CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209022Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	209022
Submission Date	11/18/2016
Brand Name	Xhance (proposed)
Generic Name	Fluticasone propionate
Reviewer	Mohammad Absar, Ph.D.
Team Leader (Acting)	Bhawana Saluja, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Applicant	Optinose US Inc.
Formulation; Strength	Aqueous nasal suspension spray; 93 mcg of fluticasone propionate per spray
Dosage Regimen	One spray per nostril twice daily
Relevant IND/NDA	IND 110089
Indication	Treatment of nasal polyps in patients 18 years of age or older

Table of Contents

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

Optinose US Inc. has submitted NDA 209022 under the 505(b)(2) pathway seeking marketing approval for fluticasone propionate aqueous nasal spray suspension for the treatment of nasal polyps in patients 18 years of age or older. The drug product (OPN-375) is an aqueous suspension of fluticasone propionate, and each metered spray delivers 93 mcg of fluticasone propionate. The proposed dosing regimen is one spray per nostril twice daily.

The clinical development program included a single two-part Phase 1 comparative pharmacokinetic (PK) study and two pivotal Phase 3 efficacy studies. In addition, the applicant conducted 12- and 52-week Phase 3 studies to assess safety of OPN-375. In the Phase 1 study (OPN-FLU-1102), systemic exposure of fluticasone propionate following administration of single dose of fluticasone propionate from OPN-375 was compared with that from Flonase® nasal spray (Part 1) and Flovent® HFA inhalation aerosol (Part 2). The two Phase 3 efficacy studies were randomized, double-blind, placebo-controlled, parallel-group, dose

ranging trials (Study OPN-FLU-NP-3101 and OPN-FLU-NP-3102) that evaluated the efficacy of doses ranging from 93 mcg BID to 372 mcg BID of OPN-375 in patients with bilateral nasal polyps. The following are the major findings from the current review –

1. Following single dose administration of 186 mcg OPN-375 (one 93 mcg fluticasone propionate spray per nostril) in healthy subjects, the mean peak concentration (C_{max}) and total systemic exposure ($AUC_{0\text{-}inf}$) of fluticasone propionate were 17.2 pg/mL and 111.7 pg.h/mL, respectively. In the same study, the C_{max} and $AUC_{0\text{-}inf}$ of fluticasone propionate following single dose administration of 372 mcg OPN-375 (two 93 mcg fluticasone propionate sprays per nostril) in healthy subjects were 25.3 pg/mL and 171.7 pg.h/mL, respectively. (Study OPN-FLU-1102; Part 1).
2. The C_{max} and $AUC_{0\text{-}inf}$ of fluticasone propionate following single dose administration of OPN-375 (186 mcg) in healthy subjects (Study OPN-FLU-1102; Part 1) were 37% higher and 6% lower, respectively, as compared to that attained following single dose administration of 400 mcg Flonase® (four 50 mcg sprays per nostril). The C_{max} and $AUC_{0\text{-}inf}$ of fluticasone propionate following single dose administration of 372 mcg OPN-375 were 101% and 45% higher, respectively, compared to single dose administration of 400 mcg Flonase®. (Study OPN-FLU-1102; Part 1).
3. Following single dose administration of 372 mcg OPN-375 (two 93 mcg fluticasone propionate sprays per nostril) in subjects with mild-to-moderate asthma, the C_{max} and $AUC_{0\text{-}inf}$ of fluticasone propionate were 28.7 pg/mL and 222.6 pg.h/mL, respectively. (Study OPN-FLU-1102; Part 2)
4. The C_{max} and $AUC_{0\text{-}inf}$ of fluticasone propionate following single dose administration of OPN-375 (372 mcg) in subjects with mild-to-moderate asthma were approximately 37% and 50% lower, respectively, as compared to that attained following single dose administration of 440 mcg Flovent® HFA (two 220 mcg inhalation) (Study OPN-FLU-1102; Part 2). Therefore, some relevant information for fluticasone propionate, including pharmacokinetics (PK), drug interaction, PK in special populations, systemic safety and others, could rely on the approved US labeling for Flovent® HFA.
5. The dosing regimen for OPN-375 has been adequately explored in two Phase 3 efficacy trials. In both Phase 3 studies, in terms of the co-primary efficacy endpoints (i.e., change from baseline to Week 4 in reduction of nasal congestion/obstruction and change from baseline to Week 16 in total polyp grade), [redacted] (b) (4) doses for OPN-375 [redacted] (b) (4), 186 and 372 mcg BID) showed a statistically significant difference from placebo. The co-primary efficacy endpoints showed a dose dependent improvement numerically in Study OPN-FLU-NP-3101. In Study OPN-FLU-NP-3102, no apparent dose-dependent trend in the co-primary efficacy endpoints was observed. Please refer to the Clinical Review by Dr. Courtney McGuire and the Statistical Review by Dr. Feng Li regarding the final risk/benefit assessment for the proposed doses for OPN-375 based on the efficacy and safety analysis of Phase 3 studies (Studies OPN-FLU-NP-3101 and OPN-FLU-NP-3102).

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 209022 and finds the application approvable from a clinical pharmacology perspective.

1.2. Post Marketing Requirement

None.

1.3. Summary of Important Clinical Pharmacology Findings

The Clinical Pharmacology package submitted for this NDA consisted of a single Phase 1 relative bioavailability study (OPN-FLU-1102). The study consisted of two parts: Part 1 was a 3-way, 3-treatment, 3-sequence crossover study in healthy subjects (n=90) where the systemic exposures of fluticasone propionate following single dose administration of OPN-375 [186 mcg (one 93 mcg fluticasone propionate spray per nostril) and 372 mcg (two 93 mcg fluticasone propionate sprays per nostril)] were compared to that from Flonase® nasal spray [400 mcg (four 50 mcg sprays per nostril)]. Part 2 of this study was a 2-way, 2-treatment, 2-sequence crossover study in subjects with mild-to-moderate asthma (n=30) where systemic exposure of fluticasone propionate following single dose administration of OPN-375 [372 mcg (two 93 mcg fluticasone propionate sprays per nostril)] was compared to that from Flovent® HFA inhalation aerosol, 440 mcg (two inhalations from 220 mcg strength of Flovent® HFA). The treatment arms and the statistical summary are presented below. This reviewer has reanalyzed the pharmacokinetic information submitted for the study by employing WinNonlin version 7.0 to obtain the non-compartmental pharmacokinetic (PK) parameters, and performed the BE analysis. The results of this reanalysis are in agreement with the results submitted by the Applicant.

Study OPN-FLU-1102 (Part 1): Treatment arms –

- Treatment A = 186 mcg (1 x 93 mcg spray to each nostril) OPN-375 nasal spray
- Treatment B = 372 mcg (2 x 93 mcg sprays to each nostril) OPN-375 nasal spray
- Treatment C = 400 mcg (4 x 50 mcg sprays to each nostril) Flonase® nasal spray

Comparative summary of pharmacokinetic parameters for fluticasone propionate following single dose administration of OPN-375 and Flonase® nasal spray are outlined below.

PK parameter	**Geometric mean %ratio (90% CI)**	
	OPN-375 186 mcg vs Flonase® 400 mcg	**OPN-375 372 mcg vs Flonase® 400 mcg**
C_{max}	137.1 (126.8, 148.1)	201.7 (186.7, 218.0)
$AUC_{(0-t)}$	101.8 (93.3, 111.2)	159.8 (146.4, 174.4)
$AUC_{(0-inf)}$	94.4 (83.4, 106.8)	144.6 (128.1, 163.3)

Reviewer's calculation

The C_{max} of fluticasone propionate was approximately 37% higher following single dose administration of 186 mcg OPN-375 as compared to that from 400 mcg Flonase® nasal spray. Further, C_{max} and AUC_{0-inf} were approximately 101% and 45% higher, respectively, following single dose administration of 372 mcg OPN-375, compared to that from 400 mcg Flonase® nasal spray.

Study OPN-FLU-1102 (Part 2): Treatment arms –

- Treatment B = 372 mcg (2 x 93 mcg sprays to each nostril) OPN-375 nasal spray
- Treatment D = 440 mcg (2 x 220 mcg) Flovent® HFA inhalation aerosol

Summary of PK parameters from Part 2 of the study is outlined below.

PK parameter	**Geometric mean %ratio (90% CI)**
	OPN-375 372 mcg vs Flovent® HFA 440 mcg
C_{max}	63.2 (50.6, 78.8)
$AUC_{(0-t)}$	49.2 (40.0, 60.6)
$AUC_{(0-inf)}$	49.9 (41.0, 60.7)

Reviewer's calculation

The C_{max} and $AUC_{0\text{-}inf}$ for fluticasone propionate were approximately 37% and 50% lower, respectively, following single dose administration of 372 mcg OPN-375 as compared to that from 440 mcg Flovent® HFA. The highest proposed dose of OPN-375 is 372 mcg BID (total daily dose of 744 mcg), while the maximum approved dose of Flovent® HFA in patients aged 12 years and older is 880 mcg BID (total daily dose of 1760 mcg)[1]. Therefore, the systemic exposure of fluticasone propionate for the highest proposed total daily dose of OPN-375 (i.e., 744 mcg) is expected to be lower than that for the reference product, Flovent® HFA.

Overall, Clinical Pharmacology recommends approval of NDA 209022.

2. QUESTION-BASED REVIEW

2.1. Background

The active pharmaceutical ingredient in the proposed drug product, fluticasone propionate, belongs to the corticosteroid class of drugs. Fluticasone propionate, alone or in combination with other products, has been in clinical use in the US for over 25 years for several conditions, including allergic and non-allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), dermatoses etc. Table 1 lists all the fluticasone propionate brand products approved in the US.

Table 1: Approved fluticasone propionate brand products in the US

Brand Name	Sponsor	Approval date
Advair Diskus	Glaxo Grp Ltd	08/24/2000
Advair HFA	Glaxo Grp Ltd	06/08/2006
Airduo Respiclick	Teva	01/27/2017
Armonair Respiclick	Teva	01/27/2017
Cutivate	Fougera	12/14/1990
Dymista	Mylan	05/01/2012
Flonase	GlaxoSmithKline	10/19/1994
Flovent Diskus	Glaxo Grp Ltd	09/29/2000
Flovent HFA	Glaxo Grp Ltd	05/14/2004

2.1.1. What is the regulatory background pertinent to this application?

The applicant carried out the development program for OPN-375 under IND 110089. During a face-to-face meeting held in December 20, 2010, the applicant discussed the feasibility to pursue OPN-375 in the treatment of nasal polyps. During that meeting, DPARP advised the applicant to characterize the PK profile and conduct a dose-ranging study for the proposed drug product. The applicant proposed to conduct a dose-ranging program within its two Phase 3 efficacy studies, which the division deferred to the applicant's discretion. During the pre-NDA meeting dated November 8, 2015, the applicant shared the outcome of the relative bioavailability study, two Phase 3 pivotal dose-ranging studies, and two Phase 3 safety studies for OPN-375. In the Phase 3 efficacy studies, the applicant investigated a total of three doses – 93 mcg BID, 186 mcg BID and 372 mcg BID in patients with bilateral nasal polyps with nasal congestion.

2.1.2. What are the clinical pharmacology studies submitted in the NDA?

The clinical pharmacology studies/clinical studies are summarized below:

[1] Flovent® HFA is approved for the maintenance treatment of asthma as prophylactic therapy in patients aged 4 years and older.

Table 2: Listing of clinical pharmacology/clinical studies

	Study ID	Objectives	Population	Study Design	Treatment and Device
PK study	OPN-FLU-1102: Part 1	PK	HS (n=90)	R, OL, 3-way crossover, SD	OPN-375: 186 mcg (93 mcg x 2) OPN-375: 372 mcg (93 mcg x 4) Flonase®: 400 mcg (50 mcg x 8)
	OPN-FLU-1102: Part 2	PK	Mild-to-moderate asthma (n=30)	R, OL, 2-way crossover, SD	OPN-375: 372 mcg (93 mcg x 4) Flovent® HFA: 440 mcg (220 mcg x 2)
Efficacy/safety study	OPN-FLU-NP-3101	Dose-ranging, efficacy, safety	Bilateral nasal polyps with nasal congestion (n=323)	R, DB, PC, PG, 16-week treatment, followed by 8-week OL extension	OPN-375: 93 mcg BID OPN-375: 186 mcg BID OPN-375: 372 mcg BID Placebo
	OPN-FLU-NP-3102	Dose-ranging, efficacy, safety	Bilateral nasal polyps with nasal congestion (n=323)	R, DB, PC, PG, 16-week treatment, followed by 8-week OL extension	OPN-375: 93 mcg BID OPN-375: 186 mcg BID OPN-375: 372 mcg BID Placebo
	OPN-FLU-CS-3203	Long-term safety	Chronic sinusitis with or without bilateral nasal polyps (n=223)	OL, MC, 52-week treatment	OPN-375: 372 mcg BID
	OPN-FLU-CS-3204	Short-term safety	Chronic sinusitis with or without bilateral nasal polyps (n=705)	OL, MC, 12-week treatment	OPN-375: 372 mcg BID

Source: NDA 209022 module 2.7.6.

2.2. General Attributes

2.2.1.What are fluticasone propionate's key physicochemical properties?

Fluticasone propionate is a white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, slightly soluble in methanol and 95% ethanol. It has a structural formula of $C_{25}H_{31}F_3O_5S$ with the following chemical name: *S*-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate. The chemical structure is shown in Figure 1 below.

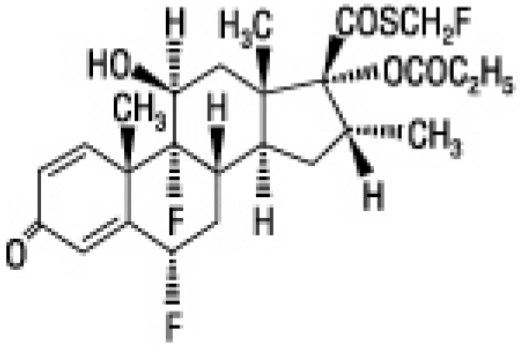


Figure 1: Chemical structure of fluticasone propionate

2.2.2. What is the formulation for the drug product?

OPN-375 is an aqueous suspension of fluticasone propionate. The drug product is contained in a (b) (4) amber glass vial closed by a non-pressurized, metering pump with a crimp seal (Figure 2). Once primed, OPN-375 contains 120 metered sprays; each delivers 93 mcg of fluticasone propionate in 106 mg of aqueous suspension. The formulation composition of the drug product is outlined in Table 3.

Figure 2: OPN-375 drug delivery system (Source: Module 2.7: Summary of Biopharmaceutic Studies)

Table 3: Composition of OPN-375 formulation

Component	Function	Concentration (% w/w)	Amount per Spray (µg)[a]	Amount per Vial (mg)	Reference to Quality Standards
Fluticasone propionate	Drug substance	(b) (4)	93	(b) (4)	USP/NF, Ph Eur (see *section 3.2.S.4.1*)
Polysorbate 80[c]	(b) (4)		(b) (4		USP/NF, Ph Eur
Microcrystalline cellulose and carboxymethylcellulose sodium[d]					USP/NF, Ph Eur
Benzalkonium chloride		0.02			USP/NF, Ph Eur
EDTA disodium, dihydrate[e]		(b) (4			USP/NF, Ph Eur
Dextrose					USP/NF, Ph Eur
(b) (4)					USP/NF, Ph Eur
					USP/NF, Ph Eur
					USP/NF, Ph Eur
Purified water					USP/NF, Ph Eur

Ph Eur = European Pharmacopoeia; (b) (4) USP/NF = United States Pharmacopeia/ National Formulary; — (b) (4)
[a] = Each spray is (b) (4) 106 mg).
(b) (4)
[c] = Tradename (b) (4)
[d] = Tradename (b) (4)
[e] = Edetate disodium, dihydrate.
(b) (4)
Source: *section 3.2.P.1 and section 3.2.S.4.1.*

Source: NDA 209022 module 3.2.P.1

2.2.3. What are the proposed mechanism of action and therapeutic indications?

Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. The precise mechanism through which fluticasone propionate affects nasal polyps and associated inflammatory symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. The anti-inflammatory action of corticosteroids contributes to their efficacy.[2]

OPN-375 is being proposed for the treatment of nasal polyps in patients 18 years of age or older.

2.2.4. What are the proposed dosages and routes of administration?

The proposed dosage of OPN-375 is one 93 mcg spray of fluticasone propionate per nostril twice daily (total daily dose of 372 mcg). Two sprays per nostril twice daily may also be effective in some patients (total daily dose of 744 mcg).

2.3.General Clinical Pharmacology

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

The Clinical Pharmacology package submitted for this NDA consisted of a single Phase 1 relative bioavailability study (OPN-FLU-1102) aimed to compare the systemic exposure of fluticasone propionate from OPN-375 with that from Flonase® nasal spray and Flovent® HFA inhalation aerosol. The study consisted of two parts. Part 1 was a 3-way crossover, 3-treatment, 3-sequence study conducted in 90 healthy adult subjects who received one of the following three treatments in a randomized fashion.

- Treatment A (test): 186 mcg (1x93 mcg spray to each nostril) OPN-375 nasal spray
- Treatment B (test): 372 mcg (2x93 mcg sprays to each nostril) OPN-375 nasal spray
- Treatment C (reference): 400 mcg (4x50 mcg sprays to each nostril) Flonase® nasal spray

Part 2 of the study was performed in subjects with mild-to-moderate asthma as a 2-way crossover, 2-treatment, 2-sequence study where subjects were randomized to each of the following treatments:

- Treatment B (test): 372 mcg (2x93 mcg sprays to each nostril) OPN-375 nasal spray
- Treatment D (reference): 440 mcg (2x220 mcg) Flovent® HFA inhalation aerosol

In each study part, every subject received a single dose of one of the treatments. Each treatment was separated by no less than 7-day washout period. Blood samples were collected predose and at 0.167, 0.333, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.5, 3, 4, 6, 9 12, 16, and 24 hours post dose. For Part 2, samples were collected up to 36 hours.

No separate dose-ranging study was conducted for OPN-375; instead, three different doses were investigated in two Phase 3 efficacy studies based on previous correspondence with the Agency (See regulatory history in Section 2.2). The study results for the two Phase 3 studies are discussed in Section 2.5.2.

2.3.2. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameter and exposure response relationships?

Fluticasone propionate in plasma samples was measured. No metabolites were quantified because the metabolite is not active, and are not known to be associated with efficacy or safety.

[2] Prescribing information of Flovent® HFA.

2.4. Dose/Exposure-Relationship

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

For intranasal fluticasone propionate, the systemic exposure is not related to clinical response – i.e., reduction of nasal congestion/obstruction and change in total polyp grade.

2.4.2. Have the dosing of OPN-375 been adequately explored?

The applicant did not conduct dedicated dose-ranging study for OPN-375. Instead, the dosing regimens of 93 mcg BID, 186 mcg BID and 372 mcg BID were investigated in two Phase 3 efficacy studies – OPN-FLU-NP-3101 and OPN-FLU-NP-3102 (see Section 2.1.1).

Phase 3 studies for OPN-375:

Studies OPN-FLU-NP-3101 and OPN-FLU-NP-3102 were Phase 3, 16-week (followed by 8-week open label extension) randomized, double-blind, placebo-controlled, parallel-group studies in adults (≥18 years) with bilateral nasal polyps. Both studies had identical design and enrollment criteria. The co-primary efficacy endpoints for both studies, including change from baseline to Week 4 in reduction of nasal congestion/obstruction and change from baseline to Week 16 in total polyp grade are shown in Table 4.

In both Phase 3 studies, in terms of the co-primary efficacy endpoints, all the doses of OPN-375 (i.e., 93, 186, and 372 mcg BID) showed a statistically significant difference from placebo. In Study OPN-FLU-NP-3101, the co-primary efficacy endpoints OPN-375 showed a dose dependent improvement numerically. In Study OPN-FLU-NP-3102, no apparent dose-dependent trend in primary efficacy endpoints was observed. Please refer to the Clinical Review by Dr. Courtney McGuire and the Statistical Review by Dr. Feng Li regarding the final risk/benefit assessment on the proposed doses for OPN-375 based on the efficacy and safety analyses of Phase 3 studies.

Table 4: Efficacy results from Studies OPN-FLU-NP-3101 and OPN-FLU-NP-3102

		93 mcg BID	186 mcg BID	372 mcg BID
OPN-FLU-NP-3101		N= 81	N=80	N=79
Reduction of nasal congestion/obstruction at Week 4	Difference (active- PBO), PBO= -0.24 (0.07)	-0.25	-0.30	-0.38
	p value versus PBO	0.010	0.002	<0.001
Change in total polyp grade at Week 16	Difference (active- PBO), PBO= -0.45 (0.135)	-0.51	-0.59	-0.62
	p value versus PBO	0.004	<0.001	<0.001
OPN-FLU-NP-3102		N= 80	N=80	N=82
Reduction of nasal congestion/obstruction at Week 4	Difference (active-PBO), PBO=-0.24(0.07)	-0.36	-0.45	-0.38
	p value versus PBO	<0.001	<0.001	<0.001
Change in total polyp grade at Week 16	Difference (active-PBO), PBO= -0.61(0.107)	-0.70	-0.60	-0.80
	p value versus PBO	<0.001	<0.001	<0.001

Source. NDA 209022 module 2.7.3

2.5. What are the PK characteristics of the drug?

2.5.1. What are the single dose PK parameters of parent drug and relevant metabolites in adult subjects?

Single intranasal doses of OPN-375 were administered to healthy subjects (Part 1) and to subjects with mild-to-moderate asthma (Part 2) in Study OPN-FLU-1102. The mean PK profiles of fluticasone propionate are shown in Figure 3. In healthy subjects, C_{max} and $AUC_{0\text{-}inf}$ following single dose administration of 186 mcg OPN-375 (one 93 mcg fluticasone propionate spray per nostril) were 17.2 pg/mL and 111.7 pg.h/mL, respectively. The C_{max} and $AUC_{0\text{-}inf}$ following single dose administration of 372 mcg OPN-375 (two 93 mcg sprays per nostril) in healthy subjects were 25.3 pg/mL and 171.7 pg.h/mL, respectively. In subjects with mild-to-moderate asthma, C_{max} and $AUC_{0\text{-}inf}$ following single dose administration of 372 mcg OPN-375 (two 93 mcg sprays per nostril) were 28.7 pg/mL and 222.6 pg.h/mL, respectively. The pre-dose concentrations of fluticasone propionate between the study periods were not quantifiable, suggesting that the washout period of 7 days was adequate and pre-dose concentrations did not contribute to the PK results.

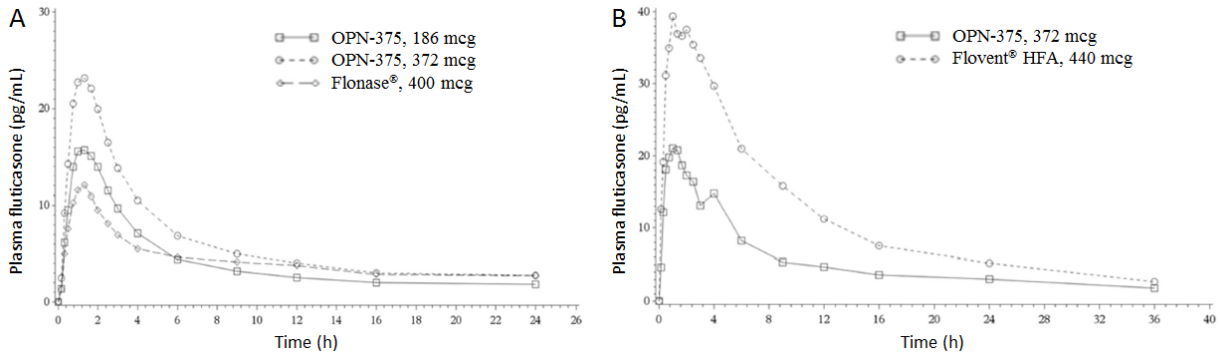


Figure 3: Mean plasma concentrations of fluticasone propionate vs. time following single dose administration of (A) OPN-375 and Flonase® in study part 1; (B) OPN-375 and Flovent® HFA in study part 2 (source module 2.7.2)

Table 5: Pharmacokinetic parameters of fluticasone propionate after single dose administration in Study OPN-FLU-1102 (Part 1)

	Study OPN-FLU-1102 (Part 1)		
	PK parameter: Arithmetic mean ± SD		
	OPN-375 186 mcg (N=86) 1x93 mcg each nostril	OPN-375 372 mcg (N=86) 2x93 mcg each nostril	Flonase® 400 mcg (N=85) 4x50 mcg each nostril
C_{max} (pg/mL)	17.2 ± 7.40	25.3 ± 10.34	13.4 ± 8.01
$AUC_{(0\text{-}t)}$ (pg.h/mL)	91.9 ± 41.04	144.4 ± 65.60	94.7 ±46.56
$AUC_{(0\text{-}inf)}$ (pg.h/mL)	111.7 ± 49.75	171.7 ± 85.55	126.0 ± 70.51

$AUC_{(0\text{–}inf)}$ = area under the plasma concentration-versus-time curve from time zero to infinity; $AUC_{(0\text{-}t)}$ = area under the plasma concentration-versus-time curve from time zero to the time of the last quantifiable concentration; C_{max} = peak plasma concentration.
OPN-375 186 mcg = OPN-375 1 x 93 mcg to each nostril
OPN-375 372 mcg = OPN-375 2 x 93 mcg to each nostril
Flonase® 400 mcg = Flonase® nasal spray 4 x 50 mcg to each nostril
Source: Study OPN-FLU-1102 Module 2.7.2

Table 6: Pharmacokinetic parameters of fluticasone propionate after single dose administration in Study OPN-FLU-1102 (Part 2)

	Study OPN-FLU-1102 (Part 2)	
	PK parameter: Arithmetic mean ± SD	
	OPN-375 372 mcg (N=26) 2 x 93 mcg each nostril	Flovent® HFA 440 mcg (N=26) 2 x 220 mcg inhaled
C_{max} (pg/mL)	28.7 ± 18.72	44.0 ± 19.12
$AUC_{(0-t)}$ (pg.h/mL)	188.0 ± 84.55	408.3 ± 265.79
$AUC_{(0-inf)}$ (pg.h/mL)	222.6 ± 84.60	468.7 ± 278.17

$AUC_{(0-inf)}$ = area under the plasma concentration-versus-time curve from time zero to infinity; $AUC_{(0-t)}$ = area under the plasma concentration-versus-time curve from time zero to the time of the last quantifiable concentration; C_{max} = peak plasma concentration.
OPN-375 372 mcg = OPN-375 2 x 93 mcg to each nostril
Flovent® HFA 440 mcg = Flovent® HFA inhalation aerosol 2 x 220 mcg inhaled
Source: Study OPN-FLU-1102 Module 2.7.2

Excluded subjects

In Part 1, Subjects 6, 26, 37, and 46 did not complete the study and, therefore, were excluded from the descriptive statistics. Subject 55 in Period 2 (Flonase® 400 mcg) had a measurable predose plasma fluticasone propionate concentration that was higher than 5% of the C_{max} of this study subject and, therefore, was excluded from the descriptive statistics for the Flonase® 400 mcg treatment cohort.

In Part 2, Subjects 95, 107, 110 and 1095 did not complete the study and, therefore, were excluded from descriptive statistics.

Bioequivalence

The GMR and 90% CI of the ratio with single dose treatments of OPN-375 and Flonase® nasal spray, based on log-transformed parameters, are represented in Table 7 (from Part 1 of the study). The 90% CI of the GMR of $AUC_{(0-t)}$, $AUC_{(0-inf)}$ were contained within the BE limits of 80.00-125.00% following single 186 mcg dose of OPN-375; C_{max}, however, was beyond the 125.00% limit, compared to 400 mcg single dose of Flonase® nasal spray. Upon 372 mcg single dose administration of OPN-375, the upper limit of 90% CI of the GMR of C_{max}, $AUC_{(0-t)}$, $AUC_{(0-inf)}$ were all beyond the 125.00% limit compared to 400 mcg single dose of Flonase® nasal spray.

Table 8 represents the GMR and 90% CI of the ratio with single dose treatments of OPN-375 and Flovent® HFA inhalation aerosol based on log-transformed parameters (from Part 2 of the study). The upper limit of 90% CI of the GMR of C_{max}, $AUC_{(0-t)}$, $AUC_{(0-inf)}$ were below the upper BE limits of 125.00% following 372 mcg single dose treatment with OPN-375 compared to Flovent® HFA 440 mcg.

Table 7: 90% CI on the GMR of fluticasone propionate PK parameters following a single dose administration of OPN-375 and Flonase® nasal spray

PK parameter	Geometric mean %ratio (90% CI)	
	OPN-375 186 mcg vs Flonase® 400 mcg	OPN-375 372 mcg vs Flonase® 400 mcg
C_{max}	137.1 (126.8, 148.1)	201.7 (186.7, 218.0)
$AUC_{(0-t)}$	101.8 (93.3, 111.2)	159.8 (146.4, 174.4)
$AUC_{(0-inf)}$	94.4 (83.4, 106.8)	144.6 (128.1, 163.3)

Reviewer's calculation

Table 8: 90% CI on the GMR of fluticasone propionate PK parameters following a single dose administration of OPN-375 and Flovent® HFA inhalation aerosol

PK parameter	Geometric mean %ratio (90% CI)
	OPN-375 372 mcg vs Flovent® HFA 440 mcg
C_{max}	63.2 (50.6, 78.8)
$AUC_{(0-t)}$	49.2 (40.0, 60.6)
$AUC_{(0-inf)}$	49.9 (41.0, 60.7)

Reviewer's calculation

2.5.2. How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

The pharmacokinetics of fluticasone propionate in patients with nasal polyps was not characterized in this NDA submission.

2.7.3. How is the proposed to-be-marketed formulation linked to the clinical formulation?

The size of the clinical batches used in Phase 1 and Phase 3 studies were (b) (4) which is consistent with the proposed commercial batch size. The formulation of the drug product used in the clinical batches is the same as the to-be-marketed product. The applicant used a (b) (4) to preclude the need to (b) (4) and adopted a minor change in external geometry of the pump in the final device. These changes were communicated to the Agency in a pIND meeting dated July 21, 2015. For additional details, please refer to the CMC review.

2.6. Bioanalytical

2.6.1. Are the bioanalytical methods properly validated to measure fluticasone in plasma samples?

Fluticasone propionate concentrations were determined in human plasma samples using a validated high performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) method. Fluticasone propionate was extracted from human plasma treated with K_2EDTA using a liquid-liquid extraction. The lower limit of quantification (LLOQ) was 1.00 pg/mL (Bioanalytical method validation report AA96580-01). Calibration was performed over an analytical range of 1.00 to 150 pg/mL, using linear regression model with a weighting factor of 1/concentration^2. The intra- and inter-batch accuracy and precision of at least 67% of all quality controls were within ± 20% of their nominal concentrations and at least 50% of quality controls at each concentration were within ± 20% of their nominal values. Freeze-thaw and bench-top stability was adequate to cover the sample handling condition during sample analysis. The incurred sample reanalysis of a subset of study samples had acceptable reproducibility.

3. LABEL RECOMMENDATIONS

Labeling statements to be removed are shown in ~~red strikethrough~~ font and suggested labeling to be included is shown in underline blue font.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate is a substrate of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin, conivaptan, lopinavir, (b) (4) voriconazole) with (b) (4) is not recommended because increased systemic corticosteroid adverse effects may occur.

Ritonavir

A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations [*see Clinical Pharmacology (12.3)*]. During postmarketing use, there have been reports of clinically

significant drug interactions in patients receiving fluticasone propionate products with ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

Ketoconazole

Coadministration of orally inhaled fluticasone propionate [redacted] (1000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

8 USE IN SPECIFIC POPULATIONS

8.6 Hepatic Impairment

Formal pharmacokinetic trials using [redacted] have not been conducted in subjects with hepatic impairment. Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic trials using [redacted] have not been conducted in subjects with renal impairment.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

HPA Axis Effect

The potential systemic effects of [redacted] on the HPA axis have not been evaluated. [redacted]

Serum cortisol concentrations, urinary excretion of cortisol, and urine 6-β- hydroxycortisol excretion collected over 24 hours in 24 healthy subjects following 8 oral inhalations [redacted] of fluticasone propionate 44, 110, and 220 mcg decreased with increasing dose. However, in patients with asthma treated with 2 oral inhalations [redacted] fluticasone propionate 44, 110, and 220 mcg twice daily for at least 4 weeks, differences in serum cortisol $AUC_{0\text{-}12h}$ (n = 65) and 24-hour urinary excretion of cortisol (n = 47) compared with placebo were not related to dose and generally not significant.

The potential systemic effects of orally inhaled fluticasone propionate [redacted] on the HPA axis were also studied in subjects with asthma [*see Warnings and Precautions (5.5) and Adverse Reactions (6)*]. Fluticasone propionate given by inhalation aerosol [redacted] dosages of 440 or 880 mcg twice daily was compared with placebo in oral corticosteroid-dependent subjects with asthma (range of mean dose of prednisone at baseline: 13 to 14 mg/day) in a 16-week trial. Consistent with maintenance treatment with oral corticosteroids, abnormal plasma cortisol responses to short cosyntropin stimulation (peak plasma cortisol less than 18 mcg/dL) were present at baseline in the majority of subjects participating in this trial (69% of subjects later randomized to placebo and 72% to 78% of subjects later randomized to fluticasone propionate HFA). At week 16, 8 subjects (73%) on placebo compared with 14 (54%) and 13 (68%) subjects receiving fluticasone propionate HFA (440 and 880 mcg twice daily, respectively) had poststimulation cortisol levels of less than 18 mcg/dL.

12.3 Pharmacokinetics

The activity of [redacted] is due to the parent drug, fluticasone propionate. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data were obtained via other routes of administration.

Absorption

[redacted]

[redacted] The mean (SD) peak exposure (C_{max}) and total exposure ($AUC_{0-\infty}$) following a dose of 186 mcg of [redacted] were 17.2 ± 7.40 pg/mL and 111.7 ± 49.75 pg·h/mL, respectively, and were 25.3 ± 10.34 pg/mL and 171.7 ± 85.55 pg·h/mL, respectively, following a dose of 372 mcg of [redacted] in healthy subjects. The Cmax and AUC0-∞ following a dose of 372 mcg of Xhance in patients with mild to moderate asthma were 28.7±18.72 pg/mL and 222.6±84.60 pg.h/mL, respectively. [redacted]

Distribution

Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin. [redacted]

Elimination

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. The total blood clearance of fluticasone propionate is high (average: 1093 mL/min), with renal clearance accounting for less than 0.02% of the total.

Metabolism: The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite had less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion: Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations

[redacted] was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.

Pediatrics: [redacted] was not studied in pediatric patients, and no pediatric-specific pharmacokinetic data have been obtained with the product.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using [redacted] have not been conducted in patients with hepatic or renal impairment. However, since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Race: No significant difference in clearance (CL/F) of fluticasone propionate in Caucasian, African-American, Asian, or Hispanic populations has been observed.

Drug Interactions

Inhibitors of Cytochrome P450 3A4

Ritonavir: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor, ritonavir, is not recommended based upon a multiple-dose, crossover drug interaction trial in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (< 10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (C_{max}) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{0-\tau}$ averaged 8.43 pg·h/mL (range: 4.2 to 18.8 pg·h/mL). Fluticasone propionate C_{max} and $AUC_{0-\tau}$ increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3102.6 pg·h/mL (range: 1207.1 to 5662.0 pg·h/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: Coadministration of fluticasone propionate orally inhaled into the lungs (1000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

Following orally-inhaled fluticasone propionate alone, $AUC_{2\text{-last}}$ averaged 1559 pg·h/mL (range: 555 to 2906 pg·h/mL) and $AUC_{2\text{-}\infty}$ averaged 2269 pg·h/mL (range: 836 to 3707 pg·h/mL). Fluticasone propionate $AUC_{2\text{-last}}$ and $AUC_{2\text{-}\infty}$ increased to 2781 pg·h/mL (range: 2489 to 8486 pg·h/mL) and 4317 pg·h/mL (range: 3256 to 9408 pg·h/mL), respectively, after coadministration of ketoconazole with orally-inhaled fluticasone propionate. This increase in plasma fluticasone propionate concentration resulted in a decrease (45%) in serum cortisol AUC.

Erythromycin: In a multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (b) (4) (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

4. APPENDIX

4.1. Analysis

Geometric means of fluticasone propionate PK parameters in Study OPN-FLU-1102 (Part 1 and Part 2), and bioequivalence determination between OPN-375 and Flonase® nasal spray (Part 1), and between OPN-375 and Flovent® HFA inhalation aerosol (Part 2) were confirmed by independent analysis and were found to be similar to that reported by the Applicant.

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

/s/

MOHAMMAD S ABSAR
08/12/2017

BHAWANA SALUJA
08/14/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	209022	**SDN**	1
Applicant	Optinose US Inc.	**Submission Date**	November 18, 2016
Generic Name	Fluticasone propionate	**Brand Name**	(b) (4) (proposed)
Drug Class	Corticosteroid		
Indications	Treatment of nasal (b) (4) in patients 18 years and older		
Dosage Regimen	One exhalation (93 mcg) per nostril twice daily		
Dosage Form	Aqueous Nasal Suspension Spray	**Route of Administration**	Intranasal
OCP Division	DCP II	**OND Division**	DPARP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Mohammad (Abir) Absar, Ph.D.	Bhawana Saluja, Ph.D.
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	1/17/2017	**74-Day Letter Date**	1/31/2017
Review Due Date	8/14/2017	**PDUFA Goal Date**	9/18/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

The applicant conducted 4 Phase 3 clinical studies (OPN-FLU-3101, OPN-FLU-3102, OPN-FLU-3203, OPN-FLU-3204).

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		

☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☑ Relative Bioavailability	1	Study OPN-FLU-1102: An open-label, 2-part, randomized, crossover study to compare the bioavailability of intranasal administration of 200 and 400 µg of Optinose™ fluticasone with 400 µg of Flonase (fluticasone propionate) nasal spray (Part 1), and intranasal administration of 200 and 400 µg alone of Optinose™ fluticasone with 440 µg of Flovent HFA (fluticasone propionate) inhalation aerosol (Part 2) (Module 5.3.1.2).
☐ Bioequivalence		
☐ Food Effect		
☑ Other		Bioanalytical and Analytical Methods for Human Study OPN-FLU-1102 (Module 5.3.1.4).
Human Pharmacokinetics		
Healthy Subjects ☑ Single Dose		Part 1 of Study OPN-FLU-1102 was a single dose study conducted in healthy subjects.
Healthy Subjects ☐ Multiple Dose		
Patients ☐ Single Dose		
Patients ☐ Multiple Dose		
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		

☐ Exposure-Safety					
Total Number of Studies	**In Vitro**	1	**In Vivo**	1
Total Number of Studies to be Reviewed		1		1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	According to the applicant, the drug product used in the pivotal clinical trials is the same as the to-be-marketed product. In addition, it is a locally acting drug product proposed for the treatment of nasal (b) (4)
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	Cross-referenced Flonase® (NDA 020121) and Flovent® HFA (NDA 021433).
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	Study OPN-FLU-1102
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	Study OPN-FLU-1102
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	Two Phase 3 studies (3101 and 3102) are submitted in support of the proposed dosing.
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	The submission contains PK datasets in .xpt format.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks	☑Yes ☐No ☐N/A	

work leading to appropriate sections, reports, and appendices?		
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. 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)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. 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?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	The applicant requests a (b) (4) waiver for pediatric studies in children <6 years of age, and a deferral for children ≥6 years of age.
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

Background

Optinose US, Inc. (the applicant) has submitted a 505(b)(2) new drug application for fluticasone propionate nasal spray (OPN-375) for the proposed indication of treatment of nasal (b) (4) in patients 18 years of age and older. The product consists of fluticasone propionate aqueous suspension nasal spray administered intranasally.

The clinical development program consisted of one Phase 1 pharmacokinetic and four Phase 3 efficacy and safety studies; Table 1 summarizes the clinical studies submitted in support of this NDA. This NDA relies on the Agency's previous findings of systemic safety for Flovent HFA and Flonase (listed drugs).

Table 1: List of clinical studies

Study Identifier	Type of Study	Population	Treatment Groups	Duration of Treatment	Number of Subjects
OPN-FLU-1102: part 1	Phase 1 bioavailability	Healthy subjects	OPN-375 200 µg OPN-375 400 µg Flonase 400 µg	Single dose (crossover design)	Enrolled: 90 Completed: 86
OPN-FLU-1102: part 2	Phase 1 bioavailability	Mild to moderate asthmatics	OPN-375 400 µg Flovent HFA 440 µg	Single dose (crossover design)	Enrolled: 30 Completed: 26
OPN-FLU-NP-3101	Pivotal, Phase 3 double-blind dose-ranging with open-label extension	Bilateral nasal polyposis with nasal congestion	OPN-375 100 µg bid OPN-375 200 µg bid OPN-375 400 µg bid Placebo	Double-blind: 16 weeks	Enrolled: 323 Completed: 292 (double-blind)
			OPN-375 400 µg bid	Open-label: 8 weeks	Enrolled: 282 Completed: 274 (open-label)
OPN-FLU-NP-3102	Pivotal, Phase 3 double-blind dose-ranging with open-label extension	Bilateral nasal polyposis with nasal congestion	OPN-375 100 µg bid OPN-375 200 µg bid OPN-375 400 µg bid Placebo	Double-blind: 16 weeks	Enrolled: 323 Completed: 306 (double-blind)
			OPN-375 400 µg bid	Open-label: 8 weeks	Enrolled: 299 Completed: 294 (open-label)
OPN-FLU-CS-3203	Phase 3 long-term safety open-label	Chronic sinusitis with or without bilateral nasal polyps	OPN-375 400 µg bid	52 weeks	Enrolled: 224[a,b] Completed: 144
OPN-FLU-CS-3204	Phase 3 short-term safety open-label	Chronic sinusitis with or without bilateral nasal polyps	OPN-375 400 µg bid	12 weeks	Enrolled: 706[c] Completed: 601

Please refer to the slides below for further details. The NDA is considered fileable from a clinical pharmacology perspective.

APPENDIX A

Background

- This is a 505b(2) application for Fluticasone propionate nasal spray (OPN-375)
- Proposed brand name (b) (4)
- Sponsor: Optinose US Inc.
- Strength: 93 µg
- Indication: Treatment of nasal (b) (4) in patients ≥18 yr
- Proposed dose: One (b) (4) per nostril twice daily (total daily dose, 372 (b) (4) 2 (b) (4) per nostril twice daily (total daily dose 744 (b) (4)

2

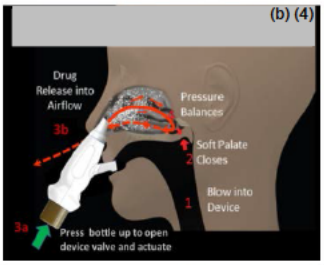
Regulatory history

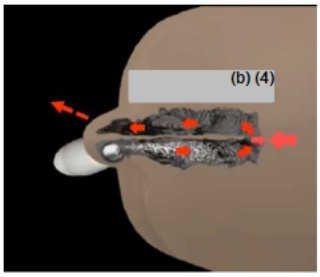
- Two type-B pre-IND meetings to discuss the development program
- Type-B pre-NDA meeting on November 18, 2015; One clinical pharmacology study (2 parts) to demonstrate systemic safety of the test product
- Study OPN-FLU-1102 (single dose study)
  Relative bioavailability comparing test product (400 µg dose) to Flonase (400 µg dose): Part 1
  Relative bioavailability comparing test product (400 µg dose) to Flovent HFA (440 µg dose): Part 2

3

For internal discussion

The drug product





14

Submitted studies

Study Identifier	Type of Study	Population	Treatment Groups	Duration of Treatment	Number of Subjects
OPN-FLU-1102	Phase 1 bioavailability	Healthy subjects	OPN-375 200 µg OPN-375 400 µg Flonase 400 µg	Single dose (crossover design)	Enrolled: 90 Completed: 86
	Phase 1 bioavailability	Mild to moderate asthmatics	OPN-375 400 µg Flovent HFA 440 µg	Single dose (crossover design)	Enrolled: 30 Completed: 26
OPN-FLU-NP-3101	Pivotal, Phase 3 double-blind dose-ranging with open-label extension	Bilateral nasal polyposis with nasal congestion	OPN-375 100 µg bid OPN-375 200 µg bid OPN-375 400 µg bid Placebo	Double-blind: 16 weeks	Enrolled: 323 Completed: 292 (double-blind)
			OPN-375 400 µg bid	Open-label: 8 weeks	Enrolled: 282 Completed: 274 (open-label)
OPN-FLU-NP-3102	Pivotal, Phase 3 double-blind dose-ranging with open-label extension	Bilateral nasal polyposis with nasal congestion	OPN-375 100 µg bid OPN-375 200 µg bid OPN-375 400 µg bid Placebo	Double-blind: 16 weeks	Enrolled: 323 Completed: 306 (double-blind)
			OPN-375 400 µg bid	Open-label: 8 weeks	Enrolled: 299 Completed: 294 (open-label)
OPN-FLU-CS-3203	Phase 3 long-term safety open-label	Chronic sinusitis with or without bilateral nasal polyps	OPN-375 400 µg bid	52 weeks	Enrolled: 224[a,b] Completed: 144
OPN-FLU-CS-3204	Phase 3 short-term safety open-label	Chronic sinusitis with or without bilateral nasal polyps	OPN-375 400 µg bid	12 weeks	Enrolled: 706[c] Completed: 601

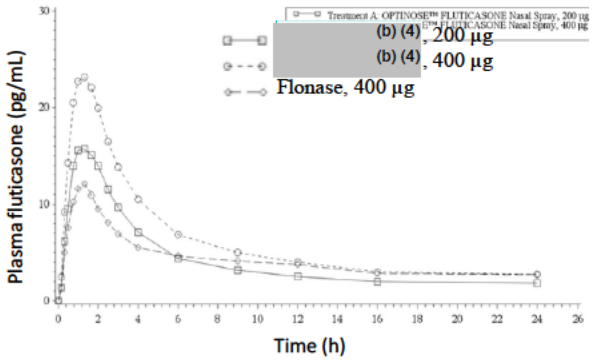
4

Study OPN-FLU-1102: Part 1

- 3-way crossover, 3-treatment, 3-sequence study in healthy subjects (n=90)
- Compare the systemic exposure of a single dose of 200 and 400 µg of Optinose Fluticasone with 400 µg Flonase®
  - Treatment A: 200 µg (2x100 µg) Optinose Fluticasone N/S
  - Treatment B: 400 µg (4x100 µg) Optinose Fluticasone N/S
  - Treatment C: 400 µg (4x50 µg to each nostril) Flonase®
- No less than 7 days washout between each treatment
- PK samples collected up to 24 h

5

Study OPN-FLU-1102: Part 1



Parameter	GM % Ratio (90% CI upper limit)	
	(b) (4) 200 µg/Flonase 400 µg	(b) (4) 400 µg/Flonase 400 µg
C_{max} (pg/mL)	137.4 (148.5)	201.5 (217.8)
AUC_t (pg/h/mL)	101.9 (111.2)	160.0 (174.8)
AUC_{∞} (pg.h/mL)	97.7 (110.3)	147.2 (166.1)

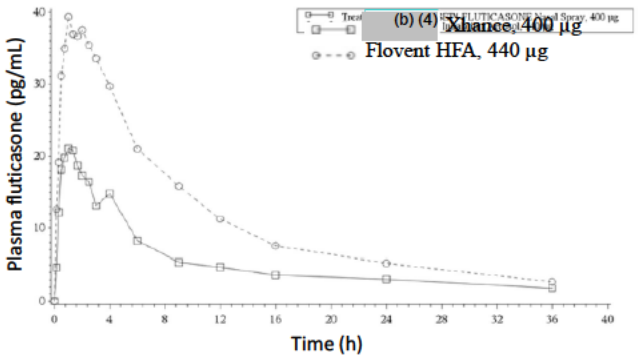
6

Study OPN-FLU-1102: Part 2

- 2-way crossover, 2-treatment, 2-sequence study in mild-to-moderate asthmatic subjects (n=30)
- Compare the systemic exposure of a single dose of 400 µg of OPN-375 to Flovent® HFA.
  - Treatment B: 400 µg (4x100 µg) Optinose Fluticasone N/S
  - Treatment D: 440 µg (2x220 µg) Flovent® HFA
- No less than 7 days washout between each treatment
- PK sample collected up to 36 h

7

Study OPN-FLU-1102: Part 2



Parameter	GM % Ratio (90% CI upper limit)
	(b) (4) 400 µg/Flovent HFA 440 µg
C_{max} (pg/mL)	63.2 (78.8)
AUC_t (pg/h/mL)	49.3 (60.7)
AUC_∞ (pg.h/mL)	49.6 (60.7)

8

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

/s/

MOHAMMAD S ABSAR
01/17/2017

BHAWANA SALUJA
01/17/2017