# 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) %), and is (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**

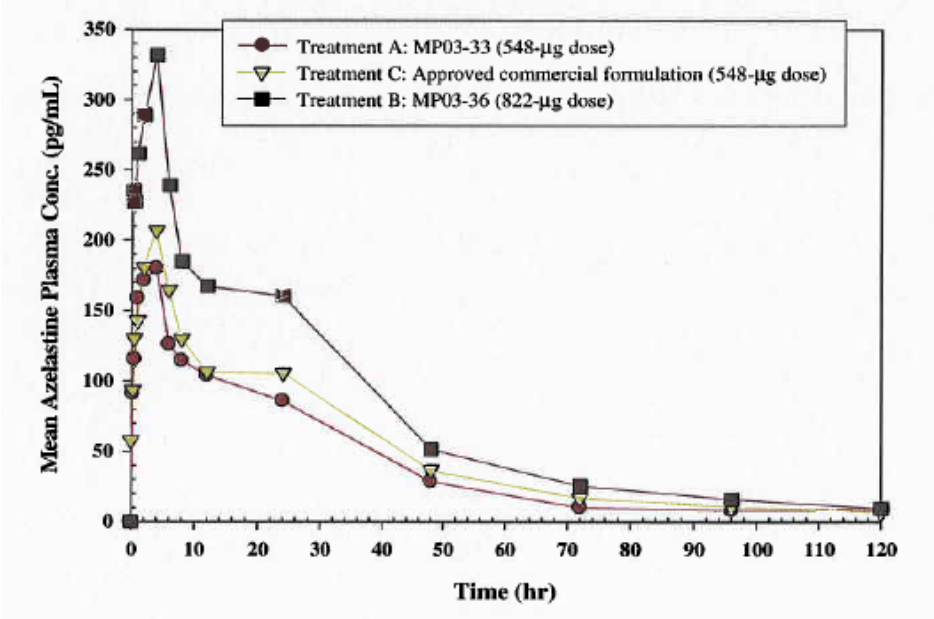



**Figure 2. Mean desmthyazelastine plasma concentration vs. time profiles for 2 sprays of 0.1% Astelin® (548 mcg), 0.1% Astepro (548 mcg) and 0.15% Astepro (dose: 822 mcg) solution per nostril**

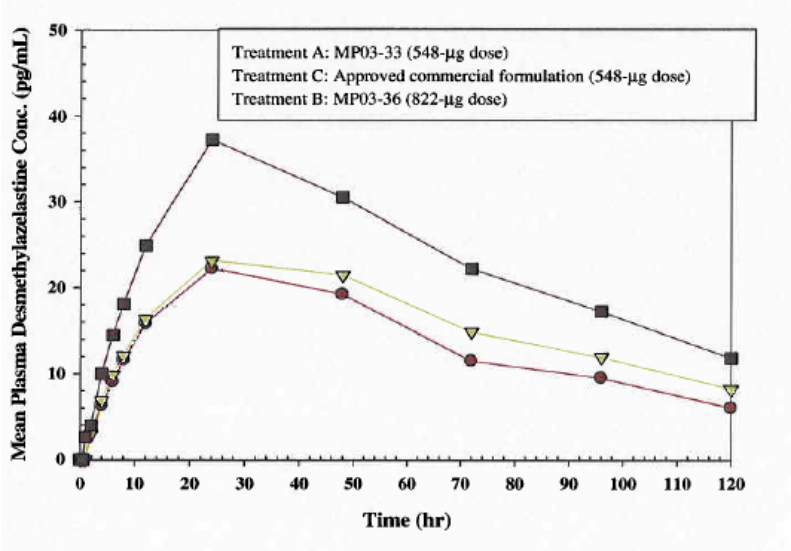



**Table 2. Mean ± SD pharmacokinetic parameters of azelastine and desmethylazelastine following 2 sprays of 0.1% Astelin® (548 mcg), 0.1% Astepro (548 mcg) and 0.15% Astepro (dose: 822 mcg) solution per nostril**

| 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= $\alpha$*Dose$^{\beta}$) for the azelastine dose-proportionality evaluation in healthy subjects. In the power model, $\beta$ is the dose-proportionality factor and $\alpha$ is the subject, period, and model error factor. After logarithmic transformation ($\ln(C_{max})$ or $\ln(AUC) = \ln(\alpha) + \beta*\ln(Dose)$), $\beta$ should be equal to 1 when the exposure (AUC and Cmax) change is proportional to dose change. Values of $\beta$ 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)**

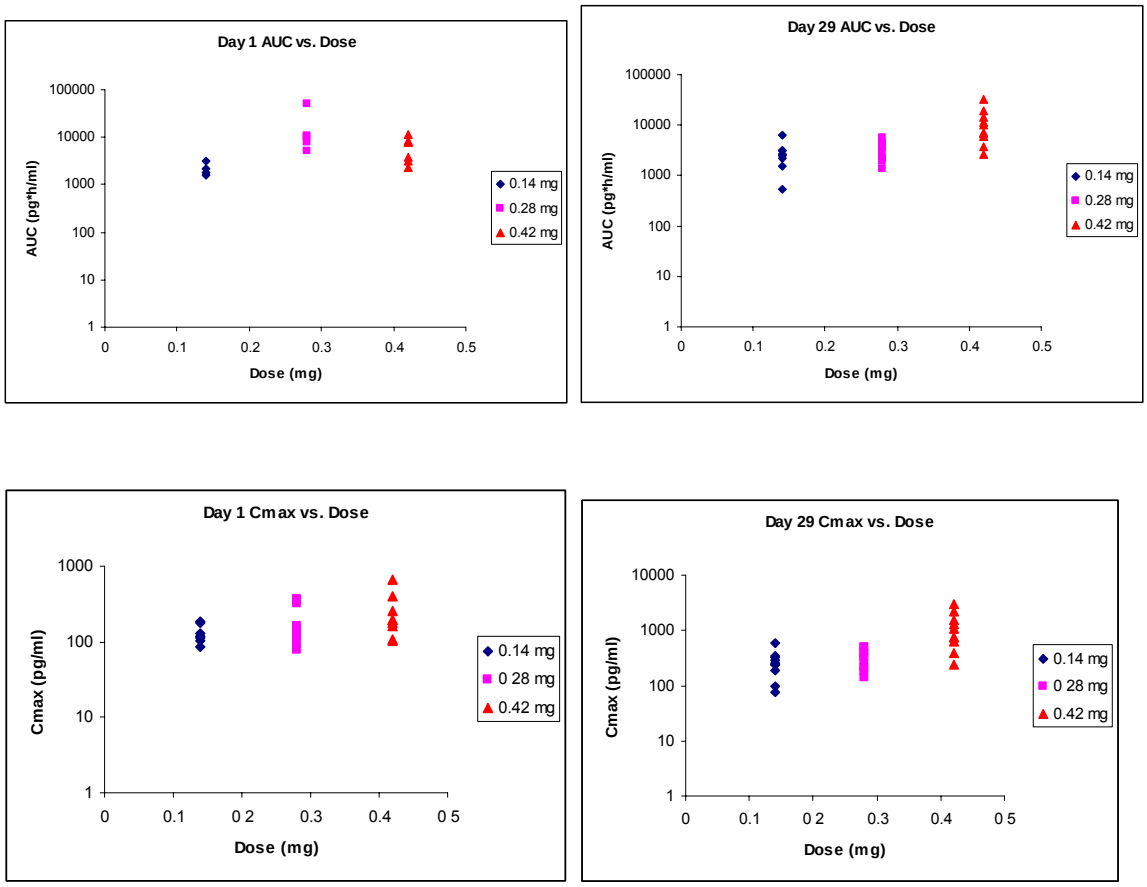



**Table 3. Slope of ln (AUC) or ln (Cmax) of Azelastine and its 90% CI from power model assessing the dose proportionality across the doses of 0.14, 0.28, and 0.42 mg at various days.**

| 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 = $2.16 \times 10^{-5}$

**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.

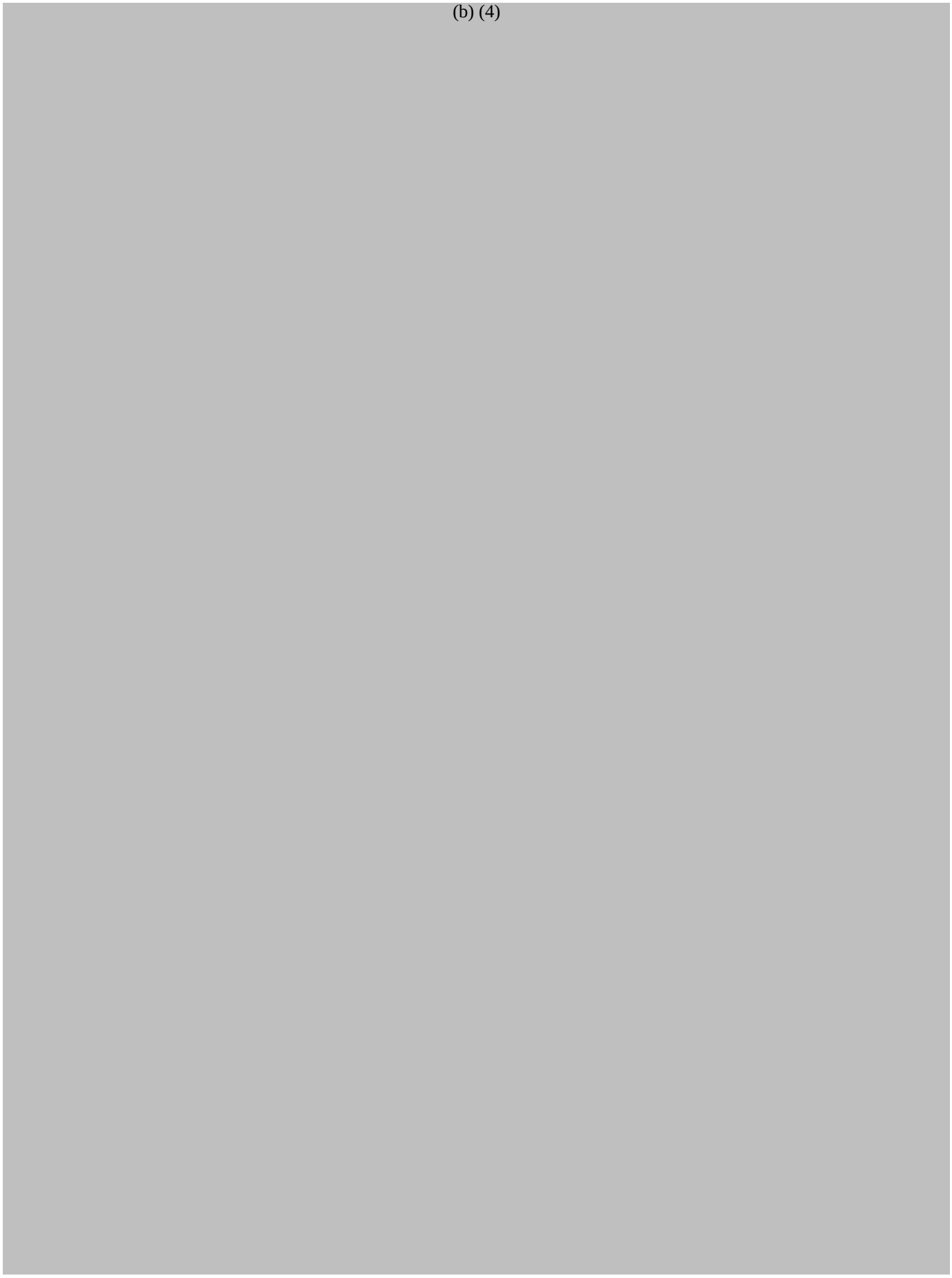
## 3 DETAILED LABELING RECOMMENDATIONS

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)

(b) (4)



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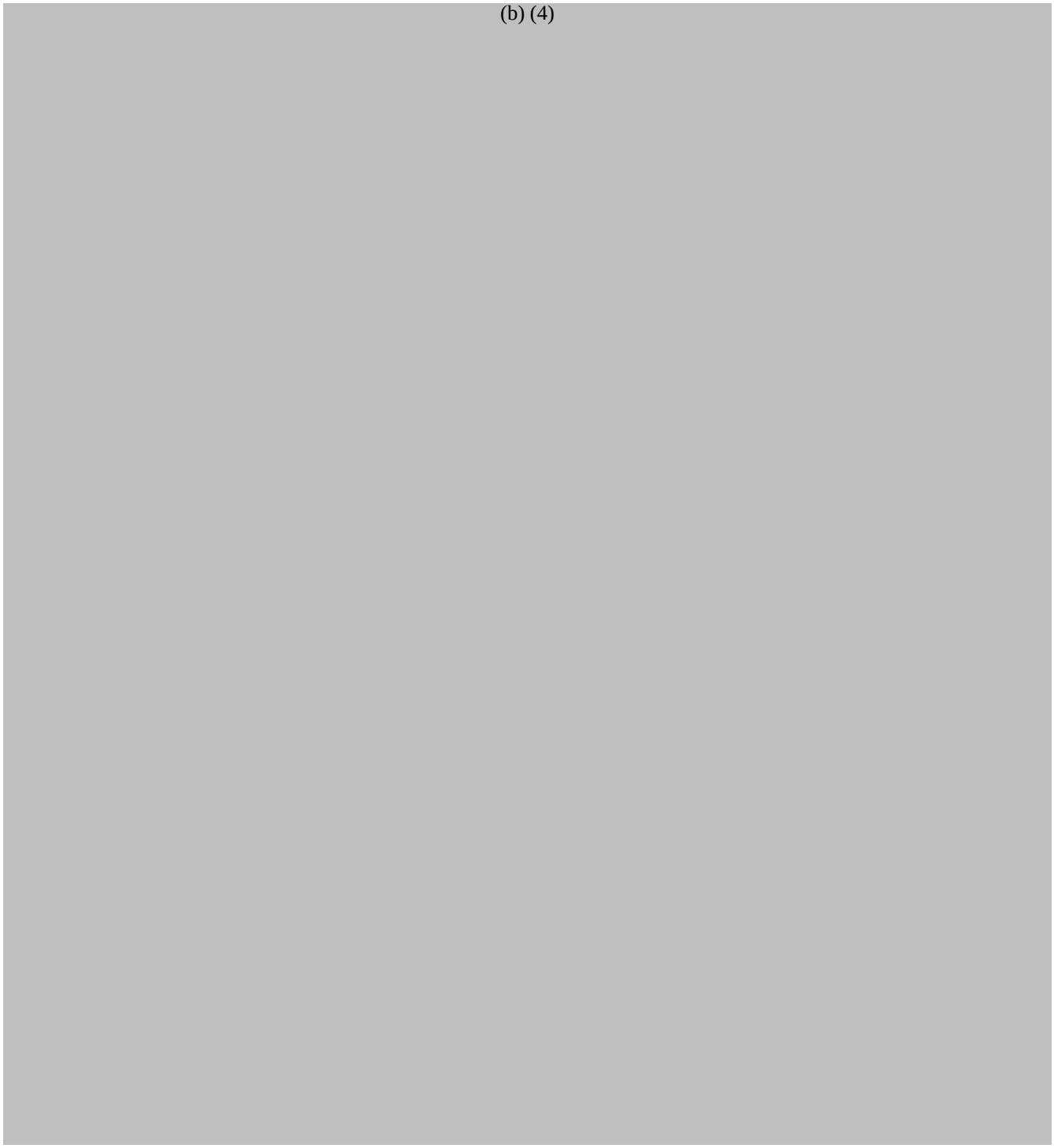

**4. Appendix**
**The sponsor's original proposed label**

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

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