ± 857
AUC_{0-inf} (pg.hr/mL)	6122 ± 2373	5122 ± 1546	9312 ± 3950	2615 ± 779	2131 ± 609	3824 ± 1184
AUC_{0-inf}** (pg hr/mL/µg)	11.17 ± 4.33	9.35 ± 2.82	11.32 ± 4.81	4.77 ± 1.42	3.89 ± 1.11	4.65 ± 1.44
C_{max} (pg/mL)	235 ± 88	200 ± 67	409 ± 160	24 ± 7.8	23 ± 11	38 ± 15
Cmax** (pg/ml/µg)	0.43 ± 0.16	0.36 ± 0.12	0.50 ± 0.19	0.04 ± 0.01	0.04 ± 0.02	0.05 ± 0.02
T_{max} (hr)*	4.0 (0.25-6.0)	3.0 (0.5 – 4.0)	4.0 (0.25-6.0)	24 (24-72)	24 (12 – 96)	24 (24-48)
$T_{1/2}$ (hr)	24 ± 6.0	22 ± 7.5	25 ± 8.7	60 ± 22	52 ± 21	57 ± 23
CL/F (mL/min/kg)	25 ± 18	26 ± 9.5	26 ± 15	53 ± 24	61 ± 16	57 ± 23

* median (range)
** dose-normalized

2.2.2 Does the azelastine demonstrate the dose proportional and time independent pharmacokinetics (PK)?

No. The sponsor did not demonstrate the dose proportional and time independent pharmacokinetics.

A double-blind, placebo-controlled, randomized, parallel study was to determine the tolerability and safety of 0.1% azelastine hydrochloride nasal spray solution when administered for 29 consecutive days. This study was resubmitted to characterize the dose proportionality property and time independent pharmacokinetics of azelastine. Azelastine hydrochloride nasal spray was administered in metered-dose spray pump designed to deliver 0.14 mg azelastine hydrochloride nasal spray per stroke. Thirty-nine healthy male subjects were apportioned into three groups and randomly allocated to treatment or placebo. Within each of the three groups, ten subjects were administered one, two, or three sprays per nostril of azelastine hydrochloride nasal spray, and three subjects were administered placebo nasal spray. On Study Day 1 and 29 each subject received one dose. On each of Study Days 2 through 28 each subject received doses every twelve hours. Subjects fasted for ten hours before and until four hours after administration of the study drug on Study Day 1, 8, 15, 22, and 29. Blood samples for assay of azelastine and desmethylazelastine were collected at the following time points:

- 0 hour (predose), 0.25, 0.50, 1, 2, 4, 6, 8, 12, and 24 hours after administration of the morning dose on Study Day 1
- 0 hour (predose), 0.25, 0.5, 1, 2, 4, 6, 8, and 12, after the morning dose on Study Days 8, 15, and 22
- 0 hour (predose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after the morning dose on Study Day 29

The plasma samples were assayed by (b) (4) utilizing (b) (4) .

Figure 3 shows the relationship between azelastine AUC vs. dose at Day 1, Day 29 and azelastine Cmax vs. dose at Day 1, Day 29. This reviewer used the power model (C_{max} or AUC= α*Dose$^{\beta}$) for the azelastine dose-proportionality evaluation in healthy subjects. In the power model, β is the dose-proportionality factor and α is the subject, period, and model error factor. After logarithmic transformation ($\ln(C_{max})$ or $\ln(AUC) = \ln(\alpha) + \beta*\ln(Dose)$), β should be equal to 1 when the exposure (AUC and Cmax) change is proportional to dose change. Values of β and its 90% confidence interval (CI) are shown in Table 3. The power model regression analyses indicate that there is inconsistency in the dose proportionality evaluation. For example, the slopes are greater than 1 with its 90% CIs not including 1 on Days 15, 22, and 29 for AUC and Days 8, 15, and 29 for Cmax indicating azelastine might have greater than dose proportionality increase in Cmax and AUC. However, Days 1 and 8 for AUC and Day 22 for Cmax had slopes greater than 1 but 90% CIs including 1, which makes the data questionable on greater than dose proportionality increases. In addition, 90% CIs of the slope are quite wide on Day 1 for both AUC and Cmax.

Figure 3: Relationship between azelastine AUC vs. dose at Day 1 (upper left) or at Day 29 (upper right), and azelastine Cmax vs. dose at Day 1 (lower left) or at Day 29 (lower right)

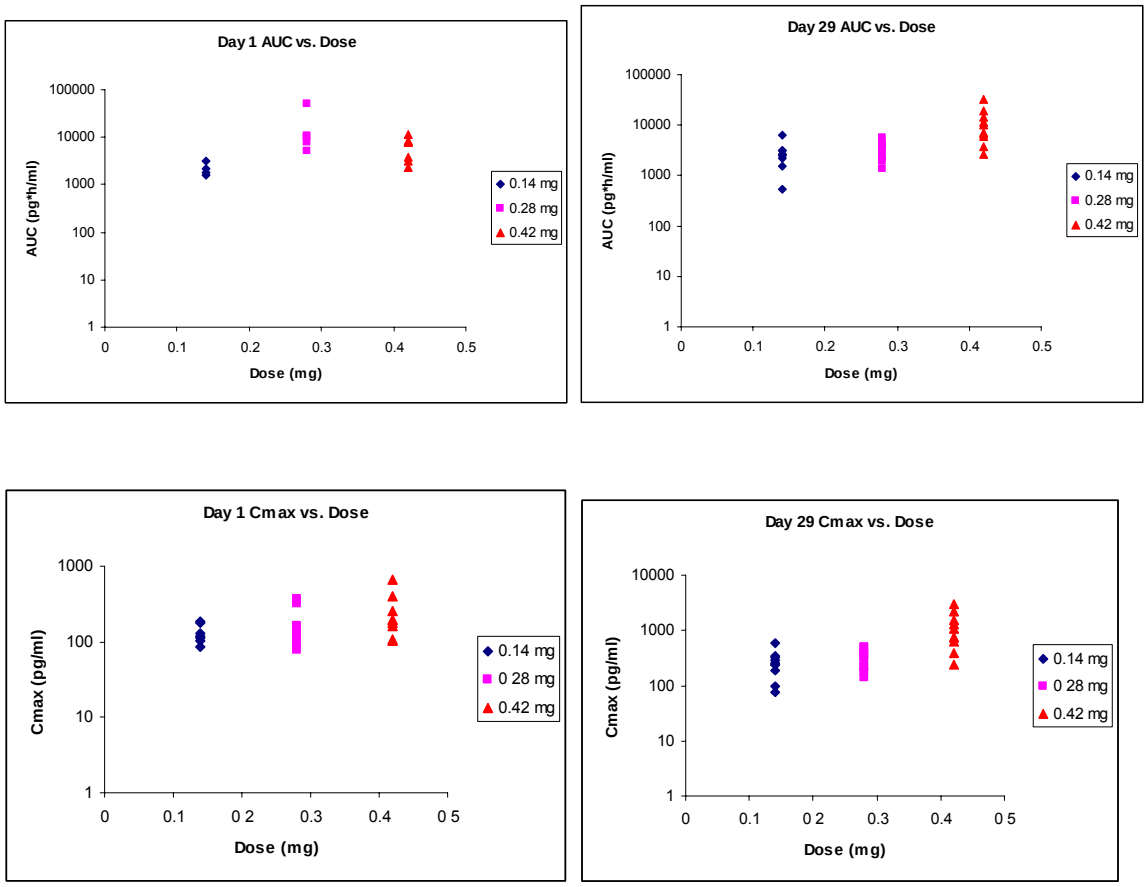


Table 3. Slope of ln (AUC) or ln (Cmax) of Azelastine and its 90% CI from power model assessing the dose proportionality across the doses of 0.14, 0.28, and 0.42 mg at various days.

AUC (pg h/ml)	Slope	90% CI (lower)	90% CI (upper)
Day 1	1.18	-0.195	2.551
Day 8	1.16	0.764	1.565
Day 15	2.13	1.401	2.858
Day 22	1.85	1.160	2.532
Day 29	2.13	1.335	2.915

Cmax (pg/ml)	Slope	90% CI (lower)	90% CI (upper)
Day 1	0.47	0.065	0.872
Day 8	1.81	1.145	2.467
Day 15	1.76	1.009	2.511
Day 22	1.65	0.969	2.337
Day 29	2.19	1.423	2.950

Therefore, the reviewer additionally evaluated the dose-proportionality of azelastine using comparability among dose normalized AUC and Cmax. The statistical significance among dose normalized AUC and dose normalized Cmax are evaluated using the one-way ANOVA test and results are summarized in Table 4. There is no significant difference seen in the dose normalized AUCs and Cmaxs among different doses on each day ($p > 0.01$), which can indicate there is a dose proportionality increase for azelastine. However, there is a trend in changes of dose normalized AUCs with changes of doses where dose normalized AUCs decreases from 0.14 mg to 0.28 mg (AUC change is less proportional to dose change) but increases from 0.28 mg to 0.42 mg (AUC change is more proportional to dose change) at Day 15 to Day 29.

In order to analyze the inconsistence on the dose-proportionality further, accumulation ratios and variability as CV% are evaluated. The accumulation ratios are overall consistent (Table 5) except 0.28 mg (e.g, D15/D1=0.185, D8/D1=0.249). The CV% for both AUCs and Cmaxs appears to be comparable in different doses and different days (Table 6).

The sponsor evaluated azelastine pharmacokinetics parameters among different time points (e.g., Day 1 vs. Day 8) at a given dose, which is the approach to evaluate the time-independent PK. However, it appears that AUC at Day 29 is calculated from time 0 to 48 hours, which is more than dosing interval, and it should not be included in the time-independent PK analysis.

Because the sponsor evaluated the time-independent PK, the reviewer also used the sponsor's approach to assess whether azelastine PK changes with time. Table 4 shows the dose normalized AUC and Cmax on different days at each dose. The dose normalized AUC and Cmax are not statistically significant different among different days at each dose except at dose 0.28 mg for AUC ($p < 0.01$), which indicate the time-independent PK except on dose 0.28 mg. There was one outlier for 0.28 mg at Day 1 for AUC and the statistical significance remains unchanged excluding the outlier ($p < 0.001$). Therefore, the time-independent PK is also not consistent based on the AUC and Cmax.

Table 4 (1) The comparison of the dose normalized AUC of Azelastine in different days and different doses

Dose (mg)	**Dose normalized AUC (pg.hr/ml/mg)**				
	Day 1 (AUC_{0-inf})	**Day 8 (AUC_{0-12})**	**Day 15 (AUC_{0-12})**	**Day 22 (AUC_{0-12})**	***p* value**
0.14	15474.79	14102.74	16448.93	18663.16	0.607
0.28	59542.31*	14797.45	11043.64	11370.01	0.0042 ***
0.42	15666.5	20561.75	24643.09	22986.99	0.631
p value	0.108 **	0.374	0.040	0.059	0.063

*If one of the outlier for 0.28 mg is excluded, the dose normalized AUC = 29961.37
** If one of the outlier for 0.28 mg is excluded, *p* value = 0.018
*** If one of the outlier for 0.28 mg is excluded, *p* value = 2.16×10^{-5}

Table 4 (2) The comparison of the dose normalized Cmax of Azelastine in different days and different doses

Dose (mg)	**Dose normalized Cmax (pg/ml/mg)**					
	Day 1	**Day 8**	**Day 15**	**Day 22**	**Day 29**	***p* value**
0.14	931.163	1596.286	2122.629	2064.7	1886.671	0.039
0.28	702.409	1435.982	1195.432	1110.743	1095.75	0.048
0.42	599.312	2087.052	2547.262	2320.445	2845.6	0.036
p value	0.249	0.376	0.046	0.034	0.026	

Table 5 (1) The accumulation ratios by AUC of Azelastine at different doses

Dose (mg)	**Accumulation ratio of AUC**					
	D15/D8	D22/D8	D22/D15	D8/D1	D15/D1	D22/D1
0.14	1.172	1.357	1.170	0.911	1.063	0.821
0.28	0.788	0.803	1.071	0.249	0.185	0.191
0.42	1.300	1.241	0.987	1.641	1.966	1.83

Table 5 (2) The accumulation ratios by Cmax of Azelastine at different doses

Dose (mg)	**Accumulation ratio of Cmax**					
	D15/D8	D22/D8	D22/D15	D8/D1	D15/D1	D22/D1
0.14	1.330	1.293	0.973	1.714	2.280	2.217
0.28	0.832	0.774	0.929	2.044	1.702	1.581
0.42	1.221	1.112	0.911	3.482	4.250	3.872

Table 6 (1) The comparison of the Azelastine AUC (CV%) at different doses among different days

Dose (mg)	AUC (CV%)					
	Day 1	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**P-value**
0.14	2166.47 (32)	1974.38 (46)	2302.85 (49)	2612.84 (47)	2692.23 (62)	0.675
0.28	16671.85 (112)	4143.29 (47)	3092.22 (42)	3183.60 (37)	3180.28 (63)	0.0014
0.42	52639.45 (49)	86359.35 (68)	103501 (70)	96545.34 (67)	114185.2 (58)	0.654

Table 6 (2) The comparison of the Azelastine Cmax (CV%) at different doses among different days

Dose (mg)	Cmax (CV%)					
	Day 1	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**P-value**
0.14	130.36 (29)	223.48 (39)	297.17 (45)	289.06 (41)	264.13 (55)	0.039
0.28	196.67 (55)	402.08 (39)	334.72 (47)	311.01 (42)	306.81 (58)	0.048
0.42	251.71 (58)	876.56 (58)	1069.85 (46)	974.59 (37)	1195.15 (55)	0.036

Overall, it was concluded that the dose proportionality and time-independent PK are inconclusive because of the inconsistency observed in results.

3 DETAILED LABELING RECOMMENDATIONS

Presented below are preliminary labeling comments from the Clinical Pharmacology perspective. The ***blue bolded italic*** words indicate the addition text, and the ~~**bold strike through**~~ words indicate the deletion.

Based on the results from the analysis of dose proportionality in the multiple dose azelastine, the statement about the dose proportional increase was recommended to be deleted.

(b) (4)

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

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

/s/

Ying Fan
4/13/2009 02:30:00 PM
BIOPHARMACEUTICS

Sally Choe
4/13/2009 03:30:53 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology

New Drug Application Filing Form

General Information About the Submission

	Information		Information
NDA Number	**22-371**	**Brand Name**	(b) (4)
OCP Division	**DCP2**	**Generic Name**	**Sweetened Azelastine Hycdrochloride 0 15%**
Medical Division	**DPAP (OND-570)**	**Drug Class**	**H_1-histamine receptor antagonist**
OCP Reviewer	**Ying Fan**	**Proposed Indication(s)**	**Allergic rhinitis (seasonal and perennial) in patients 12 years of age and older**
OCP Team Leader (Acting)	**Wei Qiu**	**Dosage Form**	**Nasal Spray**
		Dosing Regimen	**1 to 2 sprays (205.5 mcg each) per nostril twice daily**
Date of Submission	**01 August 2008**	**Route of Administration**	**Intranasal**
Estimated Due Date of OCP Review	**15 March 2009**	**Sponsor**	**MEDA (MedPointe) Pharmaceuticals**
PDUFA Due Date	**01 June 2009**	**Priority Classification**	**Standard**
Division Due Date	**01 April 2009**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**2**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
1 Healthy Volunteers-				
single dose:				
multiple dose:				
2 Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		1		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		
3				

4 Filability and QBR comments

5	**"X" if yes**	**6 Comments**
Application filable?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	**x**	**The following comment needs to be conveyed to the sponsor as appropriate:** **The submission lacks multiple-dose PK information for 0.15% Sweetened Azelastine hydrochloride. To help addressing this, assuming that you do not have such data for the new formulation, please provide the following:** **1. Clarification on whether azelastine exhibits time-independent pharmacokinetics in the proposed dose range. In other words, you need to address whether the steady-state PK can be predicted from the single dose PK data for 0.15% Sweetened Azelastine hydrochloride.** **2. Multiple dose PK data in healthy and/or patient population for the currently marketed 0.1% Astelin® product.**
QBR questions (key issues to be considered)	**1. What is the bioavailability of the 0.15% Sweetened Azelastine hydrochloride relative to approved commercial formulation of 0.1% Azelastine hydrochloride (Astelin®)?** **2. What are the PK characteristics following the multiple dose administration of 0.10% Sweetened Azelastine hydrochloride?**	

Introduction

Sweetened Azelastine hydrochloride 0.15% w/v nasal spray is proposed for the relief of symptoms associated with allergic rhinitis (seasonal and perennial) in patients 12 years of age and older. Azelastine hydrochloride is a phthalazinone derivative. It exhibits histamine H1-receptor antagonist activity in isolated tissues, animal models, and humans. The major metabolite, desmethylazelatine, also possesses H1 receptor antagonist activity.

The proposed dose of Sweetened Azelastine hydrochloride 0.15% w/v Nasal Spray is 2 sprays per nostril once or twice daily for seasonal allergic rhinitis and 2 sprays per nostril twice daily for perennial allergic rhinitis.

The new formulation contains 205.5 mcg of azelastine hydrochloride per spray and is a higher concentration (0.15%) than the currently marketed Astelin® Nasal Spray (NDA 20-114) which contains 0.1% azelastine hydrochloride (137 mcg per spray). This represents a total daily dose of 822 mcg to 1,644 mcg for Azelastine hydrochloride 0.15% w/v Nasal Spray compared to a total daily dose of 548 mcg to 1,096 mcg for Astelin® Nasal Spray.

This higher concentration 0.15% azelastine hydrochloride formulation was developed to demonstrate improved efficacy over the marketed Astelin® Nasal Spray formulation and support once daily administration. In Astelin® Nasal Spray clinical trials, a distinctive bitter taste, which is associated with the active ingredient, azelastine hydrochloride, has been reported as an adverse effect in approximately 15% to 20% of subjects. Thus, in an effort to develop a formulation containing a higher concentration of azelastine hydrochloride that also has a reduced incidence of bitter taste, this new azelastine hydrochloride 0.15% w/v formulation (also referred to as formulation MP03-36) was developed. Like NDA22-203, this new sweetened formulation vehicle contains the taste masking agent sucralose (b) (4), and is adjusted for (b) (4) with sorbitol.

The filing meeting for this NDA took place on September 10, 2008. The Clinical Pharmacology slides are attached at the end of this document.

This submission contains chemistry, manufacturing and control study, non-clinical pharmacology and toxicology study, clinical pharmacology/biopharmaceutics study, and efficacy/safety studies to support the indications of treatment of SAR and PAR.

Clinical Pharmacology Program

Azelastine hydrochloride 0.1% w/v nasal spray is currently marketed as Astelin® Nasal Spray (NDA20-114, approved November 1, 1996). A comprehensive clinical pharmacology evaluation of azelastine hydrochloride following intranasal and oral administration was submitted in support of NDA 20-114 for Astelin® Nasal Spray. This information is incorporated by reference to NDA 20-114.

Based on the current Astelin® label, data from a placebo-controlled study (95 patients with allergic rhinitis) found no evidence of an effect of azelastine hydrochloride 0.1%

nasal spray (2 sprays per nostril twice daily for 56 days) on cardiac repolarization as represented by the corrected QT interval (QTc) of the electrocardiogram. At higher oral exposures (≥4 mg twice daily), a mean increase on the QTc (3-7 millisecond) was observed although this increase was deemed not clinically significant.

In addition to the cross-reference to NDA 20-114, the clinical pharmacology program contains one bioavailability study (#MP429) which compared the PK of Sweetened 0.15% Azelastine (MP03-36) with marketed Astelin® Nasal Spray and Sweetened 0.1% Azelastine (MP03-33). This study was previously submitted to NDA22-203 to support the sweetened 0.1% azelastine. On May 30, 2008, the Division issued a not approvable letter due to: 1) Inadequate data of establishing efficacy and safety of Sweetened 0.1% Azelastine for the relief of symptoms of vasomotor rhinitis for patients 12 years of age and older; 2) Inadequate to establish efficacy and safety of for relief of symptoms of seasonal allergic rhinitis for patients 5 to 11 years of age; 3) The onset of action labeling claim for seasonal allergic rhinitis was not supported by the submitted data. The sponsor requested for formal dispute resolution (FDRR) on July 1, 2008. Complete response to an action letter was submitted on Aug 14, 2008 and the resubmission is currently under review.

Study MP429:

Study design: This was a Phase 1, open-label, single-center, randomized, parallel-group study. Fifty four (54) healthy males were randomized to one of three treatment groups: the commercial formulation of azelastine hydrochloride (Astelin®), MP03-33 (0.1% azelastine with (b) (4) sucralose), or MP03-36 (0.15% azelastine with (b) (4) sucralose). All treatments were administered as a single dose of two sprays per nostril.

Primary Objective: To determine the bioavailability of three formulations of azelastine hydrochloride in healthy subjects.

Results:

The PK results for azelastine and desmethylazelastine are presented in Table 1 and Table 2, respectively.

Table 1. Summary of Azelastine PK results

Study No.	Study Objective	Study Design	Treatments 2 sprays per nostril	Mean Parameters (+/- SD)				Study Report Location
				C_{max} (pg/mL)	AUC (pg•hr/ml)	t_{max} (hours)	$t_{½}$ (hours)	
MP429	determine the BA of 3 formulations of azelastine hydrochloride nasal sprays	open-label, single dose single-center, randomized, parallel-group study 54 healthy male volunteers Mean age=28 (range 19-50)	Astelin N.S. 548 mcg total dose (n=18)	235 (±88)	6122 (±2373)	3.2 (±1.8)	24 (±6)	Module 5 Volumes [redacted]
			MP03-33 548 mcg total dose (n=18)	200 (±67)	5122 (±1546)	2.7 (1.4)±	22 (±7.5)	
			MP03-36 822 mcg total dose (n=18)	409 (±160)	9312 (±3950)	3.1 (±2)	25 (±8.7)	

Table 2. Summary of Desmethylazelastine PK results

PK parameters	Desmethylazelastine		
	Astelin N.S. 548 µg total Dose (n = 18)	**MP03-33 548 µg total Dose (n =18)**	**MP03-36 822 µg total Dose (n =18)**
AUC_{0-t} (pg.hr/mL)	1873 ± 553	1634 ± 603	2780 ± 857
AUC_{0-inf} (pg.hr/mL)	2615 ± 779	2131 ± 609	3824 ± 1184
C_{max} (pg/mL)	24 ± 7.8	23 ± 11	38 ± 15
T_{max} (hr)*	24 (24-72)	24 (12 – 96)	24 (24-48)
$T_{1/2}$ (hr)	60 ± 22	52 ± 21	57 ± 23
CL/F (mL/min/kg)	53 ± 24	61 ± 16	57 ± 23

The data indicated that the systemic exposure of azelastine and its metabolite, desmethylazelastine evidenced by mean Cmax, AUC $_{0\rightarrow t}$, and $AUC_{0\rightarrow\infty}$ from MP03-36 was higher compared to MP03-33 and Astelin® Nasal Spray. The mean Cmax, AUC $_{0\rightarrow t}$, and $AUC_{0\rightarrow\infty}$ of azelastine and desmethylazelatine from MP03-33 were slightly lower compared to Astelin® Nasal Spray. All other pharmacokinetic parameters including time to peak plasma concentration (T_{max}), elimination half-life ($T_{1/2}$) were comparable among three treatments.

Comments to the sponsor:

This submission lacks the multiple-dose PK information for 0.15% Azelastine hydrochloride. To help addressing this, assuming that you do not have such data for the new formulation, please provide the following:

1. Clarification on whether azelastine exhibits time-independent pharmacokinetics in the proposed dose range. In other words, you need to address whether the steady-state PK can be predicted from the single dose PK data for 0.15% Sweetened Azelastine hydrochloride.
2. Multiple dose PK data in healthy and/or patient population for the currently marketed 0.1% Astelin® product.

Key QBR questions:

1. What is the bioavailability of 0.15% Azelastine hydrochloride relative to approved commercial formulation of 0.1% Azelastine hydrochloride (Astelin®)?
2. What are the PK characteristics following the multiple dose administration of 0.10% Sweetened Azelastine hydrochloride?

NDA 22-371

Azelastine Hydrochloride 0.15% w/v Nasal Spray

FILING MEETING

Clinical Pharmacology

Ying Fan, Ph.D.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Previous Submission

- Astelin® Nasal Spray (approved)
  - NDA 20-114 (November 1, 1996)
  - Strength: 137 mcg per spray (0.1%)
  - Dose: 1-2 sprays per nostril twice daily (≥ 12 years old)

(b) (4)

  - NDA 22-203 (July 30, 2007), reviewed by Partha Roy
  - Sweetened Azelastine hydrochloride
  - Strength: 137 mcg per spray (0.1%)
  - Contain new components: sucralose and sorbitol
  - Proposed dose: 1 or 2 sprays per nostril twice daily (≥ 12 years old)

Product/Dose/Indication

- **Sponsor:** Meda Pharmaceuticals Inc.
- **Formulation:** Nasal spray
- **Dose:** Adults and children ≥ 12 years

  Seasonal allergic rhinitis (SAR): 2 sprays per nostril once or twice daily

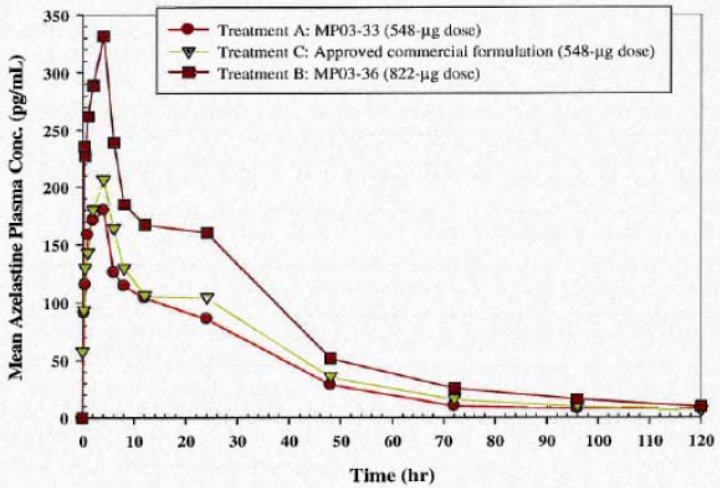
  Perennial allergic rhinitis (PAR): 2 sprays per nostril twice daily

  Total daily dose: 0.822 mg to 1.644 mg (based on 0.2055 mg per spray)
- **Objective:** Minimize or mask the bitter taste associated with the drug substance, make minimal dose changes compared to the marketed Astelin formulation (0.1% azelastine hydrochloride)
- **Related IND:** 69-785

Submission

- Protocol No. MP429 (Same as NDA 22-203, reviewed by Partha Roy)
  - Treatments (Azelastine hydrochloride):
    - Treatment A: 0.1% commercially approved formulation (548 µg dose)
    - Treatment B: 0.1% new formulation (548 µg dose, MP03-33)
    - Treatment C: 0.15% new formulation (822 µg dose, MP03-06)
  - SD, R, OL, parallel bioavailability study with 54 (18/treatment) healthy male subjects, 18-50 y
  - Analytical Reports and Method Validation available

Relative BA



Relative Bioavailabilty

- Cmax, AUC of azelastine slightly lower from Treatment A compared to Treatment C.

PK parameters	Azelastine		
	Astelin (0.1%) Treatment C: approved commercial formulation (548 µg Dose)	Astelin (0 1%) Treatment A: MP03-33 (548 µg Dose)	Astelin (0 15%) Treatment B: MP03-36 (822 µg Dose)
AUC_{0-t} (pg.hr/mL)	5903 ± 2264	4917 ± 1394	8941 ± 3749
AUC_{0-inf} (pg.hr/mL)	6122 ± 2373	5122 ± 1546	9312 ± 3950
C_{max} (pg/mL)	235 ± 88	200 ± 67	409 ± 160
T_{max} (hr)*	4.0 (0.25-6.0)	3.0 (0.5 – 4.0)	4.0 (0.25-6.0)
$T_{1/2}$ (hr)	24 ± 6.0	22 ± 7.5	25 ± 8.7
CL/F (mL/min/kg)	25 ± 18	26 ± 9.5	26 ± 15

Relative Bioavailabilty

- Cmax, AUC of desmethylazelastine slightly lower from Treatment A compared to Treatment C

PK parameters	Desmethylazelastine		
	Astelin (0.1%) Treatment C: approved commercial formulation (548 µg Dose)	Astelin (0.1%) Treatment A: MP03-33 (548 µg Dose)	Astelin (0.15%) Treatment B: MP03-36 (822 µg Dose)
AUC_{0-t} (pg.hr/mL)	1873 ± 553	1634 ± 603	2780 ± 857
AUC_{0-inf} (pg.hr/mL)	2615 ± 779	2131 ± 609	3824 ± 1184
C_{max} (pg/mL)	24 ± 7.8	23 ± 11	38 ± 15
T_{max} (hr)*	24 (24-72)	24 (12 – 96)	24 (24-48)
$T_{1/2}$ (hr)	60 ± 22	52 ± 21	57 ± 23
CL/F (mL/min/kg)	53 ± 24	61 ± 16	57 ± 23

Dose Proportionality

- Treatment A exhibits slightly greater than dose proportional PK across 548-822 mcg dose range

PK parameters	Azelastine		
	Astelin (0 1%) Treatment C: approved commercial formulation (548 µg Dose)	Astelin (0.1%) Treatment A: MP03-33 (548 µg Dose)	Astelin (0.15%) Treatment B: MP03-36 (822 µg Dose)
AUC_{0-t} (pg.hr/mL)	5903 ± 2264	4917 ± 1394	8941 ± 3749
AUC_{0-inf} (pg.hr/mL)	6122 ± 2373	5122 ± 1546	9312 ± 3950
AUC_{0-inf}/D [pg.hr/mL/(µg/kg)]	**839 ± 329**	**704 ± 207**	**804 ± 375**
C_{max} (pg/mL)	235 ± 88	200 ± 67	409 ± 160
C_{max}/D [pg/mL/(µg/kg)]	**32 ± 12**	**27 ± 7.9**	**35 ± 14**
T_{max} (hr)*	4 0 (0 25-6 0)	3 0 (0 5 – 4 0)	4 0 (0 25-6 0)
$T_{1/2}$ (hr)	24 ± 6 0	22 ± 7 5	25 ± 8 7
V_z/F (L/kg)	48 ± 26	50 ± 36	52 ± 21
CL/F (mL/min/kg)	25 ± 18	26 ± 9 5	26 ± 15

Dose Proportionality

- Treatment A exhibits slightly greater than dose proportional PK across 548-822 mcg dose range

PK parameters	Desmethylazelastine		
	Astelin (0 1%) Treatment C: approved commercial formulation (548 µg Dose)	Astelin (0.1%) Treatment A: MP03-33 (548 µg Dose)	Astelin (0.15%) Treatment B: MP03-36 (822 µg Dose)
AUC_{0-t} (pg.hr/mL)	1873 ± 553	1634 ± 603	2780 ± 857
AUC_{0-inf} (pg.hr/mL)	2615 ± 779	2131 ± 609	3824 ± 1184
AUC_{0-inf}/D [pg.hr/mL/(µg/kg)]	**261 ± 120**	**292 ± 72**	**328 ± 108**
C_{max} (pg/mL)	24 ± 7 8	23 ± 11	38 ± 15
C_{max}/D [pg/mL/(µg/kg)]	**3.3 ± 1.1**	**3 1 ± 1.3**	**3.3 ± 1 3**
T_{max} (hr)*	24 (24-72)	24 (12 – 96)	24 (24-48)
$T_{1/2}$ (hr)	60 ± 22	52 ± 21	57 ± 23
V_z/F (L/kg)	261 ± 120	272 ± 140	266 ± 110
CL/F (mL/min/kg)	53 ± 24	61 ± 16	57 ± 23

- **Label (0.1% Azelastine Hydrochloride):**

'azelastine hydrochloride administered intranasally at dose above two sprays (548 µg) per nostril twice daily for 29 days resulted in greater than proportional increases in Cmax and area under the curve (AUC) for azelastine'

More than dose-proportional PK at higher dose (non-linear PK)

Comments

- Because greater than dose proportional increase was reported for dose above 548 µg/day, it is desirable to have multiple dose PK information. However during the meeting minutes from August 29, 2006, end of phase 2 meeting, it was agreed that the single dose study was acceptable.
- In addition, the sponsor evaluated the safety of the higher strength of azelastine, we will not request multiple dose PK study.

QT Study

- In a placebo-controlled study (95 subjects with allergic rhinitis), there was no evidence of an effect of Astelin nasal spray (2 sprays per nostril twice daily for 56 days) on cardiac repolarization as represented by the corrected QT interval (QTc) of the electrocardiogram. At higher oral exposures (>4 mg twice daily), a non-clinically significant mean change on the QTc (3-7 millisecond increase) was observed.

Conclusion

- Fileable
- Comments to Sponsor
  - Address the linearity of azelastine PK in the proposed dose range

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/s/

Ying Fan
9/26/2008 02:42:30 PM
BIOPHARMACEUTICS

Wei Qiu
9/26/2008 02:57:26 PM
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