CLINICAL PHARMACOLOGY REVIEW

NDA/Supporting document no.	202-236
Submission Date	04/01/11
Brand Name	TBD
Generic Name	Azelastine 0.1% and Fluticasone 0.037%
Reviewer	Lokesh Jain, Ph.D.
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OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Meda Pharmaceuticals
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	Nasal spray
Indication	Relief of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older
Dosage Regimen	• age 12 years and older: 1 spray per nostril BID (total azelastine dose of 548 µg/day and total fluticasone dose of 200 mcg/day) • not indicated in age group < 12 years

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1. Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology finds NDA 202236 acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Meda pharmaceutical, Inc. has submitted NDA #202236 seeking marketing approval for a fixed dose combination product containing azelastine hydrochloride (AZE; 0.1% w/w) and fluticasone propionate (FLU; 0.0365% w/w), presented as a nasal spray formulation MP29-02. If approved it will be the first fixed dose combination nasal spray product to be marketed in the USA.

MP29-02 is intended for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older. The monotherapy components AZE and FLU were approved under NDA 20-114 and NDA 20-121, respectively, for symptoms of seasonal allergic rhinitis (SAR), vasomotor rhinitis (VMR), and perennial allergic rhinitis (PAR).

In support of this NDA, sponsor conducted five clinical efficacy and safety studies and two clinical pharmacology single-dose relative bioavailability studies. The objective of clinical pharmacology studies was to assess the relative bioavailability of AZE and FLU from MP29-02 against monotherapy products to identify any potential drug-drug

interaction (DDI) and formulation issues. Key results from clinical pharmacology studies are listed below:

- Co-administration of FLU and AZE does not affect systemic exposures of each other
- Systemic exposure of AZE from MP29-02 was within ±20% of the exposure from Astelin®, a FDA approved commercially available AZE product
- Systemic exposure of FLU from MP29-02 is 44-61% higher than the exposure from a FDA approved commercially available FLU generic product
- Higher systemic exposures of FLU from MP29-02 fall in the range of exposures for which no significant effect on HPA-axis function has been identified

Dosing information for intrinsic and extrinsic factors was bridged from that of the individual components.

2. Question Based Review

2.1 What are the highlights of the formulations of the drug product?

The formulations used in clinical pharmacology studies were as follows:

1. investigational AZE-FLU combination product: **MP29-02**
2. investigational monotherapy products
    a. a formulation and packaging similar to MP29-02, except the absence of AZE (i.e., only FLU in MP29-02 vehicle)
    b. a formulation and packaging similar to MP29-02, except the absence of FLU (i.e., only AZE in MP29-02 vehicle)
3. commercially available monotherapy products
    a. FLU generic product, marketed by Roxane Laboratories
    b. Astelin®, an AZE monotherapy product marketed by Meda pharmaceuticals

Comparison of the composition of combination vs. monotherapy investigational products is shown in Table 1.

The to be marketed combination product is same as the MP29-02 product used in Phase 3 clinical trials supporting safety and efficacy for this NDA.

Table 1: Description and composition of MP29-02 and investigational monotherapy drug products

Ingredient	Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray			Azelastine Hydrochloride 0.1% Nasal Spray			Fluticasone Propionate 0.037% Nasal Spray		
	µg/ spray[a]	mg/g	% w/w	µg/ spray[a]	mg/g	% w/w	µg/ spray[a]	mg/g	% w/w
Drug Substances:									
Azelastine Hydrochloride	137	1.00	0.100	137	1.00	0.100	---	---	---
Fluticasone Propionate USP	50	0.365	0.0365	---	---	---	50	0.365	0.0365
Excipients:									
Glycerin USP	(b) (4		(b) (4	(b) (4		(b) (4	(b) (4		(b) (4)
Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF (b) (4)									
Polysorbate 80 NF									
Edetate Disodium USP									
Benzalkonium Chloride NF[b]		0.1	0.01		0.1	0.01		0.1	0.01
Phenylethyl Alcohol USP		2.5	0.25		2.5	0.25		2.5	0.25
Purified Water USP									(b) (4)
									(b) (4)

2.2 General Attributes of the Drug

2.2.1 What are the proposed mechanism of action and therapeutic indications?

AZE is a selective histamine H_1-receptor antagonist. Antihistamines are used for symptomatic treatment of various allergic diseases. Meda pharmaceuticals markets two of the currently approved Azelastine nasal spray products - Astelin® (NDA 20-114) and Astepro® (NDA 22-371). The major difference between Astepro and Astelin is that the former contains two additional excipients, sucralose and sorbitol, which are intended to mask the distinctive bitter taste associated with the azelastine drug substance. The approved indications for azelastine and the dosage are as below:

- Treatment of symptoms of SAR
  - Age ≥ 12 years: 1-2 sprays per nostril bid (maximum daily dose (MDD) = 548-1096 µg/day)
  - Age 5-12 years: 1 spray per nostril bid (MDD = 548 µg/day)
- Treatment of symptoms of nonallergic VMR
  - Age ≥ 12 years: 2 sprays per nostril bid (MDD = 1096 µg/day)

FLU is a synthetic glucocorticoid which acts as a glucocorticoid receptor agonist. It is an anti-inflammatory agent. The approved indications for fluticasone and the dosage are as below:

For the relief of symptoms of SAR, PAR, and nonallergic rhinitis in patients 4 years of age and older

- Adults: 2-sprays per nostril qd (200 µg/day) or 1-spray per nostril bid (200 µg/day)
- Adolescents and Children: starting dose 1-spray per nostril qd (100 µg/day) with maximum daily dose up to 200 µg/day

Purported rational for combination

Due to different primary mechanisms of action, the combination product of azelastine and fluticasone was hypothesized to have a potential for greater efficacy than with each agent alone.

2.2.2 What are the proposed dosage and routes of administration?

MP29-02 is to be administered intra-nasally at the proposed dose of 1 spray per nostril BID in patients' age 12 years and older (total azelastine dose of 548 µg/day and total fluticasone dose of 200 mcg/day). At this stage, sponsor is not seeking an indication for age group <12 years.

2.2.3 What drugs (substances, products) indicated for the same indication are approved in the US?

There are no approved fixed dose combination nasal spray products. If approved, MP29-02 will be the first product in this category.

The US approved products for monotherapy components are listed below.

Table 2: The US approved products for AZE and FLU

Product	Sponsor
AZE (metered nasal spray)	
Astelin®	Meda Pharmaceuticals
Astepro®	Meda Pharmaceuticals
Generic Azelastine	Apotex Inc.
FLU (metered nasal spray)	
Flonase®	Glaxosmithkline
Generic Fluticasone	Apotex Inc.
Generic Fluticasone	Hi Tech Pharma
Generic Fluticasone	Roxane

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The clinical pharmacology program for this NDA consisted of the following studies:

- Phase 1 (healthy volunteers) single dose PK drug-drug interaction study

1. For fluticasone (study # X-030605-3282)
2. For azelastine (study # X-030605-3283)

These studies were planned to assess the relative systemic exposures of AZE and FLU from combination product MP29-02 vs. monotherapy comparators (investigational FLU and AZE monotherapy comparators and commercial monotherapy products).

The clinical program consisted of five safety and efficacy studies, which are outlined in Table 3. Efficacy results for the primary endpoint, rTNSS (reflective combined AM+PM Total Nasal Symptom Score), from the key double-blind trials as summarized by the sponsor showing a significant difference for MP29-02 and each component drug compared to placebo are depicted in Figure 1. For final assessment of efficacy and safety findings of MP29-02 from these studies, please refer to the clinical review by Dr. Jennifer R Pippins.

Table 3. Summary of Phase 3 safety and efficacy studies

Study #	Duration	Objective
MP-4000	1-year	Randomized, open-label, active-controlled study of efficacy and safety comparing two treatments: (A) MP29-02 and (B) Generic fluticasone propionate nasal spray
MP-4001	2-week	Randomized, double-blind, placebo and active-controlled trial of efficacy and safety comparing four treatments: (A) MP29-02, (B) Astelin® nasal spray, (C) Generic fluticasone propionate nasal spray, and (D) placebo
MP-4002	2-week	Randomized, double-blind, placebo and active-controlled trial of efficacy and safety comparing four treatments: (A) MP29-02, (B) only AZE in MP29-02 vehicle, (C) only FLU in MP29-02 vehicle, and (D) placebo
MP-4004	2-week	Randomized, double-blind, placebo and active-controlled trial of efficacy and safety comparing four treatments: (A) MP29-02, (B) only AZE in MP29-02 vehicle, (C) only FLU in MP29-02 vehicle, and (D) placebo
MP-4006	2-week	Randomized, double-blind, placebo and active-controlled trial of efficacy and safety comparing four treatments: (A) MP29-02, (B) only AZE in MP29-02 vehicle, (C) only FLU in MP29-02 vehicle, and (D) placebo

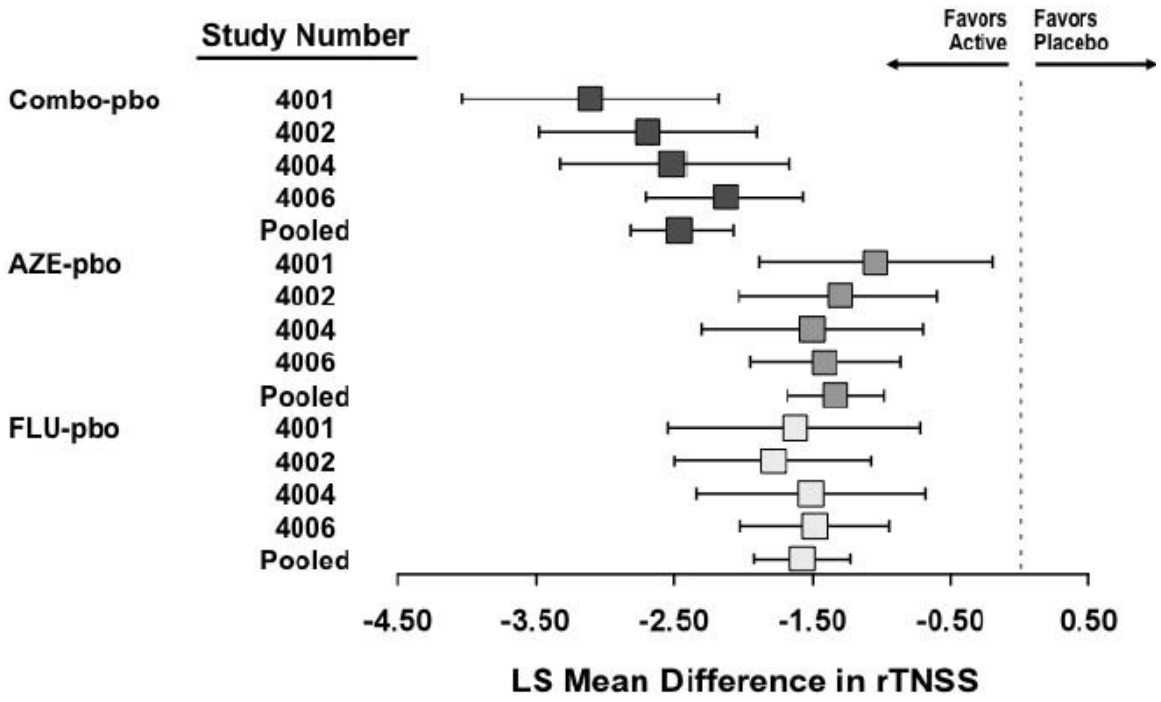

Figure 1. Treatment differences for change from baseline in rTNSS, AM and PM combined (ITT population) – least square means and 95% confidence intervals for pairwise differences from placebo

2.3.2 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters?

The moieties measured in these studies were AZE and FLU. Please see section 2.5 for further details.

2.3.3 Do the DDI studies suggest any potential change in systemic exposures of AZE and FLU for MP29-02 vs. monotherapy products (i.e., investigational monotherapy comparators and commercial monotherapy products)?

The systemic exposure of AZE from MP29-02 was equivalent to the exposure from only AZE formulated in MP29-02 vehicle and commercial Astelin® product (see Table 4).

The systemic exposure of FLU from MP29-02 was equivalent to the exposure from only FLU formulated in MP29-02 vehicle. However, fluticasone exposure from MP29-02 was 44-61% higher than the exposure from commercial generic product of fluticasone (see Table 4).

2.3.4 What are the clinical implications of comparable/relatively high exposures as discussed under 2.3.3?

With respect to FLU

(a) comparable exposure of FLU in MP29-02 versus FLU formulated in MP29-02 vehicle, indicates to no effect of azelastine co-administration on FLU systemic

exposure (i.e., no drug-drug interaction)

(b) almost 60% higher C_{max} and 44-61% higher AUC of FLU in MP29-02 versus FLU in generic nasal spray, indicates that systemic safety profile of MP29-02 with respect to FLU might be different from that of commercially available FLU generic nasal spray product (see 2.3.5 for further discussion).

With respect to AZE

(a) comparable exposure of AZE in MP29-02 versus AZE formulated in MP29-02 vehicle, indicates no effect of FLU co-administration on AZE systemic exposure (i.e., no drug-drug interaction)

(b) comparable exposure of AZE in MP29-02 versus AZE in Astelin®, indicates that systemic safety profile of MP29-02 with respect to AZE will be comparable to that of Astelin® nasal spray.

Table 4: Comparison of single-dose PK parameters for different formulations of FLU (FLU) and AZE (AZE)

	GM ratio (90% CI)					
	$_{max}$		AUC_{0-t}		$AUC_{0-\infty}$	
	N	PE(CI)*	N	PE(CI)*	N	PE(CI)*
X-03065-3282						
MP29-02 vs. FLU in MP29-02 vehicle	19/19	0.91 (0.83-1.00)	19/19	0.94 (0.84-1.05)	16/19	1.01 (0.85-1.20)
MP29-02 vs. FLU generic	19/19	1.57 (1.32-1.87)	19/19	1.61 (1.37-1.89)	16/18	1.44 (1.15-1.80)
X-03065-3283						
MP29-02 vs. AZE in MP29-02 vehicle	26/26	1.03 (0.92-1.14)	26/26	0.99 (0.91-1.07)	26/26	0.98 (0.90-1.07)
MP29-02 vs. Astelin	26/26	1.07 (0.93-1.24)	26/26	1.06 (0.96-1.16)	26/26	1.05 (0.96-1.16)

*PE(CI): point estimate (90% confidence interval)

C

2.3.5 Are there any concerns about impact on hypothalamic-pituitary-adrenal (HPA) axis function because of higher fluticasone exposure from MP29-02 compared to the commercially available generic FLU products?

No dedicated HPA axis effect study was conducted by the sponsor despite the higher systemic exposure for fluticasone component from MP29-02 compared to the marketed generic fluticasone product.

Sponsor stated that inspite of higher FLU exposure, MP29-02 is not likely to pose any additional safety concerns with respect to HPA axis function compared to the commercially available FLU products because of the following reasons:

(a) Effect on HPA axis was compared between MP29-02 and FLU generic nasal spray product by measuring the serum cortisol levels in trial MP4000. One fasting AM serum sample was drawn each at baseline, month 6, and month 12. There was no significant change in cortisol levels after 6-months or 12-months treatment with MP29-02 compared to baseline as shown in Table 5.

The current FDA guidance[1] on clinical development of allergic rhinitis drug products recommends "assessment of adrenal function using either timed urinary free cortisol level measurements (i.e., 12-hour or 24-hour), or 24-hour plasma cortisol AUC levels pretreatment and after at least 6 weeks post-treatment with study medication". Guidance also recommends including a placebo and an active control (e.g., oral prednisone) in these studies.

Sponsor's evaluation of adrenal function in trial MP4000, as stated above, falls short of the standards recommended by the FDA. Therefore, no effect on serum cortisol based on only one AM serum sample by itself would offer limited assurance about effect of MP29-02 on HPA-axis function.

(b) A higher dose of FLU (either 200 µg once-daily or 400 µg twice-daily) from a FDA approved FLU product, Flonase® nasal spray, was reported to have no effect on the adrenal response to a 6-hour consyntropin stimulation test.

To refer to the effect of Flonase® on HPA-axis information, sponsor cited the Flonase® prescribing information. The study mentioned in prescribing information to discuss the effect on HPA-axis function was published in J Allergy Clin Immunol (1998)[2], which can be referred for further information. In this study HPA-axis function was evaluated by measuring the (a) plasma cortisol response to a short cosyntropin stimulation test and (b)

[1] Allergic Rhinitis: Clinical Development Programs for Drug Products. Guidance for Industry by FDA. Draft April 2000.
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071293.pdf

[2] Vargas R, Dockhorn RJ, Findlay SR, Korenblat PE, Field EA, Kral KM. Effect of FLU aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. J Allergy Clin Immunol 1998 Aug; 102(2): 191-7

24-hour urinary excretion of free cortisol (unstimulated). In addition to FLU, this study also had active prednisone control arms (7.5 mg QD and 15 mg QD) and a placebo arm. Results from this study demonstrated that 24-hour urine cortisol levels were comparable between placebo and subjects receiving a total FLU daily dose of up to 800 µg for 4 weeks, suggesting that effect of FLU on adrenal axis function in tested doses may not be different from that of placebo.

(c) Recommended starting doses (i.e., 88-440 µg bid) for another FDA approved FLU product, Flovent® HFA, had equal or relatively high systemic FLU exposure than that for MP29-02 (see Table 6). Inspite of relatively high systemic exposure of FLU, no significant effect on HPA axis has been reported for Flovent® HFA. The label for Flovent® HFA states that (i) there was no discernable effect of Flovent 88 µg bid on the HPA axis compared to placebo in age group 1 to <4 years, (ii) geometric mean ratio of serum cortisol over 12 hours (AUC_{0-12}) was 0.95 for Flovent HFA 88 µg bid vs. placebo after 4-weeks treatment of children with reactive airways disease in age group 6 to <12 months, reassuring lack of effect on HPA axis, (iii) in patients with asthma receiving Flovent HFA at 44,110, 220 µg bid dose for at least 4 weeks, differences in serum cortisol AUC_{0-12hr} and 24-hour urinary excretion of cortisol compared to placebo were not related to dose and generally not significant, and (iv) 24 hour urinary excretion of cortisol was not affected after 4 weeks of treatment with Flovent HFA 88 µg bid compared to 2 weeks of treatment with placebo [geometric mean ratio (90% CI): 0.987 (0.796-1.223)].

Table 3: Summary of HPA axis test results (fasting serum cortisol) screening to on-treatment visits, safety population

Variable	MP29-02 (N=404)	Fluticasone Propionate (N=207)	Total (N=611)
Fasting Serum Cortisol (mcg/dL)	**Mean ± SD (n)**	**Mean ± SD (n)**	**Mean ± SD (n)**
Baseline Value for Month 6	12.21 ± 4.196 (154)	12.53 ± 4.650 (78)	12.31 ± 4.346 (232)
6-Month Post-Value	11.89 ± 4.547 (154)	11.61 ± 4.616 (78)	11.80 ± 4.562 (232)
6-Month Change from Baseline	-0.31 ± 5.142 (154)	-0.92 ± 5.319 (78)	-0.52 ± 5.199 (232)
Baseline Value for Month 12/ET	12.19 ± 4.209 (137)	12.52 ± 4.531 (73)	12.30 ± 4.316 (210)
12-Month Post-Value	12.11 ± 4.873 (137)	11.48 ± 4.653 (73)	11.89 ± 4.796 (210)
12-Month/ET Change from Baseline	-0.08 ± 5.533 (137)	-1.04 ± 4.959 (73)	-0.41 ± 5.348 (210)

ET = early termination; N = number of subjects in each treatment group; n = number of subjects with a baseline and post-baseline value for each visit

Table 4: FLU peak exposure (C_{max}) and total exposure (AUC) following an approved Flovent HFA inhalation dose compared with the MP29-02 dose administered in study X-03065-3282

	MP29-02 Single-dose	Flovent HFA† Steady-state		
	200 µg QD	88 µg BID	220 µg BID	440 µg BID
GM		Bronchodilators alone	Inhaled corticosteroids	Oral corticosteroids
AUC	88.3*	76.2**	297.5**	600.9**
C_{max}	9.6	25.2	60.8	103.1

***$AUC_{0-\infty}$ after single-dose**
**** AUC_{0-12} at steady-state**
†Data for Flovent HFA are taken from drugs@fda website (Summary Basis of Approval, Clinical Pharmacology and Biopharmaceutics Review, Table 1, Page 4)
Note: $AUC_{0-\infty,sd}$ and $AUC_{0-t,ss}$ are different PK metrics and can not be directly compared, but under the assumption of linear PK, the $AUC_{0-\infty,sd}$ after 200 µg single-dose administration of MP29-02 will be comparable to that of $AUC_{0-12,ss}$ after 100 µg BID administration of MP29-02. Therefore, $AUC_{0-\infty,sd}$ for MP29-02 can be compared with $AUC_{0-12,ss}$ for Flovent HFA.

The true effect of higher exposure of FLU in MP29-02 vs. commercial Flonase® on HPA-axis function remains unknown in the absence of a dedicated study conducted with MP29-02. However, available supportive information indirectly derived from data acquired with other approved fluticasone products seems to indicate that systemic levels of fluticasone from MP29-02 may not be high enough to cause a significant effect on HPA-axis function.

2.4 Intrinsic Factors

2.4.1 For MP29-02, what dosage regimen adjustments are recommended for each group?

2.4.1.1 Renal Impairment

Dosing information for MP29-02 in patients with renal impairment was bridged from that of the individual component drugs.

2.4.1.2 Hepatic Impairment

Dosing information for MP29-02 in patients with hepatic impairment was bridged from that of the individual component drugs.

2.5 Analytical Section

2.5.1 What bioanalytical methods are used to assess concentrations of the measured moieties?

Table 7 lists the molecules measured and validation report no. for studies submitted this NDA.

Table 7: Analytical methods for DDI studies

Study #	Moiety measured	Matrix	Method description	Validation report #
X-03065-3282	FLU	Serum	HPLC-MS/MS method	VAL-47610
X-03065-3283	AZE	Plasma	HPLC-MS/MS method	Azelastine / 100006051

2.5.2 What are the details of the bioanalytical method and validation parameters for fluticasone?

Bioanalytical method for fluticasone is detailed in Table 8 below. Based on reported validation parameters, this method is adequate for quantitation of fluticasone.

Table 8: Description of bioanalytical method for fluticasone

Parameter	**Description**
Analyte name (matrix)	Fluticasone (serum)
Method description	Take 1 mL of matrix sample, to that add 25 µL of internal standard working solution and 5 mL of DIPE. Shake tubes vigorously using a DVX-2500 multitube vortexer for 5 min for extraction. Centrifuge at 4000 rpm for 2 minutes. Store at -70˚C for about 10 minutes and decant the organic phase into centrifuge vials. Evaporate the organic phase and add 50 µL of 50% methanol to residual. Vortex and transfer approximately 45 µL volume to auto-sampler vials.
Instrument	API 5000 mass spectrometer
Limit of quantitation (LOQ)	0.250 pg/mL
Standard curve concentration range	0.250 pg/mL -50.0 pg/mL
Regression model & weighting factor	Quadratic ($y=ax^2 + bx + c$), 1/conc.
QC concentration QC Low QC Medium QC High	0.700 pg/mL 25.0 pg/mL 37.5 pg/mL
Accuracy	93.7 – 103.6 %
Precision Interbatch Intrabatch	4.76-14.68% Not reported

Selectivity	Assessed with six samples from different individuals at LLOQ level
Average recovery of drug (%)	56.4%
Matrix factor	1.06/1.08
Freeze-thaw stability in matrix	Established up to 3 cycles
Short-term stability in injection solution	Established up to 30 hours
Long-term stability	Not reported (current report states that it will be reported in an amendment to validation report)

2.5.3 What are the details of the bioanalytical method and validation parameters for azelastine?

The method used for quantitation of azelastine was validated for both azelastine and its metabolite desmethyl-azelastine. However, Table 9, below, describes the validation parameters for only azelastine. Based on reported validation parameters, this method is adequate for quantitation of azelastine.

Table 9: Description of bioanalytical method for azelastine

Parameter	**Description**
Analyte name (matrix)	Azelastine and Desmethyl-azelastine (Plasma)
Method description	To 500 µL plasma sample, add 10 µL internal standard. To this add 500 µL ammonium acetate solution of pH 9 and 2 mL ethyl acetate. Shake, centrifuge for 5 min at 3500 g, store at -80˚C for a short while and decant into new vials. To this add 150 µL water + 0.1% formic acid. Centrifuge for 5 min at 3500 g, and separate the organic ethyl acetate layer. Store samples for 5 min at approx. 60˚C in vacuum centrifuge, transfer 100 µL in new vials of which 40 µL is injected into HPLC system.
Instrument	API 4000 MS 2, Agilent 1200 Series HPLC system
Limit of detection (LOD)	0.5 pg/mL
Limit of quantitation (LOQ)	2 pg/mL
Standard curve concentration range	2 pg/mL -1000 pg/mL
Regression model & weighting factor	Linear, $1/conc^2$
QC concentration LLOQ QC Low QC Medium QC High QC Dilution	2 pg/mL 6 pg/mL 300 pg/mL 750 pg/mL 3000 pg/mL (10x dilution)
Accuracy Inter-assay Intra-assay Dilution	2.54% – 6.29 % 1.63% - 9.30% 8.10%
Precision Inter-batch	2.51-6.29%

Intra-batch	1.06% -3.09%
Selectivity	Assessed by using six different human plasma samples
Average recovery of drug (%)	74.04%
Matrix factor	0.98
Freeze-thaw stability in matrix	3 cycles
Autosampler stability	16 hours @ approx. 10˚C
Short-term stability	18 hours @ room temperature
Stock solution stability	At least for 9 weeks at 4˚C
Long-term stability	Not reported (report states that it will be reported in an amendment)

2.6 Detailed Labeling Recommendations

Following are the labeling comments for the sponsor:

- ~~Strikeout text~~ should be removed from labeling and **underlined text** should be added to labeling.

5. WARNINGS AND PRECAUTIONS

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7. DRUG INTERACTIONS

(b) (4)

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Appendix 1

Study # X-03065-3282

Title: Single dose pharmacokinetics of intranasal fluticasone delivered by a fixed combination with azelastine (MP29-02) in comparison to two different fluticasone nasal sprays.

Objectives:
Primary
To assess the effect of AZE on the relative bioavailability of FLU when administered as fixed AZE-FLU combination product (Test) compared to a similar formulation without containing AZE (i.e. FLU alone in the MP29-02 vehicle; Reference).

Secondary

- To compare the relative bioavailability of FLU when administered either as fixed AZE-FLU combination product (Test) or as marketed FLU product, FLU Nasal Spray, Roxane Laboratories (comparator)
- To compare the effects of AZE on other pharmacokinetic parameters of FLU
- To assess adverse events

Study design: Single-centre, randomized, open-label, three-period, six-sequence, cross-over trial (William's design) in healthy subjects

Number of subjects: 30 subjects were to be randomized with at least 12 female subjects

Treatments and dose:

Treatment	Dose	Total dose
Test (MP29-02) (=US formulation as used in pivotal trials)	2 sprays per nostril	548 µg AZE plus 200 µg FLU
Reference (FLU in MP29-02 vehicle) (=combination product formulation without any AZE; US FLU mono formulation as used in pivotal studies)	2 sprays per nostril	200 µg FLU
Comparator (FLU nasal spray, Roxane Laboratories) (=US marketed product)	2 sprays per nostril	200 µg FLU

Results:
Study subjects

A total of 69 subjects were screened; of which 30 subjects were randomized and exposed to at least one dose of study medication. 11 subjects were excluded from per-protocol (PP) population because of perceived protocol deviations with possible relevance to PK analyses. Two randomized/exposed subjects discontinued the study prematurely. Seven subjects were excluded from PP population, because of complete but slow (with low force) application of nasal spray, e.g., sprays (partly) applied hesitantly or weakly, spray insufficient. Two subjects were excluded because of incomplete or additional doses (one subject applied nasal spray with slow and low force with an additional spray which led to incorrect dosage and the other subject did not press down spray pump completely). Impact of exclusion of these subjects on study results was evaluated by sensitivity analysis; however, data from one subject with incorrect dosage administration was not included.

All randomized/exposed subjects were included in the safety analysis set. 19 subjects (63.3% of the randomized/exposed subjects) were included in the PP population; a total of n=26 subjects were included in the sensitivity analysis.

Pharmacokinetic analysis

The serum concentration – time curves for the test, reference, and comparator treatments are shown in Figure 1. These profiles are largely comparable for test and reference, but the profile for comparator differs from that of both test and reference. The PK parameters from these treatment arms are summarized in Table 10. Geometric mean ratio and 90% CI for comparison of PK between these treatments are shown in Table 11.

90% CI for comparison of PK parameters between test and reference were between 80%-125%. While for comparison of test and comparator, both point estimate and 90% CI were outside the 80%-125% range. The mean systemic exposure (AUC_{0-24} and C_{max}) for test were 52-57% higher than that of comparator.

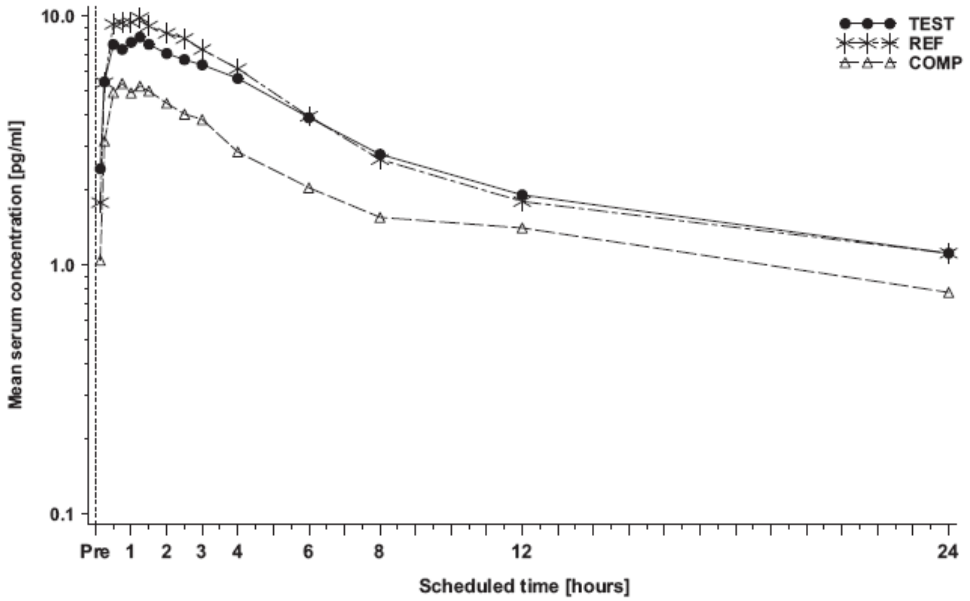

Figure 1: Time course of mean FLU concentrations (pg/mL) by treatment on log-linear scale (PP analysis)

Table 10: PK parameters for test, reference, and comparator products in study X-03065-3282

Parameter	Test		Reference		Comparator	
	N	Geometric mean	N	Geometric mean	N	Geometric mean
AUC_{0-24} [pg•h/mL]	19	61.921	19	65.690	19	40.035
$AUC_{0-\infty}$ [pg•h/mL]	16	88.301	19	87.782	18	59.163
$AUC_{0-tlast}$ [pg•h/mL]	19	61.921	19	65.690	19	37.906
C_{max} [pg/mL]	19	9.600	19	10.518	19	6.061

Table 11: Geometric mean ratio (point estimate and 90% CI) for comparison of test, reference, and comparator in study X-03065-3282

Parameter	Test/Reference		Test/Comparator	
	Point estimate	90% CI	Point estimate	90% CI
AUC_{0-24} [pg•h/mL]	93.45	83.26-104.88	152.17	130.14-177.94
$AUC_{0-\infty}$ [pg•h/mL]	100.99	84.73-120.36	143.62	114.78-179.69
$AUC_{0-tlast}$ [pg•h/mL]	93.55	83.60-104.68	161.13	137.13-189.34
C_{max} [pg/mL]	91.01	82.53-100.37	157.43	132.48-187.09

Conclusions:
Following single dose nasal administration of 200 µg, FLU maximum serum concentration and total systemic exposures, as evidenced by C_{max} and AUC, is similar between Test and Reference treatments. These results indicate that azelastine component in the combination product does not affect the systemic exposure of FLU after single dose administration.

Comparison of the combination product (Test) with the marketed monoproduct (Comparator) indicates an average increase of about 52 % to 57 % in FLU systemic exposure in terms of maximum serum concentration (C_{max}) and total (AUC_{0-24}) systemic exposure.

Study # X-03065-3283

Title: Single dose pharmacokinetics of intranasal azelastine delivered by a fixed combination with fluticasone (MP29-02) in comparison to two different azelastine nasal sprays.

Objectives:
Primary

To assess the effect of FLU on the relative bioavailability ($AUC_{0-\infty}$) of AZE when administered as fixed AZE-FLU combination product (Test) compared to a similar formulation without containing FLU (i.e. AZE alone; Reference).

Secondary

- To compare the relative bioavailability ($AUC_{0-\infty}$) of AZE when administered either as fixed AZE-FLU combination product (Test) or as marketed AZE product Astelin® Nasal Spray (Comparator);
- To compare the effects of FLU on other pharmacokinetic parameters of AZE (AUC_{0-ast}, CL/f, C_{max}, t_{max}, $t_{1/2}$;
- To assess adverse events.

Study design: Single-centre, randomized, open-label, three-period, six-sequence, cross-over trial (William's design) in healthy subjects

Number of subjects: 30 subjects were to be randomized with at least 12 female subjects

Treatments and dose:

Treatment	Dose	Total dose
Test (MP29-02) (=US formulation as used in pivotal trials)	2 sprays per nostril	548 µg AZE plus 200 µg FLU
Reference (AZE in MP29-02 vehicle) (=combination product formulation without any FLU; US AZE mono formulation as used in pivotal studies)	2 sprays per nostril	548 µg AZE
Comparator (Astelin® nasal spray) (=US marketed product)	2 sprays per nostril	548 µg AZE

Results:

Study subjects

A total of 63 subjects were screened; of which 30 subjects were randomized and exposed to at least one dose of study medication. Data from 2 subjects were excluded from PP population because of incorrect drug administration (e.g., slow application of nasal spray with low force). Data from 2 other subjects were excluded because of clinically relevant findings at the time of administration (e.g., nasal congestion, inflamed nasal mucosa). Thus, data from remaining 26 subjects were included in PP analysis.

Pharmacokinetic analysis

The mean plasma concentration - time profiles for test, reference, and comparator treatments are shown in Figure 2. Profiles for all three treatments are almost congruent across sampling time points. The PK parameters for three treatments are listed in Table 12 and comparison of geometric means is shown in Table 13. Point estimate and 90% CI for PK comparison of test vs. reference or vs. comparator are within 80-125%.

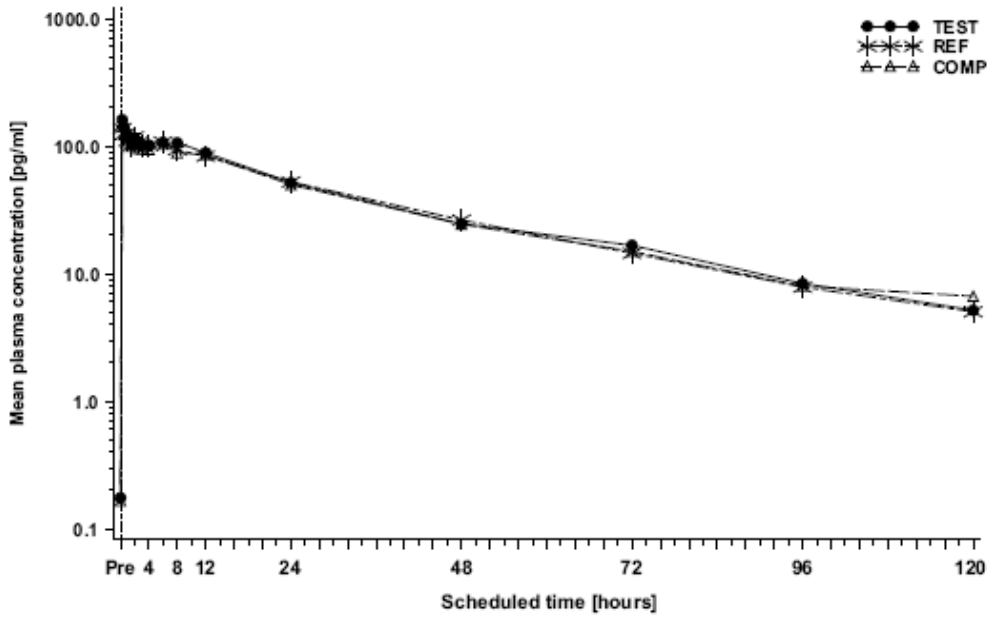

Figure 2: Time course of mean AZE concentrations (pg/mL) by treatment on log-linear scale (PP analysis)

Table 12: PK parameters for test, reference, and comparator products in study X-03065-3283

Parameter	Test		Reference		Comparator	
	N	Geometric mean	N	Geometric mean	N	Geometric mean
$AUC_{0-\infty}$ [pg•h/mL]	26	3665.53	26	3685.52	26	3453.05
$AUC_{0-tlast}$ [pg•h/mL]	26	3487.01	26	3476.38	26	3270.89
C_{max} [pg/mL]	26	180.85	26	169.66	26	164.56

Table 53: Geometric mean ratio (point estimate and 90% CI) for comparison of test, reference, and comparator in study X-03065-3283

Parameter	**Test/Reference**		**Test/Comparator**	
	Point estimate	90% CI	Point estimate	90% CI
$AUC_{0-\infty}$ [pg•h/mL]	98.09	90.26-106.60	105.14	95.68-115.53
$AUC_{0-tlast}$ [pg•h/mL]	98.82	90.96-107.37	105.50	95.60-116.43
C_{max} [pg/mL]	102.67	92.12-114.44	107.26	92.56-124.30

Conclusions:

Following single dose nasal administration of 548 µg azelastine either as fixed combination product with 200 µg of fluticasone (AZE-FLU; Test), a similar investigational nasal spray formulation without containing FLU (i.e. AZE alone; Reference), and the currently marketed AZE mono-product (Astelin® Nasal Spray; Comparator) total systemic exposure and maximum plasma concentration, as measured by $AUC_{0-\infty}$ and C_{max}, is similar between treatments.

The study results demonstrate that neither the FLU component in the combination product (Test) nor the existing qualitative and quantitative formulation differences in the composition of excipients between the currently marketed AZE mono-product (Astelin®
Nasal Spray; Comparator) and the investigational AZE-FLU combination product display significant potential to alter the systemic exposure of AZE.

Appendix 2

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**202236**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Azelastine Hydrochloride 0.1% & Fluticasone Propionate 0.037%**
Medical Division	**DPARP**	**Drug Class**	**H_1 receptor antagonist and glucocorticoid receptor agonist**
OCP Reviewer	**Lokesh Jain, Ph.D.**	**Indication(s)**	**Seasonal allergic rhinitis**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Nasal spray**
Pharmacometrics Reviewer		**Dosing Regimen**	**1 spray per nostril bid**
Date of Submission	**04/01/2011**	**Route of Administration**	**Nasal**
Estimated Due Date of OCP Review	**12/28/2011**	**Sponsor**	**Meda Pharmaceuticals**
Medical Division Due Date		**Priority Classification**	**505(b)(2)**
PDUFA Due Date	**02/01/2012**		

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:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
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:	**X**	**2**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**4**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			This information is taken from the labels of the approved individual products
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a	X			

	manner to allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	Not applicable
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Sponsor requested waiver (b) (4) WR has not been issued for this product
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			Clinical pharmacology information has been taken from individual drug labels
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other			X	Translation not

	study information) from another language needed and provided in this submission?				needed

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Yes__
If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

From your clinical pharmacology program, it appears that systemic exposure of fluticasone from your combination product is about 44-60% higher compared to reference fluticasone monotherapy product, i.e. generic Flonase. We also noted that you have not conducted an appropriately designed HPA-axis study to evaluate the impact of this increased exposure of fluticasone on circulating cortisol levels. The clinical impact of the increased fluticasone systemic exposure including the effects on HPA-axis will be a review issue.

Lokesh Jain	05/17/11
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni	05/17/11
Team Leader/Supervisor	Date

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

/s/

LOKESH JAIN
12/22/2011

SURESH DODDAPANENI
12/22/2011