CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209022Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209,022
Priority or Standard	Standard
Submit Date(s)	11/18/2016
Received Date(s)	11/18/2016
PDUFA Goal Date	9/18/2017
Division / Office	CDER/OND/DPARP
Reviewer Name(s)	Courtney McGuire, MD
Review Completion Date	8/14/2017
Established Name	Fluticasone propionate
(Proposed) Trade Name	Xhance nasal spray
Therapeutic Class	Corticosteroid
Applicant	OptiNose US, Inc.
Formulation(s)	Aqueous Nasal Spray
Dosing Regimen	93-mcg (1 spray) per nostril twice daily, 186-mcg (2 sprays) per nostril twice daily
Indication(s)	Treatment of nasal polyps
Intended Population(s)	Adults 18 years of age and older

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action from a clinical perspective is Approval of Xhance® (OPN-375), fluticasone propionate nasal spray, for the treatment of nasal polyps at a starting dosage of 186-mcg twice daily delivered as 1 spray (93-mcg) per nostril twice daily and a maximum dosage of 372-mcg twice daily delivered as 2 sprays (186-mcg) per nostril twice daily.

1.2 Risk Benefit Assessment

Based on the data submitted, there is substantial evidence of the safety and effectiveness to support the approval of Xhance® nasal spray, an intranasal corticosteroid, for the treatment of nasal polyps in patients 18 years and older.

For this NDA, the Applicant proposed a recommended total OPN-375 dosage of 186-mcg twice daily (BID)[1] and up to 372-mcg BID. The primary clinical data to support the efficacy of the proposed dosage and indication consisted of two adequate and well-controlled, phase 3 trials in adults with bilateral nasal polyps and associated moderate nasal congestion. These dose-ranging trials compared the efficacy of three OPN-375 doses (93-mcg BID, 186-mcg BID and 372-mcg BID) to placebo in the treatment of nasal polyps by improvement in the following two coprimary endpoints: total nasal polyp score after 16-weeks of treatment and nasal congestion / obstruction scores after 4-weeks of treatment.

Both trials demonstrated a statistically significant difference from placebo in total polyp grade and congestion / obstruction scores for all three OPN-375 doses tested. With respect to the coprimary endpoints, statistical comparisons of 186-mcg BID and 372-mcg BID with 93-mcg BID did not achieve statistical significance. There was a small dose-response for both coprimary endpoints in one of the two trials. However, in both trials, 372-mcg BID demonstrated a greater numeric change in total nasal polyp grade than either 186-mcg BID or 93-mcg BID, the coprimary endpoint that represents the more objective measure of efficacy.

Evaluation of the OPN-375 safety database did not identified any new safety signals that differ from the known adverse event (AE) profile of fluticasone propionate or other corticosteroids. There were no deaths, and serious adverse events (SAEs) were distributed across AE preferred terms. There was a small dose-response in overall AEs

[1] The total dosage is divided between both nostrils. For clarity, this review will refer to total dosage.

for the two pivotal trials. However, with respect to drug-specific safety concerns, epistaxis was the only AE with a clinically significant dose-response, occurring more often in all OPN-375 arms than placebo, but at a similar incidence for the 186-mcg BID and 372-mcg BID doses. Other local nasal AEs including septal ulcerations, septal perforations, and mucosal abnormalities occurred with all OPN-375 doses more than placebo and without a clear dose-response. The 3 cases of posterior subcapsular cataracts occurred in subjects taking OPN-375 186-mcg BID and 372-mcg BID. The safety profile of the two long-term OPN-375 trials evaluating 372-mcg BID in adults with chronic sinusitis with and without nasal polyps for 3 and 12 months duration was generally consistent with Trials 3101 and 3102.

In conclusion, the risk-benefit assessment for OPN-375 as an intranasal corticosteroid for treatment of nasal polyps in patients 18 years and older is favorable. Acknowledging that the development program did not demonstrate a statistically significant difference in the efficacy between the three doses, 372-mcg BID did demonstrate the largest nominal improvement in nasal polyp grade across both trials suggesting that some patients may achieve more clinical benefit from 372-mcg BID of OPN-375. Further, there were only small differences with respect to AE incidence between the three doses. The risk-benefit profile is most favorable for a recommended total starting OPN-375 dosage of 186-mcg BID and a maximum daily dosage of 372-mcg BID.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

To fulfill PREA requirements, the Applicant will complete (b) (4)

s well as a safety and efficacy study in pediatric patients with bilateral nasal polyps and associated nasal congestion. The final age groups to be included in the safety and efficacy study will be determined by the (b) (4)

No other postmarket requirements or commitments are recommended.

2 Introduction and Regulatory Background

The Applicant, OptiNose US, submitted NDA 209,022 on November 18, 2016, for an intranasal corticosteroid suspension containing the active ingredient, fluticasone propionate, for the indication treatment of nasal polyps in adults 18 years and older.

The drug product utilizes a novel delivery system that the Applicant hypothesizes will improve drug deposition in the nasal cavity.

Nasal polyps are a chronic condition characterized by benign eosinophilic inflammatory outgrowths of the nasal mucosa, often occurring bilaterally along the middle and superior meatus. While the exact etiology of nasal polyps is unknown, inflammation plays a significant role.[2] An estimated 4% of the general population develops nasal polyps.[3] The disease primarily affects adults, and more males than females (2:1 ratio).[2] While typically not life-threatening, nasal polyps may have significant impact on quality of life. Associated symptoms include nasal obstruction, facial pain, rhinorrhea, and hyposmia, and the severity depends on the size and location of the polyps. Comorbid conditions include acute rhinosinusitis, allergic rhinitis, chronic rhinitis, asthma, gastroesophageal reflux disease, sleep apnea, anxiety, and headaches.[4]

Treatment of nasal polyps includes medical and surgical therapy aimed at either complete elimination of the polyps or sufficient reduction in polyp size to alleviate nasal obstruction and associated symptoms. Intranasal corticosteroids are generally considered first-line treatment, but corticosteroids are also provided by intrapolyp injection, or systemic administration. Surgical treatment is typically reserved for refractory cases, but recurrence occurs in up to 10% of patients.[2,5]

As many patients remain symptomatic despite available medical and surgical treatment options, the Applicant proposes OPN-375 as an alternative therapy to address an unmet need in this population.

2.1 Product Information

The proposed drug product, OPN-375, is a drug-device combination containing the active ingredient fluticasone propionate. Fluticasone propionate is a synthetic corticosteroid ($C_{25}H_{31}F_3O_5S$) with a molecular weight of 500.57 grams per mole that exists as a white or almost white (b) (4) powder. The drug product is a white milky suspension of fluticasone propionate at a pH of approximately (b) (4). The drug product contains the following excipients: polysorbate 80, microcrystalline cellulose and carboxymethylcellulose sodium, benzalkonium chloride, EDTA disodium dihydrate, dextrose, (b) (4)

[2] Newton, JR and K Ah-See, 2008, Ther Clin Risk Manag, A Review of nasal polyposis, 4(2): 507-512.
[3] Hedman J, Kaprio J, Poussa T, et al. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol. 1999;28:717–22.
[4] Tan et al, 2013, Incidence and associated pre-morbid diangoses of patients with chronic hrinosinusitis, J Allergy Clin Immunol, 131:1350-1360.
[5] Fokkens W, Lund V, Mullol J. European Position Paper on Rhinosinusitis and Nasal Polyps Group. EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007. A summary for otorhinolaryngologists. Rhinology. 2007;45:97–101.

The drug product incorporates a novel, non-pressurized, metered, nasal spray pump to facilitate drug delivery to the appropriate anatomic location in the nasal cavity. A single (b) (4) actuation contains 93-mcg of fluticasone propionate. One actuation per nostril twice daily delivers the recommended starting dosage of 186-mcg BID. Two actuations per nostril twice daily deliver the maximum recommended dosage of 372-mcg BID.

The Applicant submitted a request for proprietary name review for the name "Xhance." The proprietary review is ongoing at the time of this review.

2.2 Tables of Currently Available Treatments for Proposed Indications

There is a single FDA approved intranasal corticosteroid for treatment of nasal polyps in adults 18 year and older (Table 1).

Table 1. FDA approved drugs for treatment of nasal polyps

Generic Name	Brand Name	Indication and Dosage
Mometasone furoate monohydrate	Nasonex Nasal Spray, 50 mcg	Treatment of nasal polyps in patients ≥18 years. 2 sprays in each nostril twice daily. 2 sprays in each nostril once daily may also be effective in some patients.

In addition, Beconase® AQ Nasal Spray (beclomethasone dipropionate monohydrate, 42-mcg) is approved for the prevention of recurrence of nasal polyps following surgical polyp removal in adults and children 12 years and older. The dosage in adults is 1 or 2 nasal inhalations (42-mcg or 84-mcg) to each nostril twice daily.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient fluticasone propionate is widely available in the United States and a component of multiple prescription (including generic) and over-the-counter formulations. Table 2 lists the currently approved NDA products containing the active ingredient fluticasone propionate.

Table 2. Approved NDA with active ingredient fluticasone propionate

Trade name (generic name)	NDA	Date	Formulation
Flonase® (fluticasone propionate)	020,121	10/19/1994	spray, metered
Flonase® Allergy Relief (fluticasone propionate)	205,434	7/23/2014	spray, metered
Advair® Diskus® (fluticasone propionate/salmeterol)	021,077	8/24/2000	powder for inhalation
Advair® HFA (fluticasone propionate/salmeterol)	021,254	6/08/2006	aerosol, metered
Flovent® (fluticasone propionate)	020,770	11/07/1997	powder for inhalation
Flovent® HFA (fluticasone propionate)	021,433	5/14/2004	aerosol, metered
Flovent® DISKUS® (fluticasone propionate)	020,833	9/29/2000	powder for inhalation
ArmonAir™ RespiClick® (fluticasone propionate)	208,798	1/27/2017	powder for inhalation

Trade name (generic name)	NDA	Date	Formulation
AirDuo™ RespiClick® (fluticasone propionate/salmeterol)	208,799	1/27/2017	powder for inhalation
Cutivate® (fluticasone propionate)	019,957	12/14/1990	ointment
	019,958	12/18/1990	emulsion, cream
	021,152	3/31/2005	emulsion, lotion
Dymista® (azelastine hydrochloride; fluticasone propionate)	202,236	5/1/2012	spray, metered

2.4 Important Safety Issues With Consideration to Related Drugs

While intranasal fluticasone propionate has low systemic bioavailability because of both limited systemic absorption and first pass metabolism, there is still the potential to produce systemic and local AEs. The following safety issues are listed on the labels of the approved intranasal and/or inhaled corticosteroids:

- Local nasal toxicities: epistaxis, nasal ulceration, nasal septal perforation, impaired wound healing, and *Candida albicans* infection
- Development of cataracts and glaucoma
- Immunosuppression
- Adrenal suppression
- Decreased growth in children

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant, OptiNose US, opened IND 110,089 for OPN-375 on July 18, 2012. The Applicant submitted NDA 209,022 on November 18, 2016, in support of OPN-375 for an indication of nasal polyps. The following section summarizes key regulatory interactions with the Applicant surrounding the nasal polyp development program.

Pre-IND Meeting: December 20, 2010

- Discussion of the 505(b)(2) pathway
- Must establish reliability, durability, and ruggedness of the to-be-marketed device
- Recommended selection of a single reference listed drug (RLD)
- Use highest OPN-375 to establish a pharmacokinetic (PK) bridge to the RLD
- Demonstrate local safety, systemic safety, and efficacy
- RLD may provide systemic safety if OPN-375 exposure levels ≤ RLD
- Long-term safety data of at least 1-year
- Dose-ranging needed with the to-be-marketed product

- Instantaneous symptom scores may help with dosing regimen
- Discussion of statistical approach for primary outcome variables
- Prospectively evaluate for nasal ulcerations, nasal perforation, and ocular toxicity
- Address missing data in the development program
- Justify that no drug exits the other nostril during drug delivery

SAP Review Comments for Trials 3101/3102: March 9, 2015, and April 10, 2015

- The Division and Applicant established agreement on the coprimary endpoints:
  - Reduction in a nasal polyp grading score evaluated at Week 16
  - 7-day average nasal congestion / obstruction symptoms at Week 4
- The Division requested additional analysis of 1st four weeks of nasal congestion.
- Full analysis dataset should not depend on post-treatment efficacy assessments.
- The Applicant should carefully document missing data and justify MAR assumption.
- The Division requested a tipping point multiple imputation analysis.

Pre-NDA Meeting: November 18, 2015

- Discussion of CMC, nonclinical and clinical content of submission
- Pending review of PK Study 1102, may use nonclinical information from RLD label and publically available information to support a 505(b)(2) NDA
- The Applicant may model the label after RLD label.
- Agreement to reference Flonase® and Flovent® HFA for clinical pharmacology (e.g. special populations, drug-interactions, HPA axis inhibition, and QT/QTc assessment)
- Agreement that size and duration of safety and efficacy databases, and clinical assessments are adequate for review for the planned NDA indication
- Pivotal safety and efficacy trials are OPN-FLU-NP-3101 and OPN-FLU-NP-3102
- Open-label safety studies are supportive of safety (b) (4)
- Agreement on approach for Integrated Summary of Safety, Integrated Summary of Efficacy and subgroup analysis
- Requested complete responder analysis for elimination of polyps
- A standard nasal polyp indication applies
- The dosage form is “nasal spray”
- Sinonasal Outcome Test-22 (SNOT-22) and patient global assessments (b) (4) , but may support efficacy

Agreed Initial Pediatric Study Plan: November 24, 2015

- Given rarity of pediatric nasal polyps, (b) (4) waiver for children <6 years of age and deferral in children and adolescents 6 to 17 years of age
- Two proposed studies part of Agreed Pediatric Study Plan (6 to 17 year olds):
  (1) (b) (4)
  (2) (b) (4) efficacy and safety study

2.6 Other Relevant Background Information

The Applicant does not market OPN-375 in any other country. There is no history of foreign regulatory actions on OPN-375.

In the United States, there are no fluticasone propionate drug products approved for the treatment of nasal polyps. Flonase® (intranasal fluticasone propionate) is FDA approved for the treatment of allergic rhinitis and nonallergic rhinitis in children and adults at a starting adult dose of 200-mcg once daily.

Flixonase® Nasule Drops (Glaxo Wellcome UK Limited) are approved in Europe for the treatment of mild to moderate nasal polyps and associated symptoms of nasal obstruction in patients 16 years of age and older at a total daily dosage of 400-mcg, divided between affected nostrils once or twice daily.

Reviewer comment: The proposed OPN-375 starting dosage (i.e. 186-mcg BID) provides a larger dose via a potentially more efficient delivery mechanism than Flonase®. The concentration of fluticasone propionate in Flixonase® (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant submitted NDA 209,022 on November 18, 2016. The electronic submission was appropriately indexed and complete to allow for review. The NDA included complete clinical study reports (CSRs), appropriate case report forms and proposed labeling. There were no issues with the submission quality or data integrity.

With the assistance of the statistical review team, the Division selected two foreign clinical sites for inspection because of high enrollment. The Division selected a Sponsor level inspection of OptiNose US Inc. because both pivotal trials involved a large number of sites with small subject enrollment at each site, and because the Applicant is a small, relatively unknown entity with whom we have no significant experience. Table 3 lists the sites inspected.

Table 3. OSI inspection sites

Site # (Name, Address, Phone number, email, fax #)		Protocol ID	# Subjects
Site: 203 Pavel Navratil, MD Hospital Prostejov Otorhinolaryngology Department Mathonova 291/1 779 04 Prostejov Czech Republic	Ph: 00420 608 221 103 Fax: 00420 585 227 620 Email: ordinace@seznam.cz	OPN-flu-np-3101	25
Site: 407 Silviu Albu, MD Hospital CF Cluj Napoca 16-18 Republicia 400015 Cluj Napoca Romania	Ph: 40.74.121.7301 Fax: 40.26.459.8278 Email (b) (6)	OPN-flu-np-3102	24
OptiNose US, Inc. Ramona M Lloyd, PhD, RAC 1020 Stony Hill Road, Suite 300 Yardley, PA 19067	Ph: 267-364-3519 fax(main):267-395-2119 Email: ramona.lloyd@optinose.com	Sponsor Level Inspection	

The clinical inspection (CI) determined that the two clinical sites and the Applicant are considered reliable in support of the requested indication. The CI recommended Voluntary Action Indicated for the Sponsor and No Action Indicated for Drs. Navratil and Albu.

3.2 Compliance with Good Clinical Practices

The Applicant conducted the phase 3 clinical trials in accordance with Good Clinical Practices [Module 5, Section 5.3.5.1. and Section 5.3.5.2]. The Applicant certified that they did not use and would not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with their application [Module 1, Volume 1.3, Section 1.3.3, page 1].

3.3 Financial Disclosures

The Applicant attested to compliance with the Final Rule on Financial Disclosure by Clinical Investigators. With respect to OPN-FLU-NP-3101 and OPN-FLU-NP-3102, the Applicant certified that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a), that no investigator received significant payments as defined in 21 CFR 54.2(f), that none of the investigators disclosed a proprietary interest in the product, or possessed a significant equity interest in the Applicant as defined in 21 CFR 54.2(b) [Module 1, Volume 1.3, Section 1.3.4, page 1].

Application Number: NDA 209,022

Submission Date(s): November 18, 2016

Applicant: OptiNose, US

Product: Xhance, fluticasone propionate nasal spray (OPN-375)

Reviewer: Courtney S. McGuire

Date of Review: April 27, 2017

Covered Clinical Study (Name and/or Number): OPN-FLU-NP-3101 and OPN-FLU-NP-3102

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 92		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

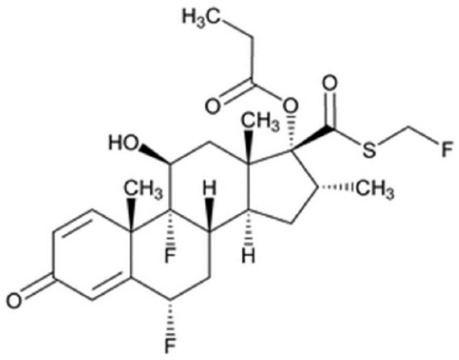
4.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Controls (CMC) review team recommends Approval pending response from the Office of Process and Facilities. For more details, see the CMC review written by Dr. Caroline Strasinger.

Drug Substance

Fluticasone propionate, S-(fluoromethyl)6α, 9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate, exists as a white or almost white (b) (4) powder. The molecular formula is $C_{25}H_{31}F_3O_5S$ and molecular weight is 500.57 grams per mole. The structure of fluticasone propionate appears in Figure 1.

Figure 1. Structure of fluticasone propionate



The drug substance is manufactured by (b) (4)

Drug Product

The drug product is an aqueous, milky white suspension of fluticasone propionate delivered by a non-pressurized, multi-dose nasal spray device (Figure 2).

Figure 2. View of fully assembled OPN-375 (without cap)

Source: Drug Product Summary. Figure 2.3.P-1

Each (b) (4) spray delivers an actual dose of 93-mcg fluticasone propionate ((b) (4)).[6] After priming, each OPN-375 device delivers 120 sprays. Table 4 lists the active ingredients and all excipients of the proposed drug product.

Table 4. Active ingredients and excipients in OPN-375

Component	Function	Concentration (%w/w)	Amount per Spray (mcg)	Amount per Vial (mg)
Fluticasone propionate	Drug substance	(b) (4)	93	(b) (4)
Polysorbate 80[a]	(b) (4			(b) (4)
Microcrystalline cellulose and carboxymethylcellulose sodium[b]				
Benzalkonium chloride		0.02		
EDTA disodium, dihydrate		(b) (4		
Dextrose				
(b) (4)				
Purified water				
(b) (4)				

[a] Tradename (b) (4).
[b] Tradename (b) (4)
Source. NDA 209,022, Module 2, Volume 2.3, Section 2.3.P, Table 2.3.P-1 From Quality Product Summary.

The Applicant describes the device as a BiDirectional Breath Powdered Exhalation Delivery System (EDS) that facilitates drug delivery to the target regions of the nasal mucosa and reduces anterior and posterior drip-out. The Applicant completed Human Factors Validation Testing with OPN-375, which was reviewed by DMEPA. DMEPA recommends Approval.

Reviewer comment: While the Applicant completed three phase 1 clinical studies with an earlier version of the delivery device (i.e. OptiNose RFCP), the to-be-marketed drug product remained unchanged throughout the Phase 3 trials. From a regulatory perspective, the dosage form is a "nasal spray."

4.2 Clinical Microbiology

[6] For purposes of this document, all doses will be referred to in terms of the actual delivered dose rather than nominal dose.

For a complete review of clinical microbiology studies submitted in support of NDA 209,022, see CMC review written by Dr. Caroline Strasinger.

The drug product contains dextrose, and includes benzalkonium chloride (BKC) and EDTA to (b) (4). The level of BKC is monitored at release and on stability to be (b) (4)% to (b) (4)% of label claim, a level acceptable to support (b) (4) The level of EDTA is monitored at release and on stability to be (b) (4)- (b) (4)% of label claim. Release and stability testing of OPN-375 includes microbial testing per USP<61> and USP <62> for specific organisms.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical team recommends Approval. The Applicant cross-references the development program for Flonase® (NDA 020,121) and Flovent® HFA (NDA 021,433) in support of the local and systemic nonclinical toxicities. No new nonclinical pharmacology or toxicology data was submitted or required for this development program. See the nonclinical review written by Dr. Brett Jones for more details.

4.4 Clinical Pharmacology

The clinical pharmacology reviewer recommends Approval. The clinical pharmacology program included a single study, OPN-FLU-1102, in support of OPN-375. The details of Study OPN-FLU-1102 are discussed further in Section 4.4.3. For a complete review of the clinical pharmacology data, see the review written by Dr. Mohammad Absar.

4.4.1 Mechanism of Action

While the exact mechanism of action of corticosteroids in the treatment of nasal polyps is incompletely understood, in general, the efficacy with corticosteroids is thought to be attributable to anti-inflammatory effects. The OPN-375 delivery system facilitates delivery of drug product to the intended site of action. The device is discussed in more detail in Section 4.1.

4.4.2 Pharmacodynamics

The Applicant conducted no new pharmacodynamic studies.

4.4.3 Pharmacokinetics

The Applicant completed Study 1102 in order to compare system exposures of OPN-375 to Flovent® HFA and Flonase® Nasal Spray (Table 5).

Table 5. Clinical pharmacology, Study 1102

Study number (time, month/year)	Study type	Design	Treatment arms	n	Population
1102 Part 1 (11/13 to 2/14)	Comparative bioavailability	2-part, R, OL, SD, crossover study under fasting conditions 1 U.S. center	Part 1: • OPN-375 186-mcg • OPN-375 372-mcg • Flonase® 400-mcg	90	M or F, healthy volunteers, 18 to 55 years
Part 2 (10/14 to 4/15)			Part 2: • OPN-375 372 mcg • Flovent® HFA 440-mcg	30	M or F, mild to moderate asthma, 18 to 55 years

R=randomized; OL= open-label; SD= single dose; M= male; F=female.
Source: NDA 209,022 Module 5, Section 5.3.1.2.

Study Overview

Study 1102 was a phase 1, 2-part adaptive design, randomized, open-label, single-dose bioavailability study under fasting conditions designed to compare the bioavailability of OPN-375 with both Flonase® and Flovent® HFA. Part 1 was a 3-way crossover, 3-treatment, 3-sequence study. The study randomized 90 adult healthy volunteers (1:1:1) to receive single doses of 186-mcg OPN-375, 372-mcg OPN-375 or 372-mcg Flonase®. Part 2 was a 2-way crossover, 2-treatment, 2-sequence study that randomized 30 healthy volunteers (1:1) to receive single doses of either 372-mcg OPN-375 or 440-mcg Flovent® HFA. Investigators collected serial PK samples pre- and post-dose for up to 24 hours (Part 1) and 36 hours (Part 2). Safety evaluation included clinical laboratory tests, physical examination (PE), vital signs (VS), 12-lead electrocardiograms (ECGs) and AEs.

Pharmacokinetic analysis

The PK analysis in Parts 1 and 2 compared each dose of OPN-375 to the respective reference drug product. The primary PK parameters were C_{max} and total exposure measured as both the AUC from zero to the time of last quantifiable concentration (AUC_{0-t}) and AUC from zero to infinity ($AUC_{0-\infty}$). The Applicant summarized the parameters using descriptive statistics, geometric mean, and geometric coefficient of variation. The Applicant compared the upper limit of the 90 percent confidence interval (CI) for geometric mean ratio of PK parameters (i.e. 125.00 percent) in order to establish an appropriate reference listed drug (RLD).

Pharmacokinetic Results

The upper limits of the CIs for all three OPN-375 PK parameters fell below the upper limits of the CIs for the corresponding Flovent® HFA PK parameters only (Table 6).

Table 6. Summary of PK data for BE in fasting state, Study 1102

PK parameter	% GLSM ratio	90% CI
OPN-375 2x93-mcg/Flonase® 400-mcg		
C_{max} (pg/mL)	137.1	126.8, 148.1
AUC_t (pg.h/mL)	101.8	93.3, 111.2
AUC_∞ (pg.h/mL)	94.4	83.4, 106.8
OPN-375 4x93-mcg/Flonase® 400-mcg		
C_{max} (pg/mL)	201.7	186.7, 218.0
AUC_t (pg.h/mL)	159.8	146.4, 174.4
AUC_∞ (pg.h/mL)	144.6	128.1, 163.3
OPN-375 4x93-mcg/Flovent® HFA 2x220-mcg		
C_{max} (pg/mL)	63.2	50.6, 78.8
AUC_t (pg.h/mL)	49.2	40.0, 60.6
AUC_∞ (pg.h/mL)	49.9	41.0, 60.7
GLSM = geometric least squares mean based on log-transformed parameters. Source: NDA 209,022 Module 2.7.1. Data analysis from Clinical Pharmacology Review by Dr. Mohammad Absar.		

Reviewer's comments: Even at low doses, the OPN-375 exposure was substantially greater than the standard basal spray fluticasone product , Flonase® nasal spray, so the Applicant relied on the inhalational product for asthma, Flovent®, for systemic safety. The Applicant sufficiently demonstrated the systemic exposure of OPN-375 at the highest dose is below the prespecified bioequivalence margin for Flovent® HFA 2x220-mcg, establishing Flovent as an appropriate RLD for systemic safety, including HPA axis data. Detailed PK data analysis can be found in the clinical pharmacology review by Dr. Mohammad Absar.

5 Sources of Clinical Data

The following section summarizes the clinical data submitted in support of this Application, including a table of studies/clinical trials (Section 5.1), an outline of the review strategy (Section 5.2), and descriptions of the phase 3 trials (Section 5.3).

5.1 Tables of Studies/Clinical Trials

Table 7. Studies and clinical trials submitted to NDA 209,022

Study #, Design and Dates*	Dose & Duration	#	Population	Objectives	Relevance
OPN-375					
OPN-FLU-1102 2-part, BA, OL, R, SD, crossover	186-mcg x1 372-mcg x1	120	HV and Asthma Sites: U.S. and Ireland	PK Safety	PK Bridge

Study #, Design and Dates*	Dose & Duration	#	Population	Objectives	Relevance
OPN-FLU-NP-3101 DR, R, DB, PC, PG, MC trial *(11/13 to 10/15)*	93-mcg BID 186-mcg BID 372-mcg BID PBO D: 16 weeks	81 80 80 82	Bilateral NP and moderate nasal congestion / obstruction, ages ≥18 years Sites: U.S., Canada, CR, Ukraine, UK, South Africa	Safety, Efficacy	Pivotal trial Dose-ranging, Safety
	OLE: 372-mcg BID D: 8 weeks	282			
OPN-FLU-NP-3102 DR, R, DB, PC, PG, MC trial *(10/13 to 7/15)*	93-mcg BID 186-mcg BID 372-mcg BID PBO D: 16 weeks	81 80 82 80	Bilateral NP and moderate nasal congestion / obstruction, ages ≥18 years Sites: U.S., Poland, Romania, Ukraine, South Africa	Safety, Efficacy	Pivotal trial Dose-ranging, Safety
	OLE: 372-mcg BID D: 8 weeks	299			
OPN-FLU-CS-3203 OL, MC trial *(9/13 to 8/15)*	372-mcg BID D: 12 months	223	Chronic sinusitis with and without NP, ages ≥18 years Sites: U.S.	Long-term safety	Long-term exposure
OPN-FLU-CS-3204 OL, MC trial *(10/13 to 2/15)*	372-mcg BID D: 3 months	705	Chronic sinusitis with and without NP, ages ≥18 years Sites: U.S.	Long-term safety	Long-term exposure
OPTINOSE-RFCP					
RFCP-PRO001 OL, R study *(8/06 to 10/06)*	400-mcg BID 800-mcg BID D: 7-days	41	HV, ages ≥18 years Site: UK	Safety, PK	Safety
RFCP-PRO002 DB, R, PG, PC study *(5/7 to 10/7)*	400-mcg BID PBO D: 12 weeks	109	Bilateral NP (grade 1/2 each nasal cavity), ages ≥18 years Site: CR	Safety, Efficacy	Safety
RFCP-PRO003 DB, R, PG, PC study *(9/7 to 9/8)*	400-mcg BID PBO D: 12 weeks	20	Chronic rhinosinusitis, ages ≥18 years Site: The Netherlands	Safety, Efficacy	Safety

D=duration; BID=twice daily; PK= pharmacokinetics; DR=dose-ranging, OL=open-label, MC=multicenter, R=randomized, DB=double-blind, PG=parallel group, PC=placebo-controlled, HV= healthy volunteer; DBP=double-blind period, OLE= open-label extension; CR=Czech republic; UK= united kingdom.
*date range presented as month/year.
Source. Summary of Clinical Safety, Table 2.7.4-69 and Table 2.7.4-70.

5.2 Review Strategy

The primary review of efficacy and safety examines two similarly designed phase 3 trials. Trials 3101 and 3102 were randomized, double-blinded, placebo-controlled, parallel-group, multicenter, dose-ranging studies evaluating the efficacy and safety of 93-mcg, 186-mcg, and 372-mcg OPN-375 twice daily compared to placebo for a period of 16-weeks. Section 5 reviews the protocols for each trial, and Sections 6 and 7 examine the efficacy and safety results, respectively. This review discusses the efficacy findings for each trial separately in order to demonstrate replicate evidence of treatment benefit for OPN-375 in nasal polyps. The safety review analyzes the pooled safety population from Trials 3101 and 3102, with particular attention on expected class effects and dose-dependency of AEs. Note that these trials included limited exploration of systemic safety, as the Applicant relies on the RLD, Flovent® HFA (NDA 021,433), to support the systemic safety of OPN-375, including drug-drug interactions, QT interaction, HPA axis and growth data.

This review examines two uncontrolled trials, Trials 3203 and 3204, to support the long-term safety of OPN-375. The trials evaluated 372-mcg OPN-375 twice daily for 12 months and 3 months duration, respectively, in a population with chronic sinusitis with and without nasal polyps. As both trials lacked a comparator group and included a population outside of the proposed indication, this review primarily uses these trials to evaluate of the time-dependence of AEs and support the long-term safety of OPN-375. Section 5.3 briefly summarizes the protocols, and Section 7 discusses relevant safety findings.

This review considers the following additional information in support of the safety profile of OPN-375. Section 9.1 contains a review of literature articles submitted by the Applicant. The literature review does not change the conclusions reached based on review of the phase 3 program. Section 7.7 includes a high-level safety summary of the OptiNose-RFCP studies. As these studies investigated a different drug product, they only offer minimal support for the safety profile.

Reviewer comment: During the pre-NDA meeting in November 18, 2015, the Division concluded that the database was adequate for filing this NDA, but noted that safety and efficacy determinations, assessment of appropriate dose, and analysis of data would be review issues. The Applicant submitted a responder analysis for complete resolution of polyps as requested by the Division.

5.3 Discussion of Individual Studies/Clinical Trials

This Section discusses the Trial 3101 in greatest detail, and Trial 3102 with a focus on protocol differences. Finally, the review includes a brief description of Trials 3203 and 3204, as these studies contribute to the long-term safety profile of OPN-375.

Trial OPN-FLU-NP-3101	
Title	A 16-Week Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 93, 186, and 372-mcg of Fluticasone Propionate Twice a Day (BID) Using a Novel Bi-directional Device in Subjects with Bilateral Nasal Polyposis Followed by an 8-week Open-label Extension Phase to Assess Safety
Trial dates	Initiated: November 19, 2013 Completed: August 6, 2015 (double-blind period) October 1, 2015 (open-label extension) Final CSR: April 29, 2016
Countries (# of Centers)	54 centers in 6 countries (2 in Canada, 7 in the Czech Republic, 6 in South Africa, 5 in Ukraine, 6 in the United Kingdom, and 28 in the United States).

The Applicant submitted 5 amendments to the initial protocol dated November 2, 2011. As the initial enrollment of subjects occurred after implementation of amendments 4 (March 7, 2013) and 5 (December 18, 2013), this following protocol summary reflects all protocol amendments.

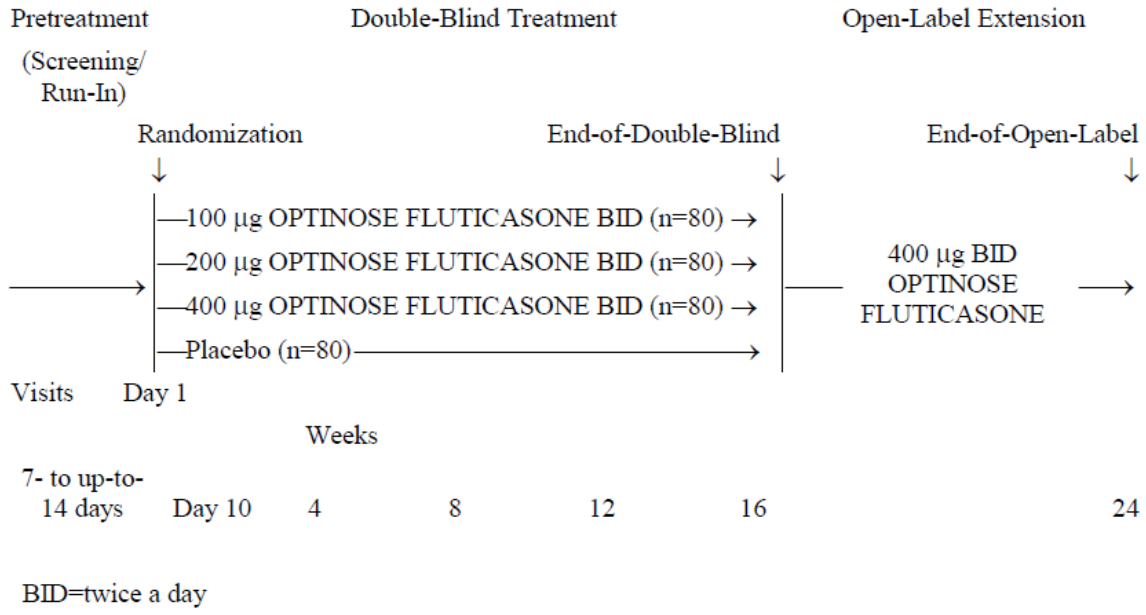
Objectives

- *Primary*: to compare the efficacy of three doses of intranasal OPN-375 with placebo in adults with bilateral nasal polyps as determined by both a reduction of nasal congestion / obstruction and bilateral polyp grade.
- *Secondary*: to compare other measures of efficacy including subject-reported outcomes, sleep quality, nasal patency, rescue medication use, and asthma.
- *Additional*: to identify the safety profile of OPN-375.

Trial Design

Trial 3101 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial in adult subjects with bilateral nasal polyps and nasal congestion evaluating 3 doses of OPN-375 (93-mcg BID, 186-mcg BID, and 372-mcg BID). After providing informed consent, subjects meeting eligibility requirements entered a 7 to 14 day single-blind placebo run-in period to establish disease severity and compliance. Investigators then randomized eligible subjects into 1 of 4 treatment arms (1:1:1:1) for a 16-week double-blind period (DBP). Clinic visits occurred every 4-weeks during the DBP for safety and efficacy assessments. Upon completion of the DBP, subjects received OPN-375 372-mcg BID in an 8-week open-label extension (OLE). There was one scheduled visit for final follow-up at Week 24 (Figure 3).

Figure 3. Trial 3101 flow diagram



Source: NDA 209,022, Module 5, CSR OPN-FLU-NP-3101, Figure 2.

Subject Population

A minimum of 320 subjects were to be randomized in the trial.

Key Inclusion Criteria

1. Males or females aged 18 and older
2. Women if effective birth control, surgically sterile or postmenopausal
3. Negative serum beta-human chorionic gonadotropin test at Visit 1
4. Bilateral nasal polyps grade 1 to 3 in each nasal cavity measured by nasoendoscopy at screening and baseline
5. At least moderate symptoms of nasal congestion/obstruction on average for 7-day period preceding screening
6. At Day 1 (baseline), moderate morning nasal congestion/obstruction on subject diary (≥2 score) for ≥5 of the last 7-days of the run-in period
7. Ability to correctly complete the daily diary during the run-in period
8. Subjects with asthma or COPD if stable without exacerbations within the preceding 3-months and inhaled corticosteroids (ICS) equivalent to ≤1,000 mcg/day of beclomethasone for ≥3 months with plans to continue
9. Ability to stop treatment with intranasal medications, ICS (except permitted doses), oral/nasal decongestants and antihistamines at Visit 1 (screening)

10. Ability to use OPN-375 correctly at Visit 1 (screening)

Key Exclusion Criteria

1. Complete or near-complete obstruction of nasal cavities
2. Inability to achieve bilateral nasal airflow for any reason
3. Inability to have each nasal cavity examined for any reason
4. Nasal septum perforation
5. ≥1 episode of epistaxis with frank bleeding in the month before screening visit
6. Evidence of significant mucosal injury, ulceration, or erosion (e.g. exposed cartilage, perforation) on nasal nasoendoscopy at screening (Visit 1)
7. History of ≥5 sinonasal surgeries for nasal polyps or nasal and/or sinus inflammation
8. History of sinus or nasal surgery within 6 months before screening (Visit 1)
9. History of any surgical procedure that prevents the ability to accurately grade polyps
10. Planned sinonasal surgery during the period of the trial
11. Symptoms of seasonal allergic rhinitis at screening, baseline and/or, based on time of year, symptoms anticipated within 4-weeks of randomization
12. Nasal candidiasis
13. Current, ongoing rhinitis medicamentosa (rebound rhinitis)
14. Significant oral structural abnormalities such as cleft palate
15. Diagnosis of cystic fibrosis, Churg–Strauss, or dyskinetic ciliary syndromes
16. Purulent nasal infection, acute sinusitis, or upper respiratory tract infection within 2 weeks before screening (Visit 1)
17. History or current diagnosis of glaucoma or ocular hypertension (intraocular pressure [IOP] >21 mmHg)
18. History of increased IOP on any form of steroid therapy
19. Presence ≥grade 1 cataract per eye examination worksheet or <grade 1 cataract with visual impairment
20. Women pregnant or lactating
21. Glucocorticoid treatment with potential systemic effects within 1-month of screening (Visit 1)
22. Use of potent P450 3A54 (CYP3A4) inhibitor within 14-days of screening (Visit 1)
23. Any serious or unstable concurrent disease, psychiatric disorder, or condition that could interfere with participation or compliance in the trial
24. Allergy, hypersensitivity, or contraindication to corticosteroids

Reviewer Comment: The defined population appears acceptable for the intended indication. Note that the trial excluded subjects at higher risk for local toxicities from intranasal corticosteroid use, including but not limited to history of recent nasal surgery, multiple nasal surgeries, epistaxis and nasal septal perforation. The trials did not evaluate special populations such as cystic fibrosis.

Concomitant Medications

Table 8. Allowed and prohibited concomitant medications

Permitted	• Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDS) for analgesia • Aspirin for cardiovascular prophylaxis • Antibiotic medications for bacterial infections developing during the trial • Prophylactic antibiotics if intended to be taken for trial duration • Intranasal saline spray except within 2 hr before or after investigational drug • Saline lavage if already in use at trial entry, but no initiation during the trial or changes • Leukotriene receptor antagonists, beta-blockers and neuroleptics if stable doses • Low to medium strength topical corticosteroids for dermatologic purposes • Inhaled corticosteroids for asthma or chronic obstructive pulmonary disease (COPD) if stable doses day for ≥3 months equal to ≤ 1,000 mcg beclomethasone or equivalent • After Week 4 visit, OTC loratadine (10 mg per day) or equivalent as rescue medication
Prohibited*	• Intranasal medications • Inhaled ipratropium bromide • Corticosteroids • Oral, ocular, nasal antihistamines/decongestants (except nasal endoscopic procedure) • Topical, oral, or ocular anti-inflammatory drugs • Topical, oral, or ocular anti-fungal medication • Medications known to cause nasal congestion or rhinorrhea unless taking stable doses for 1 month before screening and intended to continue during trial • Potent CYP3A4 inhibitors within 14 days of screening and throughout the trial
*Except for allowed specific medications noted above	

Reviewer comment. After Week 4, it is reasonable and ethical to offer subjects rescue treatment for nasal congestion. Note that the concomitant use of other intranasal medications was not allowed in these studies beyond saline.

Treatments

The treatment arms for the DBP were:

- 93-mcg OPN-375 BID (186-mcg daily)
- 186-mcg OPN-375 BID (372-mcg daily)
- 372-mcg OPN-375 BID (744-mcg daily)
- Matching placebo BID

Each subject received Bottles “1” and “2” that each contained either placebo, 25 mcg per actuation (nominal) of OPN-375, or 93-mcg per actuation OPN-375. Investigators

instructed subjects to prime the medication prior to first administration, and shake before administration thereafter. Subjects self-administered 1-spray per nostril of bottle "1", followed by 1-spray per nostril of bottle "2" every 12-hours according to Table 9.

Table 9. Investigational drug dosing during double-blind period

	93-mcg BID				186-mcg BID				372-mcg BID				Placebo BID			
Time	**AM**		**PM**		**AM**		**PM**		**AM**		**PM**		**AM**		**PM**	
Bottle	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
Left nostril	25*	25	25	25	PB	93**	PB	93	93	93	93	93	PB	PB	PB	PB
Right nostril	25	25	25	25	PB	93	PB	93	93	93	93	93	PB	PB	PB	PB

PB = placebo. All doses in micrograms.
*Nominal dose, **Actual dose
Source: NDA 209,022, Module 5.3.5.1 OPN-Flu-NP-3101 CSR, Table 1.

During the OLE, each subject received a single 93-mcg bottle of OPN-375 and administered 2 sprays to each nostril twice daily (i.e. 372-mcg BID).

If a subject missed a dose, they were instructed to take the medication as soon as remembered, but not within 2 hours of the next scheduled dose. The investigators monitored compliance through visual examination of devices (i.e. remaining volume) at baseline, DBP visits, and the conclusion of the OLE.

Efficacy Variables

Nasal symptoms

Subjects recorded instantaneous and reflective nasal symptoms in electronic diaries every 12-hours throughout the run-in period and DBP. Instantaneous symptoms assessed symptoms immediately preceding the dose, while reflective symptoms assessed symptoms over the previous 12-hours. The electronic diaries transmitted subject-entered data to center staff on a daily basis, and investigators scored responses from 0 to 3 according to Table 10.

Table 10. Nasal symptom scale

Score	Description
General Symptoms (nasal congestion/obstruction, rhinorrhea, facial pain)	
0	None
1	Mild: symptoms clearly present, but minimal awareness, and easily tolerated
2	Moderate: definite awareness of symptoms that is bothersome but tolerable
3	Severe: symptoms that are hard to tolerate, cause interference with activities or daily living
Sense of smell	
0	Normal
1	Slight impaired

2	Moderately impaired
3	Absent

Nasal Polyp Grade

Nasoendoscopy with polyp grading of each nasal cavity occurred at screening (baseline) and Weeks 4, 8, 12, 16 (end of DBP or early termination [ET]) and 24 (end of OLE or ET). If the nasoendoscopy assessments could not be formed at the specified trial visit, they were performed within a 3-day window around the trial day. When multiple assessments fell on the same day, investigators performed nasoendoscopy and nasal examination before other trial procedures.

Nasal endoscopists (i.e. otolaryngologists) used a flexible or rigid endoscope for examination, with the same size and type of scope to be used for each individual during the trial. The protocol permitted use of decongestants and/or local anesthetics for each individual subject if used consistently. Where possible the same physician examined the subject. Investigators were instructed to visualize the middle meatus, answer targeted questions on the nasal exam worksheet, and draw a pictorial representation of the subject's nasal polyps to aide polyp grading and localization (Table 11).

Table 11. Nasal polyp grading scale

Score	Description
0	No polyps
1	Mild polyps: polyps not reaching below the inferior border of the middle turbinate
2	Moderate polyps: polyps reaching below the inferior border of the middle concha, but not the inferior border of the inferior turbinate
3	Severe polyps large polyps reaching below the lower inferior border of the inferior turbinate

Sinonasal Outcome Test-22

Subjects completed the SNOT-22 at baseline, Week 4, 8, 12, 16 (end of DBP / or ET), and 24 (end of OLE or ET) visits. The SNOT-22 is a subject-completed questionnaire assessing 22 symptoms and social/emotional consequences of their nasal disorder with a recall period of 2-weeks. The 22 questions are divided into 4 subscales: Rhinologic subscale (7 questions), Sleep Function subscale (3 questions), Ear and Facial subscale (4 questions) and Psychological Issues subscale (6 questions). Investigators score questions on a 5-point scale, and the total score is the sum of all questions (Table 12). Only 20 of 22 items were used for the subscales, excluding "cough" and "wake up tired."

Table 12. Sinonasal outcome test-22 scale

Score	Description
0	No problem
1	Very mild problem

Score	Description
2	Mild or slight problem
3	Moderate problem
4	Severe problem
5	Problem as bad as it can be

Peak Nasal Inspiratory Flow

Peak nasal inspiratory flow (PNIF) measured nasal patency at screening, baseline (Day 1), Week 4, 8, 12, 16 (end of DBP or ET), and 24 (end of OLE or ET) visits. Investigators measured PNIF using an In-Check portable nasal inspiratory flow meter (Clement Clarke International Ltd, Harlow, Essex, UK). The mask was placed over the nose and the subject inhaled while the inspiratory flow was recorded. The investigators completed the measurements 3 times, and recorded the highest value in the CRF.

Patient Global Impression of Change

Investigators assessed the Patient Global Impression of Change (PGIC) at Week 4, 16 (end of DBP), and 24 (end of OLE or ET) visits. The assessment involved asking subjects the following question: "Since starting the investigational drug, how would you rate the change in your symptoms." Subjects answer the question using a 7-point scale where 1 is very much improved, 4 is no change and 7 is very much worse.

Medical Outcomes Study Sleep Scale-Revised

The investigators completed the Medical Outcomes Study Sleep Scale-Revised (MOS Sleep-R) at baseline, Week 4, 8, 12, and 16 (end of DBP or ET). MOS Sleep-R is a brief, self-administered, 12-item questionnaire with a 4-week recall that measures various aspects of sleep (disturbance, adequacy, somnolence, and quantity). Scores range from 12 to 71, yielding a Sleep Problem Index that incorporates the following 6 subscales: Sleep Disturbance, Snoring, Shortness of Breath or Headache, Sleep Adequacy, Sleep Somnolence, and Sleep Quantity.

Rhinosinusitis Disability Index

Investigators measured the Rhinosinusitis Disability Index (RSDI) at baseline (Day 1) and Week 16 (end of DBP or ET). The RSDI measures self-perceived impact of disease specific to head and neck disorders across 3 domains (Physical, Functional, and Emotional), that are rated on a 5-point Likert Scale ranging from never (score=0) to always (score=4). The total score reflects the sum of all domains.

Rescue Medication Use

The investigators collected use of rescue medications in electronic diaries. Subjects answered yes or no to the use of rescue mediation for nasal symptoms.

Health Economic Assessments

The investigators completed health economic assessments by collecting information on missed work/school days, and evaluating surgical eligibility at screening, Week 16, and Week 24 (or ET). The evaluation for surgical eligibility included three criteria:

1. At least moderate nasal congestion for ≥3 months
2. Moderate symptoms despite use of conventional dose of topical intranasal steroids and saline lavage for at least 6-weeks
3. Bilateral polyps with at least 1 side being of moderate severity (grade 2).

Short Form-36 Health Survey Version 2

Subjects completed the Short Form-36 Health Survey version 2 (SF-36v2) at baseline (Day 1), end of the DBP (Week 16), and end of the OLE. The SF-36v2 is a 36-item, subject completed questionnaire that measures 8 domains of health:

1. Limitations in physical activities because of health problems
2. Limitations in social activities because of physical or emotional problems
3. Limitations in usual role activities because of physical health problems
4. Bodily pain
5. General mental health (psychological distress and well-being)
6. Limitations in usual role activities because of emotional problems
7. Vitality (energy and fatigue)
8. General health perceptions

Each question is scored on a 5-point scale where higher scores indicate a higher physical well-being. The Investigator calculates a score for each domain and summary measures for physical and emotional health. While the protocol stated that the 7-day recall would be use, the standard 4-week recall form was actually used.

Pulmonary Function Tests

The investigators measured FEV1 for asthma subjects at baseline (Day 1), Week 4, 8, 12, 16 (end of DBP), and 24 (end of OLE), or ET visits. Pulmonary function tests were performed three times and all measurements recorded in the CRF. The average of the 3 values was used for analysis.

Reviewer comment. While the protocol does not state whether spirometry was performed per ATS standards, FEV1 is only incorporated into exploratory endpoints.

Asthma Control Test

Investigators administered the Asthma Control Test (ACT) to asthma subjects at baseline (Day 1), Week 4, 8, 12, 16 (end of DBP), and 24 (end of OLE), or ET visits. ACT is a 5-item, self-rated, questionnaire aimed at identifying poor asthma control over the last 4-weeks with each item scored from 1 to 5.

Efficacy Endpoints

The two coprimary endpoints were:

1. Mean change from baseline in nasal congestion/obstruction over the 7-days of the DBP just prior to the Week 4 visit

   Nasal congestion/obstruction was defined as the change from baseline in instantaneous morning diary symptom score averaged over 7-days (ADS7-IA) prior to the Week 4 visit of the DBP. Baseline was the average score over the last 7-days of the run-in period immediately prior to Visit 2, Day 1.

2. Mean change from baseline over the 16-week treatment period in total polyp grade

   The total nasal polyp grade is defined as the sum of scores from both nasal cavities measured by nasoendoscopy at Week 16 using a 0 to 6-point severity grading scale (with 0 to 3-points per nostril). Visit 1(screening) was baseline.

The two key secondary efficacy endpoints included:

1. Mean change from baseline to Week 16 in SNOT-22 total score
2. Mean change in the Sleep Disturbance score of the MOS Sleep-R at Week 16

Other Secondary Efficacy Endpoints:

- Mean change from baseline to Week 4, 8, 12, 16, end of DBP, Week 24, and end OLE in polyp grade (total and worst nostril)
- Mean change from baseline to Week 4, 8, 12, 16, and end of DBP in:
  - 7-day average nasal symptom scores for nasal congestion / obstruction, sense of smell, rhinorrhea, and facial pain or pressure
  - SNOT-22 total and nasal symptom-related items scores (also calculated at Week 24/end of OLE)
- PNIF
- For subjects with comorbid asthma, ACT total score and FEV1
- Average monthly use of rescue medication in the DBP after Week 4
- Proportion of subjects with reductions in the nasal symptom scores by ≥ 0.5 points from baseline to end DBP
- Proportion of subjects with ≥1 point reduction in the total polyp grade from baseline to the end of DBP

- Mean change from baseline to end DBP in RSDI total score
- Mean change from baseline to end DBP SF-36v2 scores (also end of OLE)
- Mean change from baseline to Week 4, 8, 12, 16, and end DBP in MOS Sleep-R
- Comparison of health economic measures during the DBP and OLE
- Summary of subject evaluation of current/most recent nasal spray at screening and subject evaluation of investigational drug during DBP and OLE
- Summary of PGIC scores at Week 4, 16, and 24

Reviewer comment. While the nasal polyp grade provides the most objective measurement of improvement in nasal polyps, both coprimary endpoints are acceptable, validated measures that together support a nasal polyp indication. Both key secondary efficacy variables are nonspecific. While they may support general symptom improvement, the Division does not consider these endpoints validated for a nasal polyp indication.

Statistical Plan

The safety analysis set (SAS) was defined as all subjects whom received at least 1 dose of investigational drug. The full analysis set (FAS) was defined as all subjects in the SAS that had baseline assessments of polyp size and recorded morning nasal congestion/obstruction symptoms. The Applicant performed efficacy analyses using subjects in the FAS. The treatment group was classified per randomization assignment.

Analysis of the morning nasal congestion/obstruction score coprimary endpoint used an analysis of covariance (ANCOVA) model including baseline nasal symptom score as a covariate and these fixed effects: treatment and country (6 levels). After a fixed sequence multiple comparison procedure, the treatment effect of each active dose was compared to placebo using a 2-sided t-test with a 0.05 significance level.

Analysis of the reduction in total polyp grade coprimary endpoint used a mixed effect model for repeated measures (MMRM) including a covariate (baseline bilateral polyp score) and the following fixed effects: treatment, country (6 levels), visit (4 levels) and interaction of treatment-by-visit. Subject was the block factor for repeated measurements. After a multiple comparison procedure, the 2-sided t-test at significance of 0.05 was used to estimate the treatment effect for each active group.

For each coprimary endpoint, the Applicant also compared the 372-mcg BID with 93-mcg BID arm and the 186-mcg BID with 93-mcg BID.

Missing data was imputed using a multiple imputation method in the primary analyses of the coprimary efficacy variable. The statistical models used for primary efficacy assumed there would be no bias associated with missing data if the data was missing at random or negligible if not missing at random cases was small.

The following three sensitivity analyses were carried out for the coprimary endpoints:

1. The primary analyses with the FAS without missing data imputation.
2. The primary analyses using multiple imputed datasets with per protocol set with major protocol violations defined as the following:
   - Visit 1 score of 0 (or missing) for either left or right polyp score
   - Baseline average nasal congestion/obstruction score < 1.4 (or missing)
   - Use of concomitant corticosteroids other than allowed medications per protocol
   - Subjects who did not use investigational drug for more than 15 days in a month
3. Tipping point analysis where missing values were imputed over a range of possible values for each treatment group with various combinations looking for a "tipping point" that would reverse the trial observation.

Statistical multiplicity was addressed for the key secondary endpoints in Trial 3101 but not the other secondary endpoints. Inferential statistics for the two variables was conducted after both primary efficacy variables were tested, followed by a step-down method to control for statistical multiplicity.

Safety

General safety assessments included monitoring AEs, VS (heart rate, blood pressure) general PE, and pregnancy testing (screening) and concomitant medication use. An ophthalmologist performed ocular examinations including slit-lamp examination, IOP measurements, and visual acuity at baseline, end of DBP, and end of OLE. The Sponsor defined a threshold limit for elevated IOP as >21 mmHg. Investigators completed IOP measurements twice for each eye, and repeated measurements if the numbers differed by > 3 mmHg. In cases where 3 measurements were taken, investigators averaged all values. Nasoendoscopy occurred at screening, every 4-weeks during the DBP and the conclusion of the OLE. Investigators documented findings on a nasal examination worksheet (Table 13).

Table 13. Summary of nasal examination worksheet

Epistaxis	• Active bleeding vs nonactive bleeding • Origin of bleeding • Relationship to injury/nasal trauma • Relationship to investigational drug/device
Septal erosion/perforation	• Severity • Mild: evidence of epithelial erosion • Moderate: evidence of ulceration through the epithelial layer with exposed cartilage • Severe: perforation • Location of septal event • Relationship to injury/trauma • Relationship to investigational drug/device

Erosion/ulceration in areas other than the septum	• Mild: epithelial surface abnormally eroded/abraded, but not clinically significant and expected to resolve rapidly • Moderate: deeper than surface abrasion, limited clinical significance but may require monitoring or recommendation for routine care • Severe: deeper ulcers with possible effect on underlying structures, depth is clinically significant, intervention, or specific care may be warranted • Relationship to investigational drug/device
Redness/erythema: in the presence or absence of ulceration or infection	• Intensity: mild, moderate, or severe • Relationship to investigational drug/device
Mucosal candidiasis: evidence of tightly adhered white material that does not scrape off	• Intensity: mild, moderate, or severe • Relationship to investigational drug/device
Atypical Mucosal Swelling	• Mild: atypical swelling noted but no functional impairment • Moderate: atypical swelling contributes to some functional impairment but subject can still breathe through the nose. • Severe: atypical swelling creates significant functional impairment/complete obstruction. • Relationship to trial/drug device.

Appendix 9.4.1 provides a table of trial assessments.

Reviewer comment. The use of > 21 mm Hg as a cut off for increased IOP is standard for these types of assessments. While the Applicant did not complete corneal pachymetry, the included evaluations are sufficient to complete a safety review. The overall trial design is consistent with the definition of an adequate and well-controlled trial as described in the regulations and is reasonable for allowing assessment of the efficacy of OPN-375 for treatment of nasal polyps.

Trial OPN-FLU-NP-3102	
Title	A 16-Week Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 93, 186, and 372-mcg of Fluticasone Propionate Twice a Day (BID) Using a Novel Bi-directional Device in Subjects with Bilateral Nasal Polyposis Followed by an 8-week Open-label Extension Phase to Assess Safety
Trial dates	Initiated: October 30, 2013 Completed: May 11, 2015 (double-blind period) July 03, 2015 (open-label extension) Final CSR: March 4, 2016
Sites	38 centers in 5 countries (9 in the United States, 12 in Poland, 6 in Romania, 6 in South Africa, and 5 in Ukraine)

Trial 3102 was a randomized, double-blind, placebo-controlled, parallel-group with trial design virtually identical to Trial 3101 with respect to treatment arms, trial duration, inclusion/exclusion criteria, concomitant medications, safety and efficacy assessments.

The protocol did not specify any key secondary endpoints. Otherwise coprimary and secondary endpoints were identical.

Trial OPN-FLU-CS-3204	
Title	A 3-Month Open-Label Multicenter Study Evaluating the Safety of Intranasal Administration of 372 mcg of Fluticasone Propionate Twice a Day (BID) Using a Novel Bi-Directional Device in Subjects with Chronic Sinusitis with or without Nasal Polyps
Trial dates	Initiated: October 3, 2013 Completed: February 2, 2015 Final CSR: October 9, 2015
Site	38 U.S. trial centers

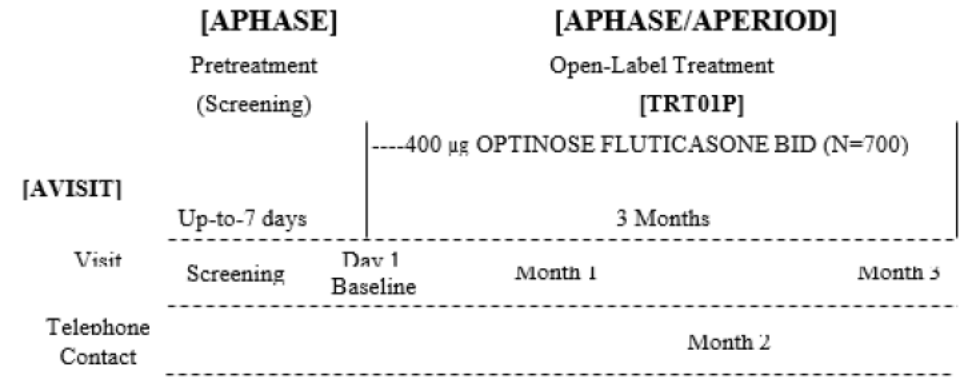
Objectives

- *Primary*: to assess the safety of intranasal OPN-375 372-mcg BID in subjects with chronic sinusitis with or without nasal polyps
- *Secondary:* to explore efficacy via objective measures of nasal blockage/obstruction, polyp score, need for surgery, SNOT-22 and PGIC

Trial Design

Trial 3204 was an open-label, multicenter trial in subjects with chronic sinusitis with or without nasal polyps. After baseline assessments and a 7-day pretreatment phase, eligible subjects received 372-mcg OPN-375 twice daily during a 3 month open-label treatment period. Scheduled clinic visits for safety and efficacy assessments occurred at baseline, Month 1, and Month 3 (EOS or ET) with additional telephone contact at Month 2. The trial flow diagram appears in Figure 4.

Figure 4. Trial 3204 flow diagram



Source: NDA 209,022, Module 5, CSR Study 3204

Population

Target enrollment was 700 subjects with chronic sinusitis with or without nasal polyps. The inclusion and exclusion criteria were identical to Trial 3101 with the following exceptions. The protocol allowed subjects to continue intranasal medications and to have a history of over 6 lifetime sinus surgeries. The protocol did not require a minimum grade of nasal polyps or moderate nasal obstruction/congestion (inclusion criteria #4, 5 and 6 from Trial 3101). Instead, subjects met the following key inclusion criterion:

1. History of chronic sinusitis with bilateral nasal polyps determined by nasoendoscopy at Visit 1 (screening) or
2. History of chronic sinusitis (without polyps) for equal to or greater than 12 weeks and currently experiencing 2 or more of the following 4 symptoms, 1 of which must be either nasal blockage/congestion or nasal discharge (anterior and/or posterior nasal discharge):
   - Nasal blockage/congestion
   - Nasal discharge (anterior and/or posterior nasal discharge)
   - Facial pain or pressure
   - Reduction or loss of smell

Reviewer comment: Note that associated polyps were bilateral, but any grade.

Treatments

The trial treatment was 372-mcg of intranasal OPN-375 BID. Subjects administered 2x93-mcg OPN-375 per nostril BID. Each trial kit contained 2 devices. Investigators instructed subjects to use one device for all AM and PM doses for 15 days, and then to use the second device for all AM and PM doses for no more than 16 days.

Missed doses were addressed as in Trial 3101. Investigators monitored treatment compliance by observation of the level of liquid in the devices at each trial visit.

Table 14. Concomitant medications, Trial 3204

Permitted	• Acetaminophen, NSIADs, aspirin, ICS, and antibiotics per Trial 3101 • Prophylactic antibiotics (except for chronic sinusitis) if intend to continue during trial • Intranasal saline spray and saline lavage except within 15 minutes before or after investigational drug • Stable doses of leukotriene receptor antagonists, beat-blockers, and neuroleptics • Low to medium strength topical corticosteroids for dermatologic purposes • Antihistamines, decongestants, ipratropium, and oxymetazoline are permitted. Nasal preparations cannot be administered 15 minutes before or after investigational drug
Prohibited	• Corticosteroids (except ICS for comorbid asthma or COPD or as noted above) • Potent CYP3A4 inhibitors within 14 days of screening and throughout the trial
Source: NDA 209,022, Module 5.3.5.2 OPN-FLU-CS-3204, Protocol and Protocol Amendments.	

Reviewer comment: The concomitant medications were more lenient, allowing use of concomitant antihistamines, decongestants, and nasal preparations. The trial allowed any dose of leukotriene receptor antagonists, beta-blockers, and neuroleptics.

Efficacy Variables

Investigators collected exploratory efficacy variables at baseline (Day 1), Month 1 and Month 3, including nasoendoscopy, surgical interventional assessment, and SNOT-22. Nasoendoscopy was performed per protocol as in Trial 3101 for nasal polyp grading (Lildholdt method). Additional assessments with nasoendoscopy included the Lund-Mackay Assessment of Nasal Cavity Appearance (Table 15):

Table 15. Lund-Mackay assessment of nasal cavity appearance

Sign	Score	Description
Edema	0 1 2	None Mild edema Gross edema
Discharge	0 1 2	None Clear and thin Thick and purulent
Crusting	0 1 2	None Mild crusting Gross crusting
Scarring/Adhesions	0 1 2	None Adhesion bands Closed cavity
Nasal Polyps	0 1 2	None Confined to middle meatus Beyond middle meatus
Source: NDA 209,022, Module 5.3.5.2 OPN-FLU-CS-3204, Protocol and Protocol Amendments, Table 2.		

Subjects completed the PGIC Month 1 and 3 only. Subjects completed a medication evaluation questionnaire at screening, Month 1 and Month 3, including questions related to ease of use, comfort, taste and drip.

Efficacy Endpoints

The trial explored the following secondary endpoints:

- Mean change in summed score (both nostrils) on each item of the Lund-Mackay assessment of nasal blockage/obstruction based on nasoendoscopy from baseline to each time point or end of trial
- Mean change in nasal polyp grading scale score from baseline to each time point or EOS for subjects with nasal polyps
- Proportion of subjects who qualify for sinus surgery at baseline and endpoint
- Mean change from baseline to each time point or EOS in total SNOT-22 score

- Subject evaluation of current/most recent nasal spray at Visit 1 (screening) and subject evaluation of investigational drug at Months 1 and 3
- PGIC scores at Months 1 and 3

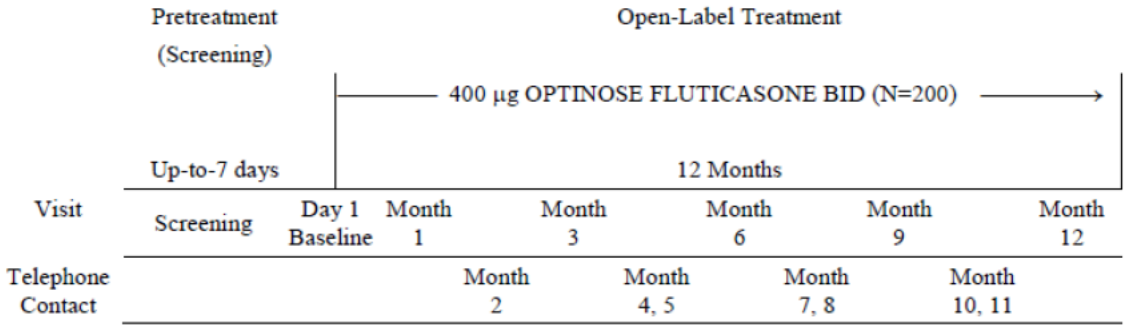
Safety

Safety assessments included monitoring AEs, nasal examinations, ocular examinations, VS (i.e. blood pressure and pulse) and concomitant medication use.

Trial OPN-FLU-CS-3203	
Title	A 12-Month Open-Label Multicenter Study Evaluating the Safety of Intranasal Administration of 372-mcg of Fluticasone Propionate Twice a Day (BID) Using a Novel Bi-Directional Device in Subjects with Chronic Sinusitis With or Without Nasal Polyps
Trial dates	Initiated: September 6, 2013 Completed: August 10, 2015 Final CSR: March 7, 2016
Site	21 U.S. centers

Trial 3203 trial was a similarly designed 12-month, open-label, multicenter safety trial. After a 7-day pretreatment phase, eligible subjects received 372-mcg of OPN-375 BID for 12 months. Safety and efficacy assessments occurred at Months 1, 3, 6, 9, and 12 (or ET), and telephone follow-up occurred on months when clinic site visits were not planned. Trial 3203 had a target enrollment of 200 subjects, with four centers from Trial 3204 permitted to roll subjects into Trial 3203. While the timing of assessments varied, the trial population, medications, safety variables, and efficacy variables were identical to Trial 3204. A trial flow diagram appears in Figure 5.

Figure 5. Trial 3203 flow diagram



Source: Figure 2, Protocol OPN-FLU-CS-3203

Reviewer Comment: Because there was no placebo group and the trial population was outside the indication, the trials are not used to support efficacy. However, because the

trials evaluated the high dose, this review uses the safety data to support long-term safety of OPN-375.

6 Review of Efficacy

Efficacy Summary

This NDA submission contains adequate data to support the efficacy of OPN-375 for the treatment of nasal polyps in patients 18 years of age and older. The primary efficacy review evaluated the double-blind period of two well-controlled phase 3 trials. Trials 3101 and 3102 were nearly identical randomized, double-blind, placebo-controlled studies comparing the efficacy of 93-mcg, 186-mcg and 372-mcg OPN-375 twice daily to placebo. The trial population included adults 18 years and older with bilateral grade 1 to 3 nasal polyps and associated moderate nasal congestion/obstruction symptoms. A demonstration of efficacy required a statistically significant difference from placebo in the following coprimary endpoints: (1) change in 7-day average nasal congestion/obstruction at Week 4 and (2) change in total bilateral polyp grade at Week 16. Trial 3101 also specified two key secondary endpoints: (1) change in total SNOT-22 store at Week 16 and (2) change in MOS Sleep-R Sleep Disturbance sub-score at Week 16.

With respect to the coprimary endpoints in both trials, all three OPN-375 doses demonstrated a statistically significant treatment effect, but Trial 3101 alone demonstrated a dose-response. While not statistically significant, there was separation in the nominal treatment effect for both the 186-mcg BID and 372-mcg BID OPN-375 doses compared to the 93-mcg BID dose with respect to both coprimary endpoints in Trial 3101, and one of two coprimary endpoints in Trial 3102 which contributed to the selection of the 186-mcg BID and 372-mcg BID doses for approval. In both trials, the highest OPN-375 dose achieved the greatest nominal improvement in Week 16 total nasal polyp grade, the more objective coprimary endpoint, suggesting that some patients may achieve additional benefit from the high dose. The key secondary endpoints, responder analyses, and additional secondary endpoints generally supported a treatment effect for all doses, but did not consistently demonstrate a dose-response. Acknowledging that the treatment differences were small, as the 372-mcg BID dose achieved the greatest percentage of responders for two of the four responder analyses and an added benefit over the 186-mcg BID dose with respect to the coprimary endpoint nasal polyp grade (and lack of any additional safety concerns), this reviewer recommends the approval of both the 186-mcg BID and 372-mcg BID OPN-375 doses for the treatment of nasal polyps.

6.1 Indication

The indication is treatment of nasal polyps in subjects 18 years of age or older. The recommended dosage is "1 spray (93-mcg of fluticasone propionate per spray) in each nostril twice daily (total daily dose, 372-mcg). A dose of 2 sprays (93-mcg of fluticasone propionate per spray) in each nostril twice daily may also be effective in some patients (total daily dose, 744-mcg)."

Reviewer Comment: While the trials separately assessed improvement in nasal congestion, improvement in nasal congestion is expected with treatment of nasal polyps. In previous discussions with the Applicant, the Division stated that a single indication of treatment of nasal polyps was appropriate.

6.1.1 Methods

The OPN-375 nasal polyp development program consisted of a single phase 1 PK study and 4 phase 3 clinical trials. The primary efficacy review evaluates the two key safety and efficacy trials submitted in support of the proposed indication and labeling claims (i.e. Trials 3101 and 3102). This review evaluates primary, key secondary, and additional efficacy endpoints from each trial separately in order to demonstrate reproducibility of the trial findings. The two uncontrolled, open-label phase 3 trials included subjects outside of the target indication and are not included in the key efficacy analysis for the proposed indication.

Sections 6.1.4 and 6.1.5 of this review discuss the primary and key secondary efficacy endpoints, respectively. Section 6.1.6 discusses additional endpoints that provide the most relevance to the indication. Finally, Section 6.1.7 explores the subpopulations from Trials 3101 and 3102.

Reviewer comment: While the Division recommended that that Applicant complete dose-ranging prior to the phase 3 trials, the Applicant chose to include dose-ranging within each pivotal trial. (b) (4) *and must have a justifiable rationale for doing so.*

6.1.2 Demographics

Overall, the age, race, ethnicity, and weight were similar across treatment arms in both Trials 3101 and 3102. Subjects were predominately white with a mean age of 44 to 47 years. The distribution of female subjects varied across treatment arms from 31.7% to 56.1%. Fewer than half of all subjects had a history of asthma, and for those subjects with concomitant asthma, mean FEV1 and Asthma Control Test scores were similar across treatment arms. Overall, Trial 3101 included a larger percentage of U.S. subjects than Trial 3102.

Table 16. Baseline demographics, Trials 3101 and 3102, ITT population

Characteristic Statistic	Placebo		OPN-375					
			93-mcg BID		186-mcg BID		372-mcg BID	
	3101 N=82	3102 N=80	3101 N=81	3102 N= 81	3101 N=80	3102 N= 80	3101 N=80	3102 N= 82
Age (years)								
Mean	45	47	45	47	46	45	44	45
SD	13	12	13	14	13	13	13	12
Range	18-74	22-76	18-68	23-82	18-71	20-74	18-73	18-69
Gender (%)								
Female	56.1%	47.5%	50.6%	48.1%	40.0%	42.5%	52.5%	31.7%
Race (%)								
White	82.9%	95.0%	91.4%	93.8%	90.0%	95.0%	86.3%	92.7%
Black	9.8%	3.8%	3.7%	3.7%	7.5%	3.8%	11.3%	4.9%
Other	6.3%	1.3%	5%	2.5%	2.5%	1.3%	2.5%	2.4%
Ethnicity (%)								
Hispanic/Latino	6.1%	1.3%	3.7%	0	0	0	6.3%	1.2%
Weight (kg)								
Mean	81.4	79.8	82.7	82.2	81.5	79.4	79.5	81.2
SD	18.03	16.45	18.49	18.63	18.50	16.74	16.69	15.16
Comorbid asthma								
Yes (%)	40.2%	43.8%	28.4%	37.0%	47.5%	36.3%	50.0%	32.9%
Region[a] (%)								
North America	48.8%	12.5%	50.6%	12.3%	50.1%	12.5%	50.0%	11.0%
Europe	40.3%	72.6%	42.0%	75.3%	40.0%	73.9%	41.3%	75.6%
Other	11.0%	15.0%	7.4%	12.3%	10.0%	13.8%	8.8%	13.4%

N = number of subjects; % = percentage of subjects in subset; SD = standard deviation. ITT= intention to treat population, included all subjects who were randomized, regardless of whether subjects received trial medication.
[a]North America includes Canada and United States, Europe = Czech Republic, Poland, Romania, UK, Ukraine; Other= South Africa.
Source: NDA 209,022, CSR OPN-FLU-NP-3101 (Table 13 and 15) and CSR OPN-FLU-NP-3102 (Table 10 and 15).

Baseline disease severity, including baseline total and worst nasal polyp grade and percentage subjects reporting prior nasal surgeries, was similar across the treatment arms. When comparing the overall trial populations, the use of corticosteroids, including oral prednisone for treatment of nasal polyps, was greater in Trial 3101 than Trial 3102. Table 17 summarizes the baseline disease severity for each trial.

Table 17. Baseline disease severity, Trials 3101 and 3102, ITT population

Characteristic	Placebo		OPN-375					
			93-mcg BID		186-mcg BID		372-mcg BID	
	3101 N=82	3102 N=80	3101 N=81	3102 N=81	3101 N=80	3102 N=80	3101 N=80	3102 N=82
Mean polyp grade								
Total grade (SD)	3.8(0.9)	3.8(1.1)	3.6(1.1)	3.8(1.0)	3.9(1.1)	3.9(1.1)	3.7(0.9)	3.9(1.0)
Worst grade (SD)	2.1(0.6)	2.0(0.6)	2.0(0.6)	2.0(0.5)	2.1(0.6)	2.1(0.6)	2.0(0.5)	2.1(0.5)
Percentage reporting corticosteroid treatment within the last 10 years								
Any corticosteroid	93.9%	91.3%	95.1%	82.7%	95.0%	87.5%	93.8%	85.4%
Oral (prednisone)	32.9%	12.5%	24.7%	11.1%	17.5%	8.8%	32.5%	7.3%
Intranasal (any)								
≤1 treatments	34.1%	70.1%	48.1%	66.7%	43.8%	68.8%	35.0%	70.7%
2-3 treatments	41.5%	23.8%	33.3%	29.6%	46.3%	26.3%	50.0%	28.0%
≥4 treatments	24.3%	6.3%	18.5%	3.7%	10.1%	5.0%	15.0%	1.2%
Mean polyp removal surgeries								
Polypectomy (SD)	0.7(1.1)	0.7(1.1)	0.7(1.1)	0.7(1.0)	0.7(1.1)	0.6(1.0)	0.6(0.9)	0.5(0.9)
Sinus surgery (SD)	0.6(1.0)	0.3(0.7)	0.6(1.0)	0.3(0.6)	0.4(0.8)	0.4(0.7)	0.4(0.8)	0.3(0.7)
Mean visits for nasal polyps in the last year								
ENT (SD)	1.8(1.7)	2.1(1.8)	1.9(1.9)	2.3(1.9)	1.7(1.5)	2.4(2.1)	1.9(1.9)	2.1(1.5)
Allergist (SD)	1.1(1.8)	0.3(0.8)	0.6(1.1)	0.3(0.8)	0.8(1.3)	0.4(1.0)	1.0(1.9)	0.2(0.5)
PCP (SD)	0.9(2.0)	1.7(2.1)	0.5(0.9)	1.4(1.7)	0.3(0.8)	1.2(1.5)	0.8(1.8)	1.0(1.2)

N = number of subjects; % = percentage of subjects in subset; SD = standard deviation.
ITT population included all subjects who were randomized, regardless of whether subjects received trial medication.
Source: adapted from CSR OPN-FLU-NP-3101 and CSR OPN-FLU-NP-3102, Table 16 and 17.

Reviewer comment. The small differences in trial population demographics and baseline characteristics may reflect regional treatment differences. Overall, the baseline trial population represents the indicated population and is adequate to provide an assessment of efficacy.

6.1.3 Subject Disposition

Trials 3101 and 3102 met goal enrollment numbers. A majority of subjects completed the double-blind period for each treatment arm. AEs leading to discontinuation occurred in 4 or fewer subjects across all treatment arms. Protocol deviations contributed a small percentage to the premature discontinuations. Within the OPN-375 arms, reasons for premature discontinuation were generally distributed across all categories. Within the placebo arm, approximately half of all premature discontinuations in the placebo arm were related to lack of efficacy (7.3% Trial 3101, 6.3% Trial 3102). Table 18 summarizes subject disposition for both trials.

Table 18. Subject Disposition in DBP, Trials 3101 and 3102, ITT population

Disposition	Number (Percent) per Treatment Arm							
	Placebo		OPN-375					
			93-mcg BID		186-mcg BID		372-mcg BID	
	3101	3102	3101	3102	3101	3102	3101	3102
Number randomized	82(100)	80(100)	81(100)	81(100)	80(100)	80(100)	80(100)	82(100)
Any treatment	82(100)	79(98.8)	81(100)	80(98.8)	80(100)	80(98.8)	79(98.8)	82(98.8)
Completed DBP	70(85.4)	70(87.5)	75(92.6)	78(96.3)	71(88.8)	76(95.0)	76(95.0)	82(100)
Prematurely discontinued	12(14.6)	10(12.5)	6(7.4)	3(3.7)	9(11.3)	4(5.0)	4(5.0)	0
Lack of efficacy	6(7.3)	5(6.3)	0	1(1.2)	3(3.8)	0	2(2.6)	0
Adverse Event	4(4.9)	2(2.5)	2(2.5)	1(1.2)	3(3.8)	1(1.3)	1(1.3)	0
Withdrawal by subject	2(2.4)	3(3.8)	2(2.5)	0	2(2.5)	3(3.8)	0	0
Protocol deviation	0	0	2(2.5)	1(1.2)	0	0	1(1.3)	0
Lost to follow-up	0	0	0	0	1(1.3)	0	0	0

Denominators for percentages are ITT population
Source: NDA 209,022, Module 5.3.5.1, OPN-FLU-NP-3101 CSR and OPN-FLU-NP-3102 CSR , Tables 14.1.1.
Reviewer confirmed using ISS ADSL.xpt dataset in JMP 12.0. Population selected IFFL (Y), comparison of DCRB, COMPDBFL, COMPOLFL, ENRLOLFL, DCROL by TRT02P.

Treatment Compliance:

The Applicant reports that 100% (Trial 3101) and 97.2% (Trial 3102) of subjects missed ≤15 days of investigational drug. The non-compliant subjects in Trial 3012 were generally distributed across treatment arms.

Reviewer comment. The method for assessing treatment compliance relied on visual inspection of investigational drug. This method appears subjective and should be interpreted with caution. However, in general, there is sufficient compliance to assess efficacy and provide safety information for Trials 3101 and 3102.

6.1.4 Analysis of Primary Endpoint(s)

The coprimary efficacy endpoints for Trials 3101 and 3102 were:

1. Reduction of nasal congestion/obstruction symptoms at the end of Week 4 of the DBP measured as the 7-day average instantaneous AM diary symptom scores (ADS7-IA)
2. Reduction in total polyp grade (sum of scores from both nasal cavities) at Week 16 of the DBP where nasal polyp grading score was measured by nasoendoscopy using a 0 to 6-point severity grading scale (with 0 to 3 points per nostril)

The coprimary endpoints generally mirror the Nasonex® development with the exception that the Nasonex® program assessed nasal congestion/obstruction symptoms over the entire initial 4-week period. OptiNose US justified including data

from the preceding 7-days noting that relief of nasal congestion due to nasal polyps may take longer due to the contribution of the physical presence of polyps (communication dated 4/10/2015, IND 110,089). The Division agreed to the Applicant's justification, but requested additional analysis of the first four weeks of nasal congestion/obstruction symptoms.

Reviewer comment. The total polyp grade endpoint represents the more objective measure of nasal polyp improvement. The time point for assessment of nasal congestion is acceptable given the use of rescue medication after 4-weeks, which may confound an interpretation of congestion scores. Overall, the coprimary efficacy endpoints provide a reasonable assessment of clinical efficacy for a nasal polyp indication, and incorporate Division feedback.

Nasal Congestion / Obstruction Symptom Scores:

Both Trials 3101 and 3102 demonstrated a statistically significant reduction in ADS7-IA scores for all three OPN-375 doses compared to placebo at Week 4. In Trial 3101, the absolute difference from placebo in LS mean ADS7-IA score increased with increasing OPN-375 dose (-0.25 [93-mcg BID] to -0.38 [372-mcg BID]. However, in Trial 3102, the 186-mcg BID dose demonstrated the greatest mean difference from placebo in ADS7-IA score. Table 19 summarizes the mean change in ADS7-IA scores.

Table 19. Coprimary efficacy endpoint, difference from vehicle placebo in LS mean change in ADS7-IA score at Week 4, Trials 3101 and 3102

	Placebo	OPN-375		
		93-mcg BID	186-mcg BID	372-mcg BID
Trial 3101	N=82	N=81	N=80	N=79
Baseline mean (SD)	2.3 (0.41)	2.2 (0.44)	2.2 (0.42)	2.3 (0.44)
Change baseline to Week 4	-0.24			
LS mean		-0.49	-0.54	-0.62
Difference (active-placebo)		-0.25	-0.30	-0.38
95% CI		(-0.43, -0.06)	(-0.48, -0.11)	(-0.57, -0.19)
p-value versus placebo		0.01	0.002	<0.001
Trial 3102	N=79	N=80	N=80	N=82
Baseline mean (SD)	2.3 (0.43)	2.2 (0.41)	2.2 (0.37)	2.2 (0.42)
Change baseline to Week 4	-0.24			
LS Mean		-0.59	-0.68	-0.62
Difference (active-placebo)		-0.36	-0.45	-0.38
95% CI		(-0.56, -0.16)	(-0.65, -0.25)	(-0.58, -0.18)
p-value versus placebo		<0.001	<0.001	<0.001

LS= least square; CI= confidence interval; SD= standard deviation. Score of 2 indicates moderate intensity.
Source: NDA 209,022, Module 5.3.5.1, OPN-FLU-NP-3101 CSR and OPN-FLU-NP-3102 CSR, Tables 14.2.1.
Confirmed by statistical reviewer Feng Li, Ph.D.

Additional sensitivity analyses including analysis of the FAS without imputation of missing data, the PPS with missing data imputed as well as tipping point analysis were consistent with the findings. Exploratory comparisons of the 186-mcg BID and 372-mcg BID doses to the 93-mcg BID dose were not statistically significant for either trial.

Reviewer comment. The endpoint supports the efficacy of all three doses of OPN-375. The trials did not demonstrate a consistent dose-response.

Mean change from baseline in polyp grade:

All three OPN-375 arms demonstrated a statistically significant reduction in mean total bilateral polyp grade at Week 16 compared to placebo. In both trials, the nominal reduction in total polyp grade was greatest for the 372-mcg BID dose. A dose-response for change in total polyp grade was only evident in Trial 3101, but the difference between 186-mcg BID and 372-mcg BID doses was small. Table 20 summarizes the mean changes from baseline in bilateral polyp grade at Week 16.

Table 20. Coprimary endpoint, difference from vehicle placebo in LS mean change total polyp grade at Week 16, Trials 3101 and 3012

	Placebo	OPN-375		
		93-mcg BID	186-mcg BID	372-mcg BID
Trial 3101	N=82	N=81	N=80	N=79
Baseline mean (SD)	3.8 (0.94)	3.6 (1.07)	3.9 (1.08)	3.7 (0.94)
Change from baseline to Week 16				
LS mean	-0.45	-0.96	-1.03	-1.06
Difference (active-placebo)		-0.51	-0.59	-0.62
95% CI		(-0.86, -0.16)	(-0.93, -0.24)	(-0.96, -0.27)
p-value versus placebo		0.004	< 0.001	<0.001
Trial 3102	N=79	N=80	N=80	N=82
Baseline mean (SD)	3.8 (1.08)	3.6 (0.98)	3.9 (1.05)	3.9 (1.00)
Change from baseline to Week 16				
LS Mean	-0.61	-1.31	-1.22	-1.41
Difference (active-placebo)		-0.70	-0.60	-0.80
95% CI		(-0.99, -0.41)	(-0.89, -0.31)	(-1.08, -0.51)
p-value versus placebo		<0.001	<0.001	<0.001

LS= least square; CI= confidence interval; SD= standard deviation; N = number of subjects in each treatment arm.
Source: NDA 209,022, Module 5.3.5.1, OPN-FLU-NP-3101 CSR and OPN-FLU-NP-3102 CSR, Tables 14.2.2.
Confirmed by statistical reviewer Feng Li, PhD.

Additional sensitivity analyses including analysis of the FAS without imputation of missing data, the per protocol set with missing data imputed, and tipping point analysis were consistent with the findings. Exploratory analysis of differences in LS mean

change from baseline between the 186-mcg BID and 372-mcg BID doses and the 93-mcg BID dose were not statistically significant for either trial.

Reviewer comment: The total polyp grade coprimary endpoint in both Trials 3101 and 3102 supports the efficacy of all doses. The high dose provided the largest nominal treatment effect in both studies.

6.1.5 Analysis of Secondary Endpoints(s)

The two key secondary endpoints in Trial 3101 were change from baseline to Week 16 in the SNOT-22 total score and MOS Sleep-R Sleep Disturbance subscale. All OPN-375 treatment arms demonstrated a statistically significant change in the SNOT-22 total score compared to placebo, with the 186-mcg BID and 372-mcg BID arms demonstrating a numerically larger improvement. Statistical significance for the change in MOS Sleep-R sleep disturbance scale was only achieved for the 186-mcg BID dose, the dose with the largest difference from placebo. A summary of the key secondary endpoints in Trial 3101 appears in Table 21.

Table 21. Key secondary endpoints, Trial 3101, FAS with imputation

	OPN-375		
	93-mcg BID (N=81)	**186-mcg BID (N=80)**	**372-mcg BID (N=79)**
SNOT-22 Total Score at 16-weeks			
n	74	70	73
LS mean change (SE)	-18.32 (2.057)	-19.56 (2.044)	-19.80 (2.047)
Difference (active-PBO), PBO= -10.96 (2.07)	-7.35	-8.59	-8.84
p value	0.005	0.001	<0.001
MOS Sleep-R Sleep Disturbance subscale at 16-weeks			
n	75	71	75
LS mean change (SE)	-9.91 (1.933)	-15.09 (1.939)	-11.0 (1.887)
Difference (active-PBO), PBO= -8.93(1.955)	-0.98	-6.16	-2.07
p value	0.694	0.014	0.403

LS= least square; n = number of subjects in each treatment arm for subset;
Applicant derived inferential statistics from a repeated measures mixed model with visit, treatment, treatment by visit, and country factors and baseline value as covariate.
Data source: NDA 209,022, Module 5.3.5.1, OPN-FLU-NP-3101 CSR, Tables 14.2.8.1 and 14.2.10.2.

While Trial 3102 did not specify key secondary endpoints, the Applicant analyzed change in SNOT-22 total score and MOS Sleep-R disturbance subscale score at Week 16 as secondary endpoints, not accounting for multiplicity. The analyses found a nominal treatment effect on the MOS Sleep-R scale and SNOT-22 for all three OPN-375 doses compared to placebo.

Reviewer comment: Both key secondary endpoints are subjective, nonspecific global assessments of response to therapy. As these are not validated instruments to assess efficacy for treatment of nasal polyps, (b) (4) *.*

6.1.6 Other Endpoints

Trials 3101 and 3102 evaluated multiple secondary endpoints during the double-blind period and open-label extension (Table 22). As these analyses did not adjust for multiplicity and because these endpoints were either of lesser importance or not validated (b) (4), the Section only briefly discusses the relevant endpoints with nominal and descriptive statistics.

Table 22. Additional secondary efficacy analyses, Trials 3101 and 3102

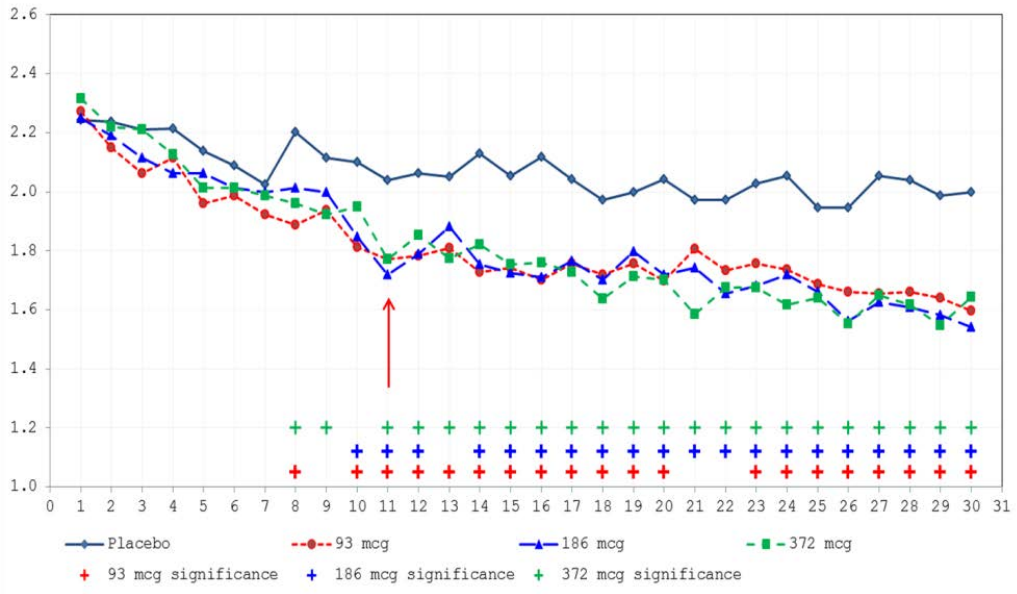
- Change from baseline in ADS7-IA/P and ADS7-RA/P (i.e., nasal congestion/obstruction symptoms, sense of smell, rhinorrhea symptoms, and facial pain or pressure symptoms)
- Change from baseline in bilateral total polyp grade at defined time points
- Percent of responders at defined time points considering:
  - Subjects with polyp grade score of 0 in ≥ 1 nostril
  - Subjects with decrease in bilateral polyp grade (≥1 point)
  - ↓Bilateral polyp grade ≥ 1 and ↓congestion score ≥ 0.5 point
- Average monthly use of rescue medication in the DBP after Week 4
- Percentage of subjects meeting criteria for nasal polyp surgery at defined time points
- Additional measures: Change from baseline in SNOT-22, PGIC, PNIF, RSDI, SF-363, MOS Sleep-R, health economic measures, subject evaluation of medication at defined points

ADS7-IA = 7-day instantaneous AM average diary symptom score; ADS7-RA = 7-day reflective AM average diary symptom score; PGIC = Patient Global Impression of Change; SNOT-22 = Sinonasal Outcome Test-22.
Source: Adapted from SCE Table 2.7.3-3

Onset of Action

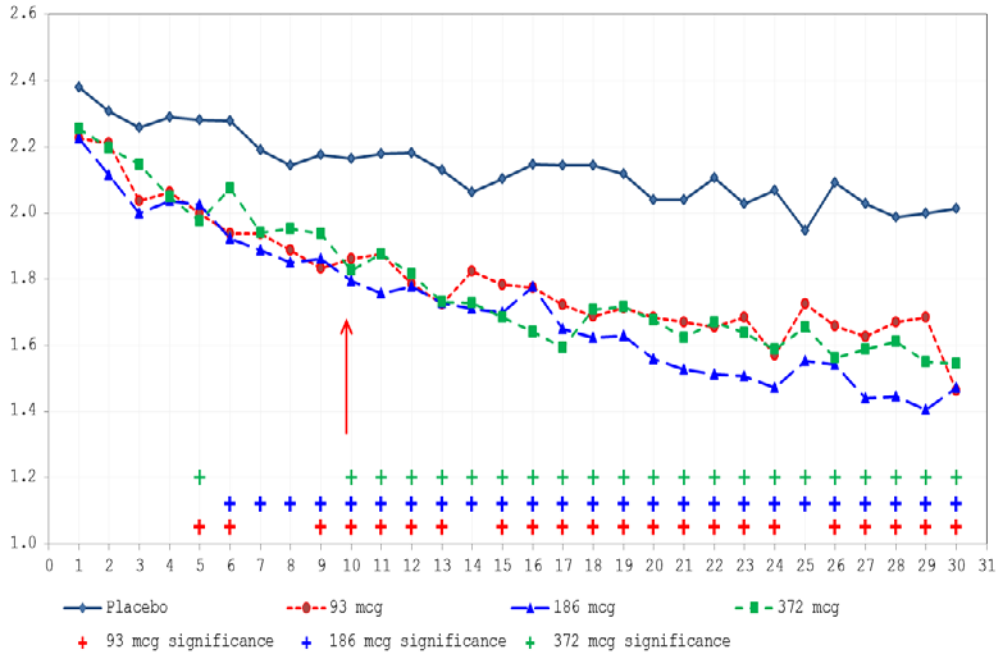
To evaluate the onset of action, the Applicant analyzed the mean change in ADS7-IA scores over the first 30 days of Trials 3101 and 3102. The protocol defined onset of action as the time when all subsequent values for ADS7-IA were statistically significant compared to placebo. In both trials, the separation in curves between all three active treatment arms and placebo achieved statistical significance simultaneously around Day 11 (Trial 3101, Figure 6) and Day 10 (Trial 3102, Figure 7), with the separation between each active treatment arm and placebo roughly maintained after this timepoint.

Figure 6. Nasal congestion score during the first 30 days, Trial 3101



Source: Figure 3 Statistical Review by Dr. Feng Li

Figure 7. Nasal congestion score during the first 30 days, Trial 3102



Source: Figure 6 Statistical Review by Dr. Feng Li

Change in Nasal Symptom Scores, Reflective and Instantaneous

Evaluation of instantaneous and reflect morning and evening symptom scores provides support for both the dosing interval and overall treatment effect. When considering the four symptom domains individually, at the conclusion of the DBP all scores showed greater improvement for each OPN-375 arm compared to the placebo arm. For all OPN-375 doses, the nominal improvement in symptom scores at each trial visit suggests a persistence of efficacy effect. Finally, the similarity of instantaneous and reflective scores for each of the four symptoms suggests a durability of effect and supports twice daily dosing. Table 23 summarizes the reflective and instantaneous AM scores for the end of the DBP.

Table 23. Change from baseline 7-day average morning instantaneous and reflective individual diary scores at the end of DBP, Trials 3101 and 3102

Trial Nasal symptom	LS mean change from baseline morning ADS7 score							
	Placebo		OPN-375 93-mcg BID		OPN-375 186-mcg BID		OPN-375 372-mcg BID	
	R	I	R	I	R	I	R	I
Trial 3101	N=78	N=78	N=79	N=79	N=77	N=78	N=77	N=77
Congestion/obstruction	-0.42	-0.48	-0.79*	-0.91*	-0.87*	-0.88*	-1.02*	-1.05*
Rhinorrhea	-0.37	-0.40	-0.73*	-0.77*	-0.83*	-0.77*	-0.91*	-0.87*
Facial pain/pressure	-0.31	-0.36	-0.60*	-0.64*	-0.68*	-0.69*	-0.69*	-0.70*
Sense of smell	-0.23	-0.23	-0.41	-0.44	-0.50	-0.48	-0.60*	-0.60*
Trial 3102	N=77	N=77	N=80	N=80	N=77	N=77	N=81	N=81
Congestion/obstruction	–0.38	-0.41	–0.94*	-0.98*	-0.92*	-0.92*	-0.95*	-0.94*
Rhinorrhea	–0.38	-0.34	–1.03*	-0.98*	-0.84*	-0.81*	-0.84*	-0.80*
Facial pain/pressure	–0.40	-0.42	–0.81*	-0.85*	-0.79*	-0.80*	-0.75*	-0.74*
Sense of smell	–0.21	-0.22	–0.52*	-0.55*	-0.47*	-0.47*	-0.59*	-0.60*

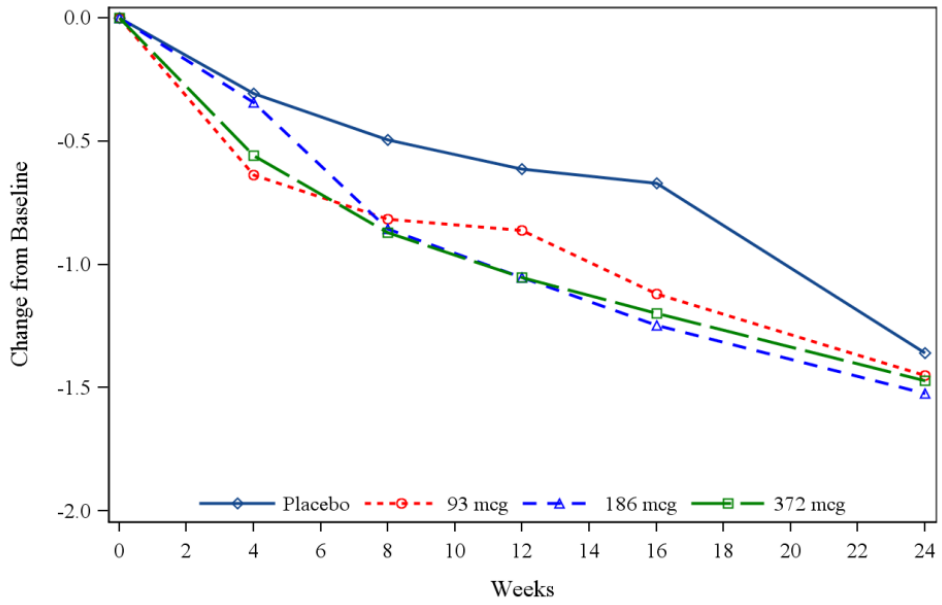
R= reflective score, I=instantaneous score. *nominal p value < 0.05 for comparison to placebo.
Source: NDA 209,022, Module 5.3.5.1, OPN-FLU-NP-3101 CSR and OPN-FLU-NP-3102 CSR Table 14.2.5.1 and 14.2.5.2.

Reviewer comment: The improvement in scores across the DBP suggests an added treatment effect despite the use of rescue medication after Week 4.

Change in Nasal Polyp Grade

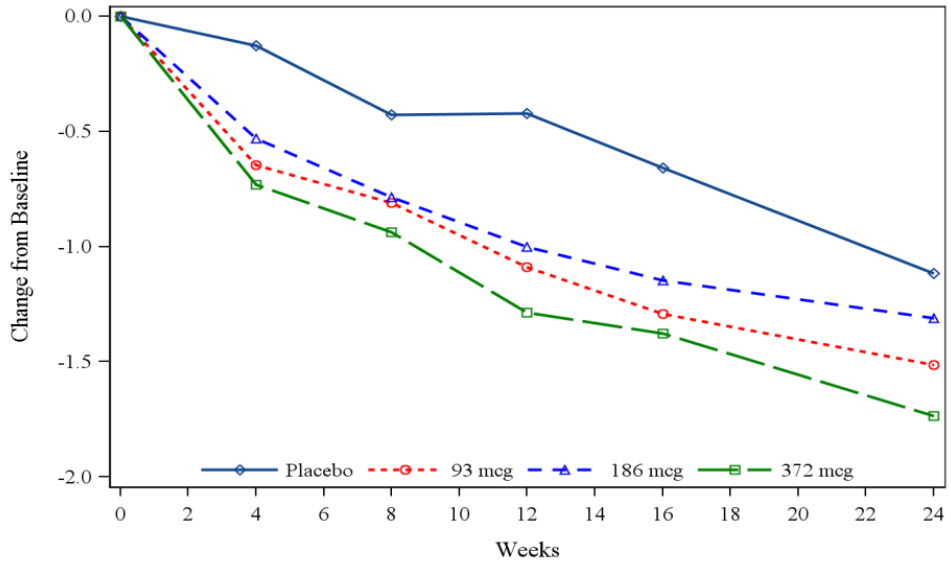
The Applicant evaluated total nasal polyp grade every 4-weeks during the double-blind period. The mean total polyp decreased with increasing treatment duration for all OPN-375 arms suggesting a persistence of efficacy. Differences in nasal polyp grade between the original placebo and OPN-375 arms diminished after all subjects transitioned to 372-mcg BID in the open-label extension, consistent with an expected treatment effect (Figure 8 and Figure 9).

Figure 8. Change in nasal polyp grade over time, Trial 3101



Source: Statistical Review by Dr. Feng Li, Figure 2

Figure 9. Change in nasal polyp grade over time, Trial 3102



Source: Statistical Review by Dr. Feng Li, Figure 5

Reviewer comment. Because the first on treatment nasal polyp assessment occurred at 4 weeks, the data do not contribute information on the onset of action within the first month.

Responder Analyses

Two responder analyses support a treatment effect for all OPN-375 doses, but do not consistently demonstrate a dose-response. The largest percentage of complete responders at Week 16, i.e. polyp grade of 0 (none) in ≥ 1 nostril, occurred in the 93-mcg BID arm in Trial 3101 and 372-mcg BID arm in Trial 3102. When considering dual responders, i.e. decrease in total bilateral polyp grade ≥ 1 and ADS7-IA score ≥ 0.5 point at Week 16, the largest percentage occurred for the 93-mcg BID dose in Trial 3102 and 372-mcg BID dose in Trial 3101 (Table 24).

Table 24. Responder analyses, Trials 3101 and 3102

Endpoint Statistic	Trial 3101				Trial 3102			
	PBO	93-mcg BID	186-mcg BID	372-mcg BID	PBO	93-mcg BID	186-mcg BID	372-mcg BID
Polyp grade of none in at least one nostril at Week 16								
N	82	81	80	79	79	80	80	82
n (%)	9 (11%)	19 (23%)	12 (15%)	14 (18%)	3 (4%)	10 (12.5%)	6 (7.5%)	11 (13%)
p-value*		0.035	0.044	0.22	—	0.045	0.31	0.03
Dual responder at Week 16								
N	82	81	80	79	79	80	80	82
n (%)	14 (17%)	34 (42%)	36 (45%)	42 (53%)	18 (23%)	44 (55%)	30 (37.5%)	32 (39%)
p-value*	—	0.0005	0.0001	<0.0001		<0.0001	0.043	0.026

N = number of subjects; % = percentage of subjects in subset; — = not applicable.
*p-value less than 0.05 from Chi-square test. Inferential statistics using GEE model with treatment and country as fixed factors.
Source: Statistical review by Dr. Feng Li, Tables 7, 8, 11 and 12.

Reviewer comment. In general, the responder analyses across the two trials support a treatment effect for all doses. The 372-mcg BID dose achieved the greatest percentage of responders for two of the four analyses, suggesting a small added treatment benefit for the 372-mcg BID dose.

Additional Endpoints

Additional endpoints included measures of nasal symptoms (i.e. PNIF, RDSI), qualifications for nasal polyp surgery and quality of life (SF-36 scale). The Week 16 nominal change from baseline in each endpoint supports the efficacy of all three OPN-375 doses, and does not reveal a consistent dose-response (Table 25).

Table 25. Change from baseline in additional secondary endpoints at end of DBP, Trials 3101 and 3102

Endpoint	Difference (active-placebo): LS mean change from baseline to Week 16					
	Trial 3101			Trial 3102		
	93-mcg BID	186-mcg BID	372-mcg BID	93-mcg BID	186-mcg BID	372-mcg BID
RSDI (total)	-6.36*	-5.72*	-5.65*	-7.74*	-7.56*	-8.89*
PNIF (L/min)	19.32*	18.68*	18.17*	25.96*	24.38*	28.10*
SF-36v2 (total)						
Mental	2.49*	3.33*	1.13	2.34*	2.02	2.11*
Physical	1.45	2.52*	0.92	1.51	1.73	2.21*

All values presented as difference from placebo in least square mean change.
*nominal p value statistically significant for comparison of treatment arm to placebo (p-value < 0.05).
Source: NDA 209,022, CSR OPN-FLU-NP-3101 and OPN-FLU-NP-3102, Table 14.2.14.1, 14.2.15, 14.2.9.

As outlined in Section 5.3.1, Trials 3101 and 3102 permitted use of nonsedating antihistamines for relief of symptoms associated with nasal polyps after Week 4. Comparison of mean monthly rescue medication use at Week 16, demonstrates that a minority of subjects used rescue antihistamines in all arms, with the placebo arms reporting the most usage (Table 26).

Table 26. Monthly use of rescue medication at Week 16, Trials 3101 and 3102

Statistic	Placebo	OPN-375		
		93-mcg BID	186-mcg BID	372-mcg BID
Trial 3101				
n[a]	63	73	64	68
n[b]	14	5	6	7
LS mean (days)	4.13	0.49*	1.44*	2.51
SE	0.72	0.70	0.71	0.69
Trial 3102				
n[a]	69	75	69	75
n[b]	17	13	10	14
LS mean (days)	5.05	2.34*	2.25*	3.06
SE	0.88	0.85	0.88	0.84

n[a] subjects with data, n[b] subjects reporting rescue use of nonsedating antihistamines.
*nominal p value less than 0.05 for comparison to placebo. Statistics from MMRM.
Source. NDA 209,022, CSR OPN-FLU-NP-3101 and OPN-FLU-NP-3102, Table 14.2.13.

Reviewer comment. The additional secondary endpoints generally support a treatment effect for all OPN-375 doses. The differences in days of rescue medication use between treatment arms is small and likely not large enough to expect an impact on other efficacy parameters.

6.1.7 Subpopulations

OPN-375 has not been studied in subjects less than 18 years of age. There were insufficient non-white subjects and subjects over 65 years of age to identify clinically meaningful differences in the subgroups.

Exploratory subgroup analysis of the efficacy database for both coprimary endpoints demonstrated that all three doses were superior to placebo for each gender and region (Table 27 and Table 28).

Table 27. Subgroup summary for reduction in nasal congestion at week 4

Subgroup		Statistic	Placebo	OPN-375		
				93-mcg BID	186-mcg BID	372-mcg BID
Trial 3101						
Gender	Female	n (%)	42 (51%)	39 (48%)	32 (40%)	42 (53%)
		Mean (SD)	-0.3 (0.6)	-0.6 (0.7)	-0.7 (0.8)	-0.7 (0.7)
	Male	n (%)	35 (43%)	39 (48%)	47 (59%)	36 (46%)
		Mean (SD)	-0.3 (0.6)	-0.5 (0.6)	-0.5 (0.6)	-0.7 (0.7)
Region	USA	n (%)	34 (41%)	36 (44%)	35 (44%)	35 (44%)
		Mean (SD)	-0.2 (0.6)	-0.4 (0.6)	-0.5 (0.6)	-0.7 (0.7)
	Other	n (%)	64 (78%)	71 (88%)	71 (89%)	67 (85%)
		Mean (SD)	-0.3 (0.6)	-0.6 (0.7)	-0.6 (0.7)	-0.7 (0.7)
Trial 3102						
Gender	Female	n (%)	35 (44%)	38 (48%)	34 (43%)	26 (32%)
		Mean (SD)	-0.2 (0.7)	-0.7 (0.7)	-0.8 (0.8)	-0.7 (0.7)
	Male	n (%)	42 (53%)	41 (51%)	44 (55%)	56 (68%)
		Mean (SD)	-0.3 (0.5)	-0.5 (0.7)	-0.6 (0.6)	-0.6 (0.7)
Region	USA	n (%)	8 (10%)	9 (11%)	8 (10%)	9 (11%)
		Mean (SD)	0.1 (0.5)	-0.5 (0.6)	-0.9 (0.7)	-0.3 (0.6)
	Other	n (%)	69 (87%)	70 (88%)	70 (88%)	73 (89%)
		Mean (SD)	-0.3 (0.6)	-0.6 (0.7)	-0.6 (0.7)	-0.7 (0.7)

N = number of subjects in each treatment arm; SD= standard deviation; BID= twice daily.
Missing values not imputed.
Source: Statistical Review by Dr. Feng Li, Table 13 and 15.

Table 28. Subgroup summary for reduction in nasal polyp grade at week 16

Subgroup		Statistic	Placebo	OPN-375		
				93-mcg BID	186-mcg BID	372-mcg BID
Trial 3101						
Gender	Female	n (%)	36 (44%)	37 (46%)	29 (36%)	41 (52%)
		Mean (SD)	-0.7 (1.4)	-1.4 (1.6)	-1 (1.3)	-1.1 (1.1)
	Male	n (%)	32 (39%)	38 (47%)	39 (49%)	34 (43%)
		Mean (SD)	-0.6 (1.4)	-0.8 (1.2)	-1.4 (1.5)	-1.2 (0.9)
Region	USA	n (%)	29 (35%)	33 (41%)	26 (33%)	33 (42%)
		Mean (SD)	-0.8 (1.5)	-1.2 (1.7)	-1.3 (1.5)	-1.1 (1)
	Other	n (%)	39 (48%)	42 (52%)	42 (53%)	42 (53%)
		Mean (SD)	-0.6 (1.3)	-1 (1.2)	-1.2 (1.4)	-1.2 (1.1)
Trial 3102						
Gender	Female	n (%)	33 (42%)	38 (48%)	33 (41%)	26 (32%)
		Mean (SD)	-0.3 (0.9)	-1.6 (1.4)	-1 (1.1)	-1.7 (1.4)
	Male	n (%)	37 (47%)	41 (51%)	42 (53%)	56 (68%)
		Mean (SD)	-1 (1.4)	-1 (1)	-1.3 (1.5)	-1.2 (1.2)
Region	USA	n (%)	5 (6%)	9 (11%)	7 (9%)	9 (11%)
		Mean (SD)	0.6 (0.9)	-1.1 (1.4)	-0.3 (1)	-1.7 (1.2)
	Other	n (%)	65 (82%)	70 (88%)	68 (85%)	73 (89%)
		Mean (SD)	-0.8 (1.2)	-1.3 (1.2)	-1.2 (1.4)	-1.3 (1.3)

N = number of subjects in each treatment arm; SD= standard deviation; BID= twice daily.
Missing values not imputed.
Source: Statistical Review by Dr. Feng Li, Table 14 and 16.

Analysis of changes in ACT and FEV1 for subjects with comorbid asthma in both pivotal trials suggests no clinically meaningful changes in either value among the four treatment arms.

Reviewer comment. This reviewer does not recommend additional labeling for subpopulations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant selected twice daily dosing for OPN-375 based on the dosing frequency of approved fluticasone products (i.e. Flovent® HFA, Flonase®) and prior clinical experience with the delivery of fluticasone propionate using a similar OptiNose device. The Applicant selected to study doses of OPN-375 that contain higher concentrations of fluticasone propionate than that recommended for allergic rhinitis based on the anticipation that higher doses are required for efficacy with nasal polyps (e.g. Nasonex® in United States, Flixonase™ Nasule Drops in Europe).

In Trials 3101 and 3102, the similarity of instantaneous and reflective nasal symptom scores suggests a durability of effect at the conclusion of the 12-hour interval, and supports the proposed twice daily dosing frequency.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Applicant collected data on multiple efficacy parameters throughout the double-blind period to demonstrate the persistence of efficacy. The nominal improvement in total polyp grade and change in congestion/obstruction symptom scores, i.e. the coprimary endpoints, support persistence of efficacy and lack of tolerance of effects over the course of the double-blind period.

6.1.10 Additional Efficacy Issues/Analyses

For Trials 3101 and 3012, the Applicant's exploratory efficacy analysis of total polyp grade demonstrated continued improvement for each treatment arm and a decrease in the treatment difference between the original placebo and OPN-375 arms during the OLE.

The Applicant completed exploratory analysis of total polyp grade in subjects with a history of chronic sinusitis and nasal polyps in Trials 3203 and 3204. At the Trial 3203 EOS visit, for the 34 subjects with chronic sinusitis and nasal polyps (baseline mean total grade 2.8, SD 1.17), 70.6% achieved ≥ 1 point improvement in total polyp grade and 47.1% achieved polyp elimination in ≥ 1 nostril. At the Trial 3204 EOS visit, among the 102 subjects with chronic sinusitis and nasal polyps (baseline mean total grade 2.9, SD 1.15), 63% of subjects demonstrated ≥ 1 point improvement in total polyp grade and 48% of subjects demonstrated polyp elimination in ≥ 1 nostril.

Reviewer comment: While acknowledging that each analysis is exploratory and the trial populations in Trials 3203 and 3204 were outside the indication, the data are supportive of a nasal polyp treatment effect for OPN-375.

7 Review of Safety

Safety Summary

This NDA submission contains adequate data to support the safety of OPN-375 for the treatment of nasal polyps in patients 18 years of age and older. The primary evaluation of safety focused on the 16-week trials in adults with nasal polyps (Trials 3101 and 3102). Trials 3203 and 3204 provide support of long-term safety of 372-mcg OPN-375 BID in a related population of adults with chronic sinusitis with and without nasal polyps.

Overall, the safety review identified no new safety signals that differ from both the known safety profile of fluticasone propionate and class effects of intranasal

corticosteroids. The development program reported no deaths. Expected drug-class AEs, including serious, non-serious and those leading to drug withdrawal, occurred more frequently in all OPN-375 arms compared to the placebo arm. The most common AEs observed in the OPN-375 arms were epistaxis, nasopharyngitis, nasal congestion, and nasal septal ulceration, with epistaxis demonstrating a small dose-response. Other local AEs of interest including posterior subcapsular cataracts, elevated IOP, and nasal septal perforation were identified in subjects exposed to OPN-375, but events occurred infrequently and without a clear dose-response.

The RLD Flovent® HFA supports the systemic safety of OPN-375 through the established PK bridge (Study 1102). The Applicant's literature summary provides supportive safety data for intranasal and inhaled fluticasone propionate, and introduces no new safety signals.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The global clinical development program for OPN-375 consisted of five clinical trials (one phase 1 PK study, two phase 3 safety and efficacy trials, and two phase 3 long-term safety trials). The safety review focused on determination of the local safety profile, dose-dependency of AEs, and corticosteroid-related class effects. The primary safety database consisted of the two randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trials that evaluated three doses of OPN-375 (93-mcg BID, 186 m mcg BID, and 372-mcg BID). Trials 3203 and 3204 evaluated long-term safety of 372-mcg OPN-375 BID. The Applicant also submitted the CSRs for two completed phase 2 studies with a related product, OptiNose-RFCP. As these trials did not use the to-be-marketed product, this review only briefly summarizes relevant safety findings in Section 7.7.

7.1.2 Categorization of Adverse Events

The Applicant defined AEs as any untoward medical occurrence in a subject associated with the use of an investigational drug whether or not considered related to the investigational drug, including new in onset or aggravated in severity or frequency from baseline. AEs included events identified by spontaneous reports, events of special interest identified on physical examination, and abnormal results from diagnostic procedures if they led to discontinuation, were clinically significant, required intervention, or further diagnostic evaluation that confirmed a significant abnormality. Treatment emergent AEs were those that occurred on or after treatment start date. For purposes of this review, summary tables present treatment emergent AEs.

The Applicant recorded all AEs in the CRF that occurred on or after the first dose of investigational drug through the final visit or early withdrawal. The Applicant used

MedDRA version 14.1 to code AEs and summarized AEs by preferred term within the System Organ Class (SOC). Investigators defined the severity of AEs per Table 29.

Table 29. Adverse event severity grading scale

Descriptor	Definition
Mild	Subject is aware of symptom, but easily tolerates it
Moderate	Subject has discomfort enough to cause interference with usual activity
Severe	Subject is incapacitated to work or perform usual activities
Source: NDA 209,022, Table 6 of protocols OPN-FLU-NP-3101 and OPN-FLU-NP-3102	

The Applicant defined SAEs as all events through 30-days after the last dose of investigational drug that met any of the following criteria:

1. Is fatal
2. Is life-threatening
3. Results in inpatient hospitalization or prolongs hospitalization
4. Results in persistent or significant disability or incapacity, or substantial disruption of the ability to conduct normal life functions
5. Congenital anomaly or birth defect
6. Important medical events thought to jeopardize the subject and/or require medical or surgical intervention to prevent 1 of the above outcomes

Investigators identified changes in nasal polyp grade or worsening symptoms associated with chronic sinusitis as AEs only if they met criteria for a SAE. Investigators recorded nasal examination findings in both the nasal examination CRF and the AE CRF when appropriate according to Table 30.

Table 30. Recording of adverse events from verbatim description in nasal examination

Verbatim Description	Preferred Terms
Sinus infection, acute sinus infection, sinusitis, acute sinusitis[a]	Acute sinusitis
Atypical congestion, atypical mucosal swelling, increased nasal stuffiness	Nasal congestion
Epistaxis, nose bleed (nonactive and active), blood-tinged mucous	Epistaxis
Redness, erythema, erosion, mucosal ulceration (area other than septum)	Nasal mucosal disorder
Redness on septum, erythema on septum	Nasal septum disorder
Septal erosion, septal ulceration	Nasal septum ulceration
Septal perforation	Nasal septum perforation
[a] For Trials 3203 and 3204, sinus infection and sinusitis coded to "sinusitis." Source: NDA 209,022, Module 2, SCS, Table 2.7.4-4.	

Reviewer comment. While the Applicant combined several verbatim terms into single preferred term (PT) categories, data from the nasal examination CRF allow for adequate evaluation of the contributing verbatim terms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant's Clinical Summary of Safety and Integrated Summary of Safety (ISS) analyzed pooled data from the following three populations across the four phase 3 trials: (1) DBP of Trials 3101 and 3102, (2) Trials 3203 and 3204, and (3) all four trials inclusive of the OLE from Trials 3101 and 3102. The number of subjects exposed to each investigational drug appears in Table 31.

Table 31. Summary of subjects in phase 3 trials

Trial	Dosing Regimen	Number of Subjects	
		OPN-375	Placebo
OPN-FLU-NP-3101	Placebo (DBP)	—	82
	OPN-375 93-mcg BID (DBP)	81	—
	OPN-375 186-mcg BID (DBP)	80	—
	OPN-375 372-mcg BID (DBP)	79	—
	OPN-375 372-mcg BID (OL)	282 (68[a])	—
OPN-FLU-NP-3102	Placebo (DBP)	—	79
	OPN-375 93-mcg BID (DBP)	80	—
	OPN-375 186-mcg BID (DBP)	80	—
	OPN-375 372-mcg BID (DBP)	82	—
	OPN-375 372-mcg BID (OL)	299 (70[a])	—
OPN-FLU-CS-3203	OPN-375 372-mcg BID (OL)	223 (193[b])	—
OPN-FLU-CS-3204	OPN-375 372-mcg BID (OL)	705	—
All Phase 3 trials	OPN-375 any dose	1518	—
	Placebo	—	161

BID=twice a day; DBP= double-blind period; OL= open-label; - = not applicable
[a]Number of placebo subjects from DB enrolling in OL with 372-mcg BID OPN-375
[b]193 new subjects exposed to OPN-375 (30 rolled over from 3204)
Source: NDA 209,022, reviewer adapted from SCS Table 2.7.4-5

This following safety review focuses on the evaluation of pooled safety data from the double-blind period of Trials 3101 and 3102, i.e. "pooled safety population." Given the differences in trial design (i.e. lack of comparator group) and subject population, this review analyzes the pooled open-label safety population from Trials 3203 and 3204 separately to provide support for short and long-term safety.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

In the phase 3 development Program, 1518 subjects received any dose of OPN-375. Exposure of 6 months or longer occurred exclusively in Trials 3203 and 3204, with 147 subjects receiving 12 months of OPN-375 (Table 32).

Table 32. Duration of OPN-375 exposure at any dose, Trials 3101, 3102, 3203, 3204

Variable Statistic	Any Exposure	≥ 3 months	≥ 6 months	≥ 12 months
Duration (days)				
N	1518	1238	605	147
Mean (SD)	136.9 (93.52)	158.2 (90.34)	224.3 (89.25)	375.6 (34.04)
Median	93.0	155.0	172.0	366.0
Range	1, 471	77, 471	165, 471	352, 471
Patient-years	568.9	536.3	371.5	151.2

N=number of subjects, SD= standard deviation. Exposure interval: 3 months = 75 days, 6 months = 165 days, 12 months = 345 days. Summary excludes data from clinical sites 069 and 105 (25 subjects).
Source: NDA 209,022, Module 5.3.5.3 ISS Tables, Summary 14.5.4.

In the double-blind period of Trials 3101 and 3102, over 93% of subjects received 85 days or more of OPN-375 in each trial arm. Mean exposure was nominally greater for all OPN-375 arms compared to the placebo arms, which may be related to subject dropouts from lack of efficacy in the placebo arm. Table 33 summarizes the duration of exposure for each treatment arm.

Table 33. Duration of OPN-375 exposure double-blind period, Trials 3101 and 3102, pooled safety population

	Placebo (N= 161)	OPN-375		
		93-mcg BID (N= 161)	186-mcg BID (N=160)	372-mcg BID (N= 161)
Double-blind period				
Mean (SD)	104.3 (28.36)	111.3 (16.85)	108.0 (23.23)	113.5 (10.82)
Median	113.0	113.0	113.0	113.0
Min, Max	2, 173	8, 143	1, 136	12, 146
1-28 days	9 (5.59)	2 (1.24)	7 (4.38)	1 (0.62)
29-56 days	8 (4.97)	3 (1.86)	2 (1.25)	0 (0)
57-84 days	3 (1.86)	0 (0)	1 (0.63)	2 (1.24)
>85 days	141(87.58)	156 (96.89)	150 (93.75)	158 (98.13)
Open-label extension				
n	138	150	139	154
Mean (SD)	57.2 (7.39)	56.8 (7.42)	56.7 (7.91)	57.4 (6.82)
Median	57	57	57	57
Min, Max	1, 73	13, 76	11, 90	1, 80

Min= minimum; Max= maximum; SD= standard deviation.

	Placebo	OPN-375
*All subjects received 372-mcg BID OPN-375. Subjects categorized according to original treatment arm. Source: NDA 209,022, MODULE 5.3.5.3 ISS Tables, Summary 14.5.1.1. Duration ranges reviewer calculated using ISS ADSL.xpt in JMP 12.0 and SAFFL(Y), PBOFL(Y), TRT02A and TR02DURD.		

Reviewer comment. The extent and duration of exposure generally meet ICH guidelines for the safety evaluation of drugs intended for chronic use for a non-life-threatening disease, and allow sufficient exposure for safety review. Trials 3203 and 3204 evaluated the highest OPN-375 dose (372-mcg BID), justifying the use of these trials for evaluation of long-term safety.

Demographics and Baseline Disease Severity

Within the pooled safety population, subjects were predominantly white, non-North American with a mean age of 45.4 years. There were relatively few Black/African American or Hispanic/Latino subjects in the safety database. While a majority of subjects were non-North American (69.2%), there were no clinically meaningful regional differences in demographics with respect to age, sex, ethnicity, and weight.

A majority of subjects had at least moderate nasal polyps with 35.7%, 79.0%, and 18.3% of subjects diagnosed with mild, moderate and severe polyp grade at baseline. The majority of subjects had no history of each type of nasal surgery, but 90.5% reported historical use of corticosteroids for the treatment of nasal polyps in the last 10 years. Small regional differences were noted in baseline treatment history; the North American subgroup reported more use of intranasal corticosteroids (97.5% vs 87.4%) and polypectomy by sinus surgery (34.3% vs 26.3%) than the non-North American subgroup.

Comparison of demographic and baseline disease severity factors between treatment arms suggests adequate randomization. Specifically, there were similar distributions of age, race, and region, with only small differences in gender between treatment arms in the pooled safety population. Fewer subjects in the 372-mcg BID arm reported history of polyp removal surgeries by both polypectomy and sinus surgery compared to the other three treatment arms. However, the similar mean and median total polyp grade, mean worse polyp grade and historical intranasal corticosteroid use across treatment arms suggests a similar disease burden (Table 34).

Table 34. Demographics and baseline characteristics, Trials 3101 and 3102, pooled safety population

Parameter Statistic	Placebo (N=161)	OPN-375			All (N=643)
		93-mcg BID (N= 161)	186-mcg BID (N=160)	372-mcg BID (N=161)	
Age (years)					
Mean (SD)	46.0 (12.5)	45.7 (13.2)	45.6 (12.8)	44.4 (12.4)	45.4 (12.7)
Range	18 to 76	18 to 82	18 to 74	18 to 73	18 to 82
Median	46	46	44.5	44	45
Age groups (%)					
≥65 years	8.7%	8.1%	6.9%	4.3%	7.0%
<65 years	91.3%	91.9%	93.1%	95.7%	93.0
Gender (%)					
Female	51.6%	49.1%	41.3%	42.2%	46.0%
Male	48.4%	50.9%	58.8%	57.8%	54.0%
Race (%)					
White	88.8%	92.5%	92.5%	89.4%	90.8%
Black	6.8%	3.7%	5.6%	8.1%	6.1%
Asian	3.1%	1.2%	1.3%	0	1.4%
Other	1.2%	2.5%	0.6%	2.5%	1.7%
Ethnicity (%)					
Hispanic/Latino	3.7%	1.9%	0	3.7%	2.3%
Weight (kg)					
Mean (SD)	80.6 (17.2)	82.4 (18.5)	80.4 (17.6)	80.4 (15.9)	81.0 (17.3)
Min, Max	46.7, 142.9	49, 166.0	48.7, 130.6	46.0, 155.6	46.0, 166.0
Region (%)					
North American	31.1%	31.1%	31.3%	29.8%	30.8%
Non-North American	68.9%	68.9%	68.8%	70.2%	69.2%
Comorbid Asthma (%)					
Yes	42%	32.7%	41.9%	41.4%	39.5%
Polyp grade					
Mean total score (SD)	3.8 (1.01)	3.7 (1.03)	3.9 (1.06)	3.8 (0.96)	3.8 (1.02)
Median total score	4.0	4.0	4.0	4.0	4.0
Mean worse score (SD)	2.1 (0.60)	2 (0.54)	2.1 (0.59)	2.1 (0.49)	2.1 (0.56)
Prior Nasal Polyp Treatment					
Any INCS last 10 yr., %	92.5%	88.8%	91.3%	89.4%	90.5%
Polyp removal via polypectomy					
≥1 surgery, %	39.1%	37.3%	36.2%	34.2%	36.7%
Mean surgeries (SD)	0.7 (1.10)	0.7 (1.08)	0.6 (1.03)	0.5 (0.89)	0.6 (1.03)

Polyp removal via sinus surgery					
≥1 surgery, %	29.2%	31.1%	31.2%	23.6%	28.8%
Mean surgeries (SD)	0.5 (0.89)	0.5 (0.84)	0.4 (0.74)	0.4 (0.78)	0.4 (0.81)

INCS= intranasal corticosteroid treatment; SD=standard deviation
Source: NDA 209,022, MODULE 5.3.5.3 ISS Tables, Summaries 14.2.1.1, 14.4.1.1, 14.3.1. Reviewer confirmed using ISS dataset ADSL.xpt in JMP 12.0.

Reviewer comment. The difference in prior polyp treatment between arms is small and unlikely to significantly affect the safety review. While the treatment arms each included only about 30% North American subjects, there is sufficient similarity between the two regional subgroups to justify the use of the Non-North American population in the safety review. Overall, the demographic and baseline characteristics adequately represent the typical profile of the indicated population to allow for a determination of safety.

7.2.2 Explorations for Dose Response

The development program explored the dose response in the two controlled, dose ranging phase 3 trials. Dose dependency of AEs is discussed in Section 7.5.1.

7.2.3 Special Animal and/or In Vitro Testing

The development program did not include special animal studies or in vitro testing.

7.2.4 Routine Clinical Testing

Routine testing included clinical laboratory studies (complete blood count [CBC], serum chemistry, urinalysis [dipstick]), urine drug screen, and pregnancy testing at screening to determine subject eligibility. The CBC included hemoglobin, hematocrit, erythrocyte count, mean corpuscular volume, leukocyte count and differential, and platelet count. The serum chemistry included alanine transferase, aspartate transferase, γ- glutamyl-transferase, albumin, total protein, glucose, sodium, potassium, calcium, chloride, urea, creatinine, and total bilirubin. Neither trial included nor required serum laboratory assessments beyond screening.

Reviewer comment: As the RLD supports the systemic safety of OPN-375, no further laboratory assessments were necessary to support the systemic safety of the proposed drug.

7.2.5 Metabolic, Clearance, and Interaction Workup

No additional studies were completed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

OPN-375 is an intranasal corticosteroid that may lead to local and systemic toxicities that are shared by similar drugs in this class. Potential systemic AEs of include hypercortisolism and adrenal axis suppression, immunosuppression, growth delay in children, and hypersensitivity reactions. Predicted local toxicities include epistaxis, nasal ulceration, nasal septal perforation, Candida infections, impaired wound healing, cataracts, and glaucoma. Cataracts may occur after prolonged corticosteroid use and are thought to be dose-related.

Given that OPN-375 appears to deliver corticosteroid more efficiently into the nasal passages and involves delivery of larger doses compared to Flonase®, the OPN-375 development program prospectively evaluated for local AEs through serial nasal and ocular examinations. This safety review evaluates the local toxicities in Section 7.3.5. As the Applicant relies on the systemic safety profile of the RLD, Flovent® HFA to support the systemic safety of OPN-375 (BE established in Section 4.4), the Applicant did not separately evaluate for systemic drug class effects.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in this submission.

7.3.2 Nonfatal Serious Adverse Events

In Trials 3101 and 3102, 5 subjects reported SAEs in the DBP, including 3 on active treatment: worsening of nasal polyps (93-mcg BID), positional vertigo (372-mcg BID), and menorrhagia (372-mcg BID). The subject with positional vertigo remained on investigational drug with resolution of the SAE following medical management. In the placebo group, 1 subject developed meningitis with associated ethmoid sinusitis on Day 97 of the trial.

Two additional SAEs occurred during the OLE of Trials 3101 and 3102, including pneumonia and worsening nasal polyps that required treatment for maxillary sinusitis. In Trials 3203 and 3204, twelve subjects reported an additional fourteen unique SAEs that were distributed across SOCs: migraine with aura, angina pectoris, gastric ulcer, gastritis, appendicitis, worsening depression, mitral valve prolapse, uterine leiomyoma, cholecystitis acute, hypotension, and dyspnea.

Reviewer comment. The two subjects on active treatment with worsening polyps likely reflect lack of efficacy. Overall, the pattern of SAE in the phase 3 program does not suggest clustering.

7.3.3 Dropouts and/or Discontinuations

In Trials 3101 and 3102, fewer OPN-375 subjects discontinued from the DBP than placebo subjects, with approximately 94.4% (93-mcg BID), 91.9% (186-mcg BID) and 97.5% (372-mcg BID) of OPN-375 subjects completing the DBP compared to 86.4% of placebo subjects. Lack of efficacy largely contributed to the observed difference between the placebo and treatment arms. Discontinuations secondary to protocol deviations occurred exclusively in the 93-mcg BID and 372-mcg BID arms, and were all related to subjects enrolling despite baseline cataracts. Examination of the general category "withdrawal by subject" and "other" revealed no consistent pattern or clinically meaningful cause for these discontinuations. Fewer subjects in the placebo (85.2%) and 186-mcg BID (86.9%) arms enrolled in the OLE, compared with both the 93-mcg BID (92.6%) and 372-mcg BID arms (95.1%); AEs diagnosed at the conclusion of the DBP contributed to the decreased enrollment for 186-mcg BID subjects. Overall, most subjects enrolling in the OLE also completed the OLE. Table 35 summarizes the discontinuations in Trials 3101 and 3102.

Table 35. Subject disposition, Trials 3101 and 3102, pooled safety population

Reason for dropout	PBO BID	OPN-375		
		93-mcg BID	186-mcg BID	372-mcg BID
ITT analysis set, n (%)	162 (100)	162 (100)	160 (100)	162 (100)
Safety Analysis set, n (%)	161 (99.4)	161 (99.4)	160 (100)	161 (99.4)
Double-blind period				
Completed DBP, n (%)	140 (86.4)	153 (94.4)	147 (91.9)	158 (97.5)
Prematurely discontinued, n (%)	22 (13.6)	9 (5.6)	13 (8.1)	4 (2.5)
Lack of efficacy	11 (6.8)	1 (0.6)	3 (1.9)	2 (1.2)
Adverse Event	6 (3.7)	3 (1.9)	4 (2.5)	1 (0.6)
Withdrawal by subject	5 (3.1)	2 (1.2)	5 (3.1)	0 (0)
Protocol deviation	0 (0)	3 (1.9)	0 (0)	1 (0.6)
Lost to follow-up	0 (0)	0 (0)	1 (0.6)	0 (0)
Open-label extension				
Enrolled in OLE, n (%)	138 (85.2)	150 (92.6)	139 (86.9)	154 (95.1)
Not enrolled in OLE, n (%)	2 (1.2)	3 (1.9)	8 (5.0)	4 (2.5)
Lack of efficacy	1 (0.6)	1 (0.6)	2 (1.3)	0 (0)
Adverse Event	1 (0.6)	0 (0)	4 (2.5)	1 (0.6)
Withdrawal by subject	0 (0)	2 (1.2)	1 (0.6)	2 (1.2)
Other	0 (0)	0 (0)	1 (0.6)	1 (0.6)
Completed OLE, n (%)	136 (84.0)	146 (90.1)	135 (84.4)	151 (93.2)
Discontinued OLE, n (%)	2 (1.2)	4 (2.5)	4 (2.5)	3 (1.9)
Lack of efficacy	1 (0.6)	0 (0)	3 (1.9)	1 (0.6)
Adverse Event	1 (0.6)	3 (1.9)	1 (0.6)	1 (0.6)
Withdrawal by subject	0 (0)	1 (0.6)	0 (0)	1 (0.6)

OLE = open-label extension; DBP= double-blind period; ITT = intention to treat, denominator for percentages are ITT population.
Source: NDA 209,022, Module 5.3.5.3 ISS Tables, Summary 14.1.1.1. Reviewer confirmed with ISS ADSL.xpt dataset, JMP 12.0, using IFFL (Y), DCRB, COMPDBFL, COMPOLFL, ENRLOLFL, DCROL by TRT02A.

In Trials 3204 and 3204, 78.8% of the 923 subjects completed the trials (inclusive of all sites). Reasons for early discontinuation included lost to follow-up (6.7%), withdrawal by subject (5.1%), protocol deviation (2.3%) and AEs (4.8%).

Reviewer comment. The increased discontinuations in Trials 3203 and 3204 are expected in a trial of longer duration. Overall, the percentage of subjects remaining in the trial allows for adequate safety evaluation.

7.3.4 Significant Adverse Events

Discontinuations

The Applicant analyzed AEs leading to discontinuation according to the actual time of discontinuation (i.e. DBP, between DBP and OLE, during OLE). However, multiple subjects discontinued prior to or during the OLE as a result AEs diagnosed during the final DBP visit when the final ocular and nasal examinations occurred (i.e.V7). Therefore, in order to fully characterize the AE profile, this review compared all AEs diagnosed in the DBP that lead to discontinuation prior to the OLE. Comparison of the reasons for discontinuation by this method captures multiple local nasal and ocular AEs leading to discontinuation in the OPN-375 arms, including nasal septal perforations, increased IOP, and cataracts (Table 36).

Table 36. Adverse events with onset in the double-blind period leading to discontinuation, Trials 3101 and 3012, pooled safety population

Treatment arm	Subject ID	Age/Sex/ Race	Onset (day)	Adverse Event	Severity
PBO	183115	66/M/W	3	Insomnia, ↑lacrimation, rhinorrhea	mild to severe
			3	Nasal congestion & discomfort, throat irritation	severe
			6		moderate
			9	Nasal septal ulceration	mild
	131202	44/F/W	9	Acute sinusitis	moderate
	304114	37/F/W	10	Asthma exacerbation	moderate
	807102	48/F/W	15	Asthma exacerbation	mild
	079204	37/F/W	22 25	Asthma Nasal congestion	moderate severe
	138108	53/M/W	34	Bronchitis	moderate
	313214	31/M/B	97(V7)*	Meningitis and Sinusitis (SAE) with subsequent ethmoid surgery	severe
	205103	66/M/W	110(V7)*	IOP increased	mild

Treatment arm	Subject ID	Age/Sex/ Race	Onset (day)	Adverse Event	Severity
93-mcg BID	805101	28/F/W	10	Throat tightness	mild
	704119	56/M/W	30	Nasal septal perforation	mild
	515201[1]	28/F/W	54	Nasal septal perforation	severe
	046105	32/M/W	111(V7)*	IOP increased	mild
	038106	36/M/B	114(V7)*	Cataract (cortical & nuclear)	mild
	511204	35/F/W	122(V7)*	IOP increased	mild
186-mcg BID	307102	54/M/W	6	Acute sinusitis	moderate
	122203	36/M/W	7	Epistaxis	mild
	027104[2]	65/M/W	9	Eye pain, vision blurred	moderate
	136106	64/M/W	35	Asthma exacerbation	moderate
	183101	36/F/W	115(V7)*	Nasal septum perforation	mild
	124201	27/M/W	116(V7)*	Cataract (subcapsular)	mild
	403208	56/F/W	134(V7)*	IOP increased	mild
	403205	44/M/W	136(V7)*	IOP increased	moderate
372-mcg BID	044105	33/M/W	34	Acute sinusitis	mild
	511202	48/M/W	105(V7)*	IOP increased	mild
	040101[3]	51/F/W	114(V7)*	Cataract subcapsular	mod

V7= visit 7/end of double-blind period
[1]Enrolled despite nasal surgery < 6 months prior to entry.
[2]Subject had a history of visual acuity changes
[3]Enrolled despite baseline bilateral grade 1 cataract
*Discontinuation after DBP, but AE leading to discontinuation noted in the DBP at V7.
Source: NDA 209,022, Module 5.3.5.1, OPN-FLU-NP-3101 CSR and OPN-FLU-NP-3102 CSR, Section 14.3.3, Patient Narratives.

In the OLE, 1 additional subject from the original OPN-375 186-mcg BID arm developed epistaxis on Day 157 leading to discontinuation.

In Trials 3203 and 3204, of the 44 (4.8%) subject withdrawals for AEs, the most common reported AE was epistaxis (1.2%). The remaining AEs of interest led to discontinuations in fewer than 1% of subjects: nasal septal ulceration (2), nasal septum perforation (2), oropharyngeal pain (2), nasal discomfort (1), nasal odor (1), increased IOP (3), oral/nasal candidiasis (2), facial swelling/edema (2), headache (5), cataract (1), Fuch's syndrome (1), acute sinusitis/sinusitis (3), ageusia (3), and anosmia (3).

Reviewer comment. Elevated IOP, epistaxis, cataract formation, and nasal septum perforations are reported with other nasal corticosteroids and are likely drug-related. The data do not suggest a dose-dependent increase in discontinuations between the middle and high OPN-375 dose.

Drug Interruption

In the pooled safety population, 6 subjects required interruption in the investigational drug for AEs in the DBP. Epistaxis was the most common reason for drug interruption, and occurred in in the OPN-375 arms exclusively. One 372-mcg BID subject required three separate periods of drug interruption for a nasal mucosal ulcer (DBP) and nasal septum ulcerations (DBP and OLE, respectively). In the OLE, two additional subjects from the original 372-mcg BID arm required drug interruption for food poisoning and epistaxis. Table 37 summarizes the number of AEs requiring drug interruption in the DBP of Trials 3101 and 3102.

Table 37. Number of adverse events requiring drug interruption in double-blind period, Trials 3101 and 3102, pooled safety population

Adverse event	Placebo (N = 161)	OPN-375		
		93-mcg BID (N = 161)	186-mcg BID (N = 160)	372-mcg BID (N = 161)
Epistaxis	0	2	1	1
Nasal mucosal ulcer (LLT)	0	0	0	1
Nasal septum ulceration	0	0	0	1
Vertigo positional	1	0	0	0

LLT= Lower-Level Term, BID = twice daily.
Source: Reviewer calculated with JMP 12.0 using ISS ADAE.xpt dataset; Population SSFL(y), PBOFL(y), APHASE (double-blind treatment), TRTEMFL(Y), AEACN/ AEACN1/AEACN2 (drug interrupted) by AEDCODE.

Severe Adverse Events

In Trials 3101 and 3102, the majority of AEs were mild or moderate in severity. A total of 8 subjects reported severe AEs, including 4 placebo and no 93-mcg BID subjects. Respiratory, thoracic and mediastinal disorders accounted for one-half of the severe AEs. The four severe AEs among OPN-375 subjects occurred exclusively in the middle and high dose arms (Table 38).

Table 38. Severe adverse events in double-blind period, Trials 3101 and 3102, pooled safety population

System Organ Class Preferred Term	Placebo (N = 161)	OPN-375		
		93-mcg BID (N = 161)	186-mcg BID (N = 160)	372-mcg BID (N = 161)
Overall	4 (2.5)	0	3 (1.9)	1 (0.6)
Infections and infestations	1 (0.6)	0	1 (0.6)	1 (0.6)
Meningitis	1 (0.6)	0	0	0
Sinusitis	1 (0.6)	0	0	0
Rhinitis	0	0	0	1 (0.6)
Gastroenteritis viral	0	0	1 (0.6)	0
Investigations	0	0	1 (0.6)	0

Intraocular pressure increased	0	0	1 (0.6)	0
Respiratory, thoracic, and mediastinal disorders	3 (1.9)	0	1 (0.6)	0
Nasal congestion	3 (1.9)	0	1 (0.6)	0
Nasal discomfort	1 (0.6)	0	0	0
Throat irritation	1 (0.6)	0	0	0

AE = adverse event; N = total number in the data set; n (%) = number (percentage) in the subset.
Source: NDA 209,022, Module 5.3.5.3 ISS Tables, Summary 14.9.1.1.

7.3.5 Submission Specific Primary Safety Concerns

The Applicant prospectively monitored subjects for local nasal and ocular AEs, including nasal mucosal and septal abnormalities, nasal candidiasis, epistaxis, cataracts, and elevated IOP. The following section reviews theses safety concerns using both spontaneous AE reports and findings from physical examinations.

Local Nasal Adverse Events

Epistaxis

The Applicant's definition of epistaxis AEs incorporated spontaneous reports and nonactive and/or active bleeding identified by endoscopic examination. Using the broad definition, epistaxis AEs occurred more frequently in all OPN-375 arms than the placebo arm, and exhibited a small dose-response, occurring in 15.5%, 21.9%, 23.0% and 6.2% of 93-mcg BID, 186-mcg BID, 372-mcg BID and placebo subjects, respectively. However, when examining only spontaneous cases, the dose-response relationship between the middle and high doses disappeared. Most epistaxis AEs resolved without treatment interruption or withdrawal, and only one subject required a medical procedure (i.e. placement of cotton ball in nasal vestibule for a few minutes). In terms of epistaxis severity, four subjects reported moderate spontaneous epistaxis (186 mcg-bid and 372-mcg BID arms), and there were no severe epistaxis AEs. Table 39 summarizes epistaxis from Trials 3101 and 3102.

Table 39. Epistaxis in double-blind period, Trials 3101 and 3102, pooled safety population

Category of Epistaxis	Placebo (N = 161)	OPN-375		
		93-mcg BID (N = 161)	186-mcg BID (N = 160)	372-mcg BID (N = 161)
Any epistaxis AE, n (%)	10 (6.2)	25 (15.5)	35 (21.9)	37 (23.0)
Spontaneous reported epistaxis, n (%)	4 (2.5)	7 (4.3)	19 (11.9)	16 (9.9)

AE = adverse event; N = total number in the data set; n (%) = number (percentage) in the subset.
Source: NDA 209,022, Module 2.7.4. Summary of Clinical Safety, Table 2.7.4-29.

The incidence and severity of epistaxis AEs in the OLE and Trials 3203 and 3204 were generally consistent with the DBP of Trials 3101 and 3102.

Reviewer comment. The overall incidence of epistaxis was higher than reported with other intranasal corticosteroids, but likely reflects the definition of epistaxis. This reviewer considers the spontaneous reports to be most clinically meaningful, and these rates were consistent with that of the Nasonex® polyp development program. However, for labeling purposes, this reviewer recommends including the overall rate in order to capture all reported events with a footnote describing the contributing cases.

Nasal Mucosal Abnormalities

The Applicant collected data on nasal mucosal disorders during nasal endoscopic examinations as described in Section 5.3.1. Investigators assigned a severity and verbatim term (VT) to each mucosal abnormality using prespecified definitions. For purposes of AE classification, the Applicant coded multiple VTs to the single MedDRA preferred term (PT) "nasal mucosal disorders," and assigned a separate AE severity. As a result, this review will consider both the MedDRA AE classification and VT as summarized in Table 40.

Table 40. Definition and coding of nasal mucosal disorders, Trials 3101 and 3102

Verbatim Term and Severity	Description	MedDRA PT / LLT
Nasal mucosal erythema	• Redness	Nasal mucosal disorder / Nasal mucosal erythema
Nasal mucosal erosion / mild	• Erosion abnormally eroded or abraded the epithelial surface • Considered not clinically significant.	Nasal mucosal disorder / Nasal mucosal ulcer
Nasal mucosal ulcerations / moderate	• Erosion deeper than a surface abrasion, of limited clinical significance • Did not require more than routine monitoring or care	Nasal mucosal disorder / Nasal mucosal ulcer
Nasal mucosal ulceration / severe	• Ulceration clinically significant with possible effects on underlying structures • Warranted intervention, or specific care.	Nasal mucosal disorder / Nasal mucosal ulcer

[1]Verbatim term and severity are determined by investigators based on nasal examination

In the pooled safety population, the overall AE incidence of "nasal mucosal disorders" (PT) was greater in all OPN-375 arms than the placebo arm: 10.6%, 8.8%, 6.8%, and 4.3% for 93-mcg BID, 186-mcg BID, 372-mcg BID and placebo arms, respectively. Both LLTs "nasal mucosa erythema" and "nasal mucosal ulcer" were reported more frequently in the OPN-375 arms than the placebo arm, and without a clear dose-response. All cases of LLT "nasal mucosal ulcer" were derived from the VT "nasal mucosal erosions," except for 3 "nasal mucosal ulcers" (VT) reported in two 93-mcg BID and one 186-mcg BID subject (Table 41). No nasal mucosal ulcers led to investigational drug discontinuation.

Table 41. Nasal mucosal disorder adverse events in double-blind period, Trials 3101 and 3102, pooled safety population

Preferred Term Lower level term	Placebo (N = 161)	OPN-375		
		93-mcg BID (N = 161)	186-mcg BID (N = 160)	372-mcg BID (N = 161)
Nasal mucosal disorders, all (PT), n (%)	7 (4.3)	17 (10.6)	14 (8.8)	11 (6.8)
Nasal mucosal erythema (LLT), n (%)	6 (3.7)	12 (7.4)	9 (5.6)	8 (5.0)
Nasal mucosal ulcer (LLT), n (%)	1 (0.6)	7 (4.3)	6 (3.8)	4 (2.5)

N = total number in the data set; n (%) = number (percentage) in the subset.
Source: Reviewer calculated using ISS ADAE.xpt data set in JMP 12.0. PBOFL(y), APHASE (DOUBLE-BLIND TREATMENT), AEDECOD and AELLT by TRTA.

Open-label data from all four phase 3 trials were generally consistent with these findings.

Reviewer comment. For labeling purposes, this reviewer recommends separation of the PT "nasal mucosal disorder" into the LLTs, as they represent adverse reactions with distinct clinical significance.

Nasal Septal Abnormalities

The Applicant coded VTs from the nasal examination to prespecified MedDRA PT. The following section compares the VTs for the treatment arms in order to understand the safety profile of OPN-375 (Table 42).

Table 42. Definition and coding of nasal mucosal disorders, Trials 3101 and 3102

Verbatim Term[1]	Description	MedDRA PT
Nasal septum, erosion	• mild, evidence of epithelial layer erosion	Nasal septum ulceration
Nasal septum ulceration	• moderate, evidence of ulceration through the epithelial layer with exposed cartilage	Nasal septum ulceration
Nasal septum perforation	• severe, perforation of the cartilage.	Nasal septum perforation

[1]Verbatim term and severity are determined by investigators based on nasal examination

Nasal septal erosions, ulcerations, and perforations occurred more often in the OPN-375 arms than the placebo arm, but there was not a consistent dose-response. The majority of septal abnormalities were erosions that resolved without treatment interruption; 5 subjects required concomitant medications for erosions or ulcerations. During the DBP, there were two ulcerations in the 372-mcg BID arm that resolved without drug interruption, and 3 perforations (93-mcg BID and 186-mcg BID arms). The 3 perforations occurred in subjects with a history of nasal and/ or sinus surgery. Only one subject progressed from erosion to ulceration (372-mcg BID arm). Table 43 summarizes the nasal septal abnormalities.

Table 43. Nasal septal abnormalities in double-blind period by verbatim term on nasal examination CRF, Trials 3101 and 3102, pooled safety population

Verbatim term	Placebo (N = 161)	OPN-375		
		93-mcg BID (N = 161)	186-mcg BID (N = 160)	372-mcg BID (N = 161)
Nasal septum erosion, n (%)	2 (1.3)	8 (5.0)	11 (6.9)	10 (6.2)
Nasal septum ulceration, n (%)	0 (0)	0 (0)	0 (0)	2 (1.2)
Nasal septum perforation, n (%)	0 (0)	2[a] (1.2)	1 (0.6)	0 (0)

N = total number in the data set with baseline and post baseline nasal examinations; n (%) = number (percentage) in the subset. Subjects counted once, for most severe finding.
[a]Subject 515201 had a septal perforation and not ulceration per narrative description.
Source: NDA 209,022, Module 5.3.5.3 ISS Tables, Summary 14.12.1.1 and errata in OPN-FLU-NP-3102 CSR.

The following section provides narrative summaries for the nasal septal perforations:

- Subject 3101-704119 in the OPN-375 93-mcg BID arm developed a 0.7 x 0.4 cm anterior nasal septal perforation at Week 4 and withdrew from the trial. The subject had a history of nasal surgery including septoplasty 15 months prior to screening and reported prior use of budesonide with formoterol fumarate and fluticasone propionate.
- Subject 3101-183101 in the OPN-375 186-mcg BID arm was diagnosed with a 5 mm anterior nasal septal perforation at Week 16 and withdrew from the trial. Investigators identified mild right sided nonactive bleeding at Visit 5 and left sided bleeding at Visit 6. The subject had a history of sinus surgery for polyp removal. Historical CT scan suggested a history of bilateral functional endoscopic sinus surgery with probable partial ethmoidectomy. The subject had multiple prior concomitant medications including fluticasone propionate, budesonide, cetirizine, allergy shots, salbutamol, and pseudoephedrine.
- Subject 3101-515201 in the OPN-375 93-mcg BID arm developed a “very small” anterior nasal septal perforation at Week 8. The subject stopped trial medication on Day 89, and final termination visit was on Day 155. The subject enrolled in the trial despite a history of septoplasty / conchoplasty 4 months prior to screening. Prior concomitant medications included fluticasone furoate.

Open-label data from all four phase 3 trials was generally consistent, and included three subjects with confirmed nasal septal perforations, 2 of which reported a history of nasal surgery. The narratives for the three nasal perforations follow:

- Subject 107304 developed an asymptomatic nasal septal perforation on Day 87, and the subject completed the trial with no change in severity. The subject’s medical history included 2 prior sinus surgeries, including one polyp removal. After review of a postoperative CT scan from 3 years prior, the investigators deemed the perforation ongoing at the time of trial entry despite lack of visualization on baseline nasal

examination. Prior concomitant medications included mometasone furoate, fluticasone propionate, and fluticasone furoate.

- Subject 018405, a 57 year old female with chronic sinusitis and nasal polyps, developed an asymptomatic anterior nasal septal perforation on Day 33 and withdrew from the trial. Investigators noted mild bilateral edema on screening nasal examination. Relevant prior medical history included a left deviated septum and two sinus surgeries, including one polyp removal. Prior concomitant medications included mometasone furoate, fluticasone propionate, fluticasone furoate, triamcinolone, and flunisolide. The subject received epinephrine during nasal endoscopic procedures.
- Subject 071403, a 54 year old black male with chronic sinusitis without polyps was diagnosed with a right sided 1 x 1 cm septal perforation on Day 29 with bordering smooth mucosa without crusting. Investigators interpreted this finding as chronic and present prior to trial entry. However, screening examination was only notable for moderate and severe erythema in the left middle turbinate and gross edema on the right inferior turbinate. The subject remained in the trial without change in the nasal septum perforation. Prior concomitant medications included fluticasone furoate for 11 months prior to trial enrollment.

Reviewer comment. Overall, the data suggest that nasal septal abnormalities occur infrequently with OPN-375 treatment. There are insufficient ulceration and perforation events to draw conclusions about dose dependency. Prior history of sinus surgery may increase the risk of nasal septal perforations and ulcerations. For labeling purposes, the Applicant's proposal to use the AE PT Nasal septum ulceration to encompass the verbatim terms nasal septal erosion and nasal septal ulceration is acceptable and consistent with this reviewer's proposed terminology for labeling nasal mucosal ulcerations. While there was evidence of a perforation on post-operative CT examination for Subject 107304, the imaging was obtained over 3 years prior to trial enrollment, and the perforation was not visualized on baseline exam. Therefore, this reviewer recommends inclusion of this case in the label.

Ocular Adverse Events

Increased intraocular pressure

In the pooled safety population, there were no meaningful differences in mean IOP at the conclusion of the 16-week DBP for any treatment arm. Change in IOP across treatment arms identified about 0 to 2 subjects per treatment arm, including placebo, with an average change from baseline of >6 mm Hg. The highest IOP in the trials was 24 mmHg, and occurred in both the placebo and 93-mcg BID arms. Table 44 summarizes all subjects with elevated IOP >21 mmHg.

Table 44. Subjects with increased intraocular pressure, Trials 3101 and 3102, pooled safety population

Subject	Treatment arm*	IOP (mm Hg) OD/OS				Comments
		V_1	V_7	V_u	V_8/EOS	
Double-blind period						
031111	PBO	19/16	19/22	14/14	14/15	↑ IOP at V7, continued into OLE.
205103	PBO	17/19	24/23	NA	NA	Completed DBP, but did not enter OLE.
046105	93-mcg	16/20	17/22	NA	18/20	Continued into OLE in error. Discontinued ~2 weeks into OLE.
511204	93-mcg	20/19	19/23	21/21	23/24	Continued into OLE in error. Discontinued d140 of OLE.
403205	186-mcg	20/20	22/23	NA	NA	Completed DBP, but did not enter OLE
403208	186-mcg	20/20	23/22	NA	NA	Completed DBP, but did not enter OLE
705204	186-mcg	20/20	23/21	17/19	19/19	Completed trial. ↑ IOP V7 due to "a stressful situation," resolved at unscheduled visit.
511202	372-mcg	20/20	21/23	20/21	22/22	↑ IOP at V7, and entered OLE in error. Discontinued Day 171 of OLE.
Open-label extension						
403215	PBO>372mcg	20/19	21/21	NA	22/22	Completed trial
405201	93>372-mcg	17/18	20/20	NA	20/20	Completed trial. AE listed as elevated IOP, but values less than 21 mmHg
205106	186>372-mcg	20/18	17/19	NA	23/24	Completed trial

DBP = double-blind period; IOP = intraocular pressure; NA= not applicable; OLE = open-label extension; U= unscheduled; OD= oculus dextrus; OS= oculus sinister, V_1= visit 1/screening, V_7= visit 7/end of double-blind period, V_u= unscheduled visit; V_8/EOS= visit 8/end of study
*all doses are BID.
Values reported as average of last 2 measurements per eye. Values over 21 mmHg are underlined.
Source: NDA 209,022, Module 5.3.5.1, OPN-FLU-NP-3101 CSR, Listings 16.2.1.1, 16.2.1.2, 16.2.8.1, 16.2.9.2; OPN-FLU-NP-3102 CSR, Listings 16.2.1.1, 16.2.1.2, 16.2.8.1, 16.2.9.2.

Open-label data from Trials 3203 and 3204 were consistent with Trials 3101 and 3102; there were no clinically significant changes in mean IOP, and 8 subjects reported increased IOP in at least one eye during the trials (Table 45).

Table 45. Subjects developing increased intraocular pressure, Trials 3203 and 3204, safety population

Trial 3203 (12 months duration)				
Subject	**IOP (mm Hg) OD/OS By Visit**			**Comments**
	V_1	**V_5**	**V_7/EOS**	
073305	17/17	19/20	18/18	Identified as IOP, but average IOP was < 21 at V5.
073306	18/18	22/24	17/16	Discontinued after IOP > 21 mm Hg at V5 (Day 178).
073313	20/19	17/18	22/22	Completed trial. IOP > 21 mm Hg at EOS visit.
080312	19/16	NA	23/24	Discontinued due to AE of headache. IOP > 21 mm Hg at the EOS visit.
080319	22/22	22/20	23/22	V1 IOP > 21 mmHg, but normal at unscheduled visit prior to enrollment. V5 IOP elevated, but discontinued after V_7.
Trial 3204 (4 months duration)				
Subject	**IOP (mm Hg) OD/OS By Visit**			**Additional Information**
	V_1		**V_4/EOS**	
088404	20/21		19/22	Completed trial
093462	16/20		22/21	Completed trial
105407*	18/20		19.5/21.5	Completed trial

Values reported as average of last 2 measurements per eye.
V= visit; EOS= end of study; IOP = intraocular pressure; OD= oculus dextrus; OS= oculus sinister.
*Subject from site 105.
Source: NDA 209,022, Module 5.3.5.2, OPN-FLU-CS-3203 CSR, Listing 16.2.8.1, Listing 16.2.11; OPN-FLU-CS-3204 CSR, Listing 16.2.8.1 and 16.2.11.

Reviewer comment: The data suggest that OPN-375 may lead to increased IOP in a minority of subjects. This finding is consistent with the known safety profile of intranasal corticosteroids where a small number of subjects will be expected to be steroid responders. Note that these data only reflect a low risk population; the protocols excluded subjects with steroid sensitivity and/or a history of glaucoma. Finally, the data do not rule out a risk of glaucoma, as glaucoma is not expected to develop within the short duration of the trials.

Cataract Formation

In the pooled safety population, 8 subjects developed treatment emergent cataracts during the DBP. The three reported posterior subcapsular cataracts occurred in subjects receiving OPN-375 186-mcg BID or 372-mcg BID, and one of these subjects had a baseline nuclear cataract (Table 46). Two additional subjects (93-mcg BID and 186-mcg BID arms) with baseline cataracts experienced no change in their cataracts while on active treatment.

Table 46. Treatment emergent cataracts, Trials 3101 and 3102, pooled safety population

Subject	Arm	Visit	Right (subtype/grade)	Left (subtype/grade)	Comments
Double-blind period					
510203	PBO	7	cortical/1	cortical/1	Completed OLE
117107	PBO	7	none	nuclear/1	Completed OLE
		8	none	nuclear/1	
802102	PBO	7	nuclear/1+	none	Completed OLE
		8	nuclear/1+	none	
038106	93-mcg	7	cortical/1, nuclear/1	cortical/1, nuclear/1	Completed DBP; discontinued OLE due to cataracts.
		8 (ET)	cortical/1, nuclear/1	cortical/1, nuclear/1	
801103	186-mcg	7	cortical/1	cortical/1	Completed OLE
		8	cortical/1	cortical/1	
124201	186-mcg	7	none	P. subcapsular/1	Completed DBP; discontinued at V7.
040101	372-mcg	1(S)	nuclear/1	nuclear/1	Enrolled in error. Completed DBP. Discontinued at V7.
		7	nuclear/1	nuclear/1, posterior subcapsular/1	
313213[a]	372-mcg	8	nuclear/1	nuclear/1	Completed OLE
Open-label extension					
513210	186>372 mcg	8	cortical/1, posterior subcapsular/1	cortical/1, posterior subcapsular/1	Completed OLE
705202	PBO>372 mcg	8	nuclear/1	nuclear/1+	Completed OLE

AE = adverse event; V = visit; S=screening; ET= early termination; PBO=placebo. All doses BID.
[a]Nuclear cataracts at V8 (24 Nov 2014) but database incorrectly lists the date as 29 Sep 2014 (V7). Errata in section 2.7.4.9.1.
Source: NDA 209,022, Module 5.3.5.1, OPN-FLU-NP-3101 CSR, Listings 16.2.1.1, 16.2.1.2, 16.2.8.1, 16.2.9.2 and OPN-FLU-NP-3102 CSR, Listings 16.2.1.1, 16.2.1.2, 16.2.8.1, 16.2.9.2. Reviewer confirmed using JMP 12.0, ISS ADOE.xpt.

Reviewer comment: Cataracts occurred in all treatment arms, including placebo, but the three posterior subcapsular cataracts only occurred in subjects receiving active treatment. The formation of posterior subcapsular cataracts is particularly suggestive of a corticosteroid-related AE. However, as cataracts are not expected in a study of short duration, confounding factors such as prior use of intranasal or systemic corticosteroids may contribute to this finding.

Trials 3203 and 3204 identified 11 subjects with treatment emergent cataracts, including no posterior subcapsular cataracts. Five subjects enrolled and received investigational drug despite the presence of baseline cataracts, and of these subjects, 3 discontinued

from the trials with stable cataracts, and two subjects noted progression of their (Table 47).

Table 47. Treatment emergent cataracts, Trials 3203 and 3204, safety population

Subject	Visit	Right (subtype/Grade)	Left (subtype/grade)	Comments
Trial OPN-FLU-CS-3203				
066320	Post-M3	No grade/subtype available		Discontinued. Bilateral cataracts noted by non-trial ophthalmologist on d116.
071326	7(M12)	Nuclear/1	Nuclear/1	Completed trial.
078308	7(EOS)	Nuclear/1	Nuclear/1	Completed trial; Final ocular exam occurred 5 months after final dose, as lost to follow up for 5 mos.
081302	1 (S)	Nuclear/2	Nuclear/2	Completed trial. Enrolled in error. Worsening of baseline cataracts at M12
	5(M6)	Nuclear/2	Nuclear/2	
	7(M12)	Nuclear/3	Nuclear/3	
114313	5(M6)	None	Nuclear/1	Completed trial. Cataract removed surgically during trial.
Trial OPN-FLU-CS-3204				
022414	4(D92)	None	None	Completed trial. AE: mild left trace cortical cataract, but normal ocular assessment.
058405	4(D85)	Nuclear/1	Nuclear/1	Completed trial.
070411	4(D85)	Nuclear/1	None	Completed trial
081405	4 (D123)	Nuclear/2	Nuclear/2	Completed trial
081406	1(S)	Nuclear/2	Nuclear/2	Completed trial. Worsening of existing cataracts
	4(D115)	Nuclear/2+	Nuclear/3	
093410	4(D80)	Nuclear/1	Nuclear/1	Completed trial

AE = adverse event; M=month; D=day; S=screening; EOS=end of study
Data source: NDA 209,022, Module 5.3.5.2, OPN-FLU-CS-3203 CSR, Listing 16.2.1 and 16.2.11; OPN-FLU-CS-3204 CSR, Listing 16.2.1 and 16.2.11.

Reviewer comment: Because cataracts may not develop until the second year of exposure, the long-term trials likely underestimate the risk of cataracts. However, in general the overall incidence does not appear to differ from experience with related intranasal steroids. Overall, while the studies enrolled few subjects with baseline cataracts, the fact that 1 of 3 subcapsular cataracts developed in a subject with preexisting cataracts and the worsening of cataracts in two subjects with preexisting cataracts, should warrant caution when prescribing OPN-375 to patients with cataracts.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the pooled safety population, the most common AEs occurred in the respiratory, thoracic and mediastinal disorders SOC, followed by infections and infestations SOC. Epistaxis was the most common AE in the OPN-375 arms, with similar incidence reported in the 186-mcg BID (21.9%) and 372-mcg BID (23.0%) arms. The next most common AEs included nasopharyngitis, acute sinusitis, nasal septum ulceration, nasal congestion, and nasal mucosal erythema. Table 48 summarizes common AEs in ≥ 1% of OPN-375 subjects, and greater than or equal to placebo.

Table 48. Adverse events with incidence ≥ 1% and greater than or equal to placebo, Trials 3101 and 3102, pooled safety population

System Organ Class Preferred Term[1]	Placebo (N=161) n (%)	OPN-375		
		93-mcg BID (N=161) n (%)	186-mcg BID (N= 160) n (%)	372-mcg BID (N= 161) n (%)
Number of subjects with ≥1 AE	80 (49.7)	79 (49.1)	84 (52.5)	96 (59.6)
Ear and labyrinth disorders	3 (1.9)	2 (1.2)	2 (1.3)	4 (2.5)
Ear pain	1 (0.6)	2 (1.2)	0	1 (0.6)
Gastrointestinal disorders	7 (4.3)	5 (3.1)	3 (1.9)	6 (3.7)
Toothache	1 (0.6)	0	1 (0.6)	2 (1.2)
Abdominal discomfort	0	0	0	2 (1.2)
Infections and Infestations	44 (27.3)	32 (19.9)	33 (20.6)	42 (26.1)
Nasopharyngitis	8 (5.0)	5 (3.1)	3 (1.9)	12 (7.5)
Acute sinusitis	6 (3.7)	5 (3.1)	7 (4.4)	8 (5.0)
Pharyngitis	2 (1.2)	2 (1.2)	2 (1.3)	5 (3.1)
Bronchitis	4 (2.5)	4 (2.5)	4 (2.5)	4 (2.5)
Sinusitis	1 (0.6)	0	0	2 (1.2)
Injury, poisoning, procedural complications	1 (0.6)	3 (1.9)	4 (2.5)	3 (1.9)
Arthropod bite	0	2 (1.2)	1 (0.6)	0
Investigations	2 (1.2)	3 (1.9)	5 (3.1)	2 (1.2)
Intraocular pressure increased	2 (1.2)	2 (1.2)	3 (1.9)	1 (0.6)
Weight increased	0	0	2 (1.3)	0
Nervous system disorders	5 (3.1)	8 (5.0)	10 (6.3)	9 (5.6)
Headache	5 (3.1)	7 (4.3)	8 (5.0)	6 (3.7)
Dizziness	0	0	1 (0.6)	2 (1.2)
Respiratory, thoracic and mediastinal disorders	37 (23.0)	47 (29.2)	54 (33.8)	59 (36.6)
Epistaxis	10 (6.2)	25 (15.5)	35 (21.9)	37 (23.0)
Nasal septum ulceration[1]	3 (1.9)	8 (5.0)	11 (6.9)	12 (7.5)
Nasal congestion	6 (3.7)	5 (3.1)	7 (4.4)	9 (5.6)
Nasal mucosal erythema[2] (LLT)	6 (3.7)	12 (7.4)	9 (5.6)	8 (5.0)

Nasal septum disorder (i.e. erythema)	3 (1.9)	8 (5.0)	6 (3.8)	7 (4.3)
Nasal mucosal ulcer[2] (LLT)	1 (0.6)	7 (4.3)	6 (3.8)	4 (2.5)
Nasal dryness	0	0	2 (1.3)	3 (1.9)
Cough	1 (0.6)	2 (1.2)	1 (0.6)	1 (0.6)
Nasal septal perforation	0	2 (1.2)	1 (0.6)	0
Oropharyngeal pain	2 (1.2)	0	3 (1.9)	0
Skin and subcutaneous tissue disorders	3 (1.9)	2 (1.2)	0	2 (1.2)
Rash	0	2 (1.2)	0	0

Note: Preferred terms are sorted by descending order of incidence within system organ class. Subjects are counted only once in each preferred term category.
[1]Preferred term "nasal septum ulceration" reflects spontaneous AE and nasal examination verbatim terms "nasal septum erosion" and "nasal septum ulceration" as defined in Table 40.
[2]Preferred term nasal mucosal disorders separated into LLTs nasal mucosal erythema and nasal mucosal ulcer.
Source: NDA 209,022, Module 5.3.5.3. ISS Tables, Summary 14.6.1.1. Reviewer confirmed using ISS ADAE.xpt dataset in JMP 12.0. PBOFL(y), APHASE (DOUBLE-BLIND TREATMENT), AEDECOD by TRTP. AELLT used to calculate incidence for AEDECOD nasal mucosal disorders.

Additional events of interest reported in <1% in any OPN-375 arm and greater than placebo included nasal odor, nasal abscess, nasal candidiasis, dry mouth / throat, rhinalgia, throat tightness, dysphagia, lower respiratory tract infections, rhinitis, laryngitis, nasal obstruction, nasal turbinet hypertrophy, rhinitis atrophic, tinnitus, fatigue, asthenia, dry eye, eye pain, and acute otitis media.

The incidence of common AEs in Trials 3203 and 3204 were generally consistent with Trials 3101 and 3102.

Reviewer comment: The Applicants proposal to include AEs reported in ≥3% of OPN-375 subjects in common adverse reactions table of the label is acceptable.

7.4.2 Laboratory Findings

For Trials 3101 and 3102, clinical laboratory tests were only conducted at screening. The phase 3 development program relies on systemic safety data from the RLD and did not assess changes in laboratory parameters.

7.4.3 Vital Signs

Vital sign assessments included systolic blood pressure, diastolic blood pressure, and pulse rate at the following times: V1 (screening), V2 (baseline), every 4-weeks during the DBP, and end of OLE or ET. The Applicant presented mean values for pulse and blood pressure. VS were measured after sitting and resting for at least 5 minutes. This reviewer identified no clinically relevant changes from baseline.

7.4.4 Electrocardiograms (ECGs)

The phase 3 program did not include ECG testing. Screening ECGs were completed in Study 1102 only, and there were no clinically significant findings. The Applicant relies on the systemic safety data and experience with Flovent® HFA to support the new drug product.

7.4.5 Special Safety Studies/Clinical Trials

The phase 3 program did not include special safety studies. The Applicant supports the systemic safety of OPN-375 as related to hypothalamic-pituitary-adrenal function with the known systemic safety profile of Flovent® HFA. Section 5.5 of the Flovent® HFA label carries a Warning and Precaution for hypercorticism and adrenal suppression.

Reviewer comment. Given the similar systemic exposure for Flovent® HFA and OPN-375 as demonstrated in Study 1102, this reviewer recommends including a similar Warning and Precaution for hypercorticism and adrenal suppression in the OPN-375 label.

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This review explored the dose dependency of AEs during the DBP of Trials 3101 and 3102. Overall, the number of subjects with at least 1 AE increased with increasing dose of OPN-375 from 49.1% (93-mcg BID) to 59.6% (372-mcg BID). A small dose-response was demonstrated for epistaxis when considering all cases (i.e. spontaneous and nasal examination). However, the difference between the middle and high dose disappeared when examining only the spontaneous reported cases (see Section 7.3.5). Smaller changes in several other AEs of interest were noted, but differences in incidence between doses were small (Table 49). No clinically meaningful differences in intensity of AEs were noted for the three OPN-375 arms.

Table 49. Adverse events with dose-response across dosage groups in DBP, Trials 3101 and 3102, pooled safety population

MedDRA Preferred Term	Placebo (N=161) n (%)	OPN-375		
		93-mcg BID (N=161) n (%)	186-mcg BID (N= 160) n (%)	372-mcg BID (N= 161) n (%)
Number of subjects with ≥1 AE	80 (49.7)	79 (49.1)	84 (52.5)	96 (59.6)
Epistaxis (all cases)	10 (6.2)	25 (15.5)	35 (21.9)	37 (23.0)
Acute sinusitis	6 (3.7)	5 (3.1)	7 (4.4)	8 (5.0)
Nasal septum ulceration	3 (1.9)	8 (5.0)	11 (6.9)	12 (7.5)
Pharyngitis	2 (1.2)	2 (1.2)	2 (1.3)	5 (3.1)
Nasal dryness	0	0	2 (1.3)	3 (1.9)
Nasal congestion	6 (3.7)	5 (3.1)	7 (4.4)	9 (5.6)
Dizziness	0	0	1 (0.6)	2 (1.2)
Cataract subcapsular	0	0	1 (0.6)	1 (0.6)
Abdominal discomfort	0	0	0	2 (1.2)

Table includes AE where AE incidence where 372-mcg BID > 186-mcg BID > 93-mcg BID, or 186-mcg BID=372-mcg BID >93-mcg BID.
Epistaxis includes spontaneous cases and findings from nasal examination.
Source: NDA 209,022, Module 5.3.5.3. ISS Tables, Summary 14.6.1.1. Confirmed with ISS ADAE.xpt data set in JMP 12.0. SAFFL(Y), PBOFL(Y), APHASE (DOUBLE-BLIND TREATMENT), TRTEMFL(Y) comparison of AEDECOD by TRTP, USUBJID.

Reviewer comment. Consistent with the Nasonex® program, there was a small dose-response in the incidence of epistaxis. However, the difference in epistaxis incidence between the middle and high dose is likely not clinically significant.

7.5.2 Time Dependency for Adverse Events

This review utilizes the safety data from Trials 3203 and 3204 to evaluate the time-dependence of AEs of interest. Overall, a smaller number of subjects reported AEs after 12 months (25.3%) than in the first 4 months (55.2%). Local nasal events occurred throughout each time period, but the greatest incidence was with drug initiation. Elevated IOP and cataracts occurred across the time intervals. While the Applicant excluded two clinical sites from this analysis because they were deemed unreliable, review of the safety data from the 25 excluded subjects did not change the safety conclusions. Table 50 summarizes the time dependency of AEs in Trials 3203 and 3204.

Table 50. Adverse events by 4-month time intervals, Trials 3203 and 3204, safety population

System order class Preferred term*	Month 0-4 N=898	Month 4-8 N=231	Month 8-12 N=171	Month >12 N=79
Number subjects with 1 AE	496 (55.2)	69 (29.9)	61 (35.7)	20 (25.3)
Eye disorders	27 (3.0)	5 (2.2)	3 (1.8)	3 (3.8)
Cataract (nuclear)	3 (0.3)	1 (0.4)	2 (1.2)	2 (2.5)
Cataract (cortical)	2 (0.2)	0	0	0
Cataract (NOS)	0	1 (0.4)	0	0
Infections and infestations	152 (16.9)	19 (8.2)	27 (15.8)	2 (2.5)
Acute sinusitis	30 (3.3)	6 (2.6)	12 (7.0)	1 (1.3)
Upper respiratory tract infection	36 (4.0)	7 (3.0)	4 (2.3)	0
Nasopharyngitis	16 (1.8)	1 (0.4)	0	0
Bronchitis	9 (1.0)	0	3 (1.8)	0
Tooth infection (infection, abscess)	3 (0.3)	2 (0.9)	0	0
Candidiasis (nasal, oral, esophageal, gastrointestinal)	5 (0.5)	2 (0.9)	1 (0.6)	0
Herpes infection (oral, zoster, nasal)	4 (0.4)	0	0	0
Investigations	10 (1.1)	4 (1.7)	0	1 (1.3)
Increased IOP	3 (0.3)	3 (1.3)	0	1 (1.3)
Nervous system disorders	58 (6.5)	6 (2.6)	9 (5.3)	2 (2.5)
Headache	35 (3.9)	2 (0.9)	7 (4.1)	2 (2.5)
Anosmia	3 (0.3)	3 (1.3)	0	0
Dizziness	6 (0.7)	0	0	0
Respiratory, thoracic and mediastinal disorders	344 (38.3)	34 (14.7)	38 (16.4)	12 (15.2)
Epistaxis	149 (16.6)	13 (5.6)	12 (7.0)	2 (2.5)
Nasal mucosal erythema (LLT)	86 (9.6)	4 (1.7)	1 (0.6)	3 (3.8)
Nasal septum disorder (erythema)	62 (6.9)	6 (2.6)	5 (2.9)	3 (3.8)
Nasal septum ulceration	46 (5.1)	6 (2.6)	9 (5.3)	2 (2.5)
Nasal congestion	29 (3.2)	1 (0.4)	2 (1.2)	2 (2.5)
Nasal mucosal ulcer (LLT)	13 (1.4)	5 (2.2)	2 (1.2)	2 (2.5)
Nasal septum perforation	3 (0.3)	0	0	0

N= number of subjects meeting the minimum time point in the column and serves as the denominator for each percentage calculation. Subjects may be counted more than once per AE category if events occurred in different time periods. Excludes data from sites 069 and 105
Source. NDA 209,022, Module 5.3.5.3. ISS Tables, Summary 14.10.2. Reviewer calculated nasal mucosal ulcer and nasal mucosal erythema incidence from ISS ADAE.xpt JMP 12.0: OLSFL(Y), TRTEMFL(Y), EXCSUMFL(not Y), by AELLT, AVISIT and USUBJID.

Reviewer comment. In general, the data suggest that infections and nervous system disorders may present early, while local nasal and ocular AEs occurred throughout the 12 months. However, the incidence rates should be interpreted with caution as there

was no comparator arm and the trial population decreased as treatment duration increased, potentially selecting for healthier population. The incidence of acute sinusitis should be interpreted with caution since the trial subjects had chronic sinusitis.

7.5.3 Drug-Demographic Interactions

The Application completed an analysis of AEs by region (North America, non-North America), gender (male or female), age (≥65 or < 65 years), and race (white and non-white). From the analysis, the Applicant concluded that no specific dosage considerations are necessary in the label for the treatment of nasal polyps based on race, gender, age, or region. The following section summarizes pertinent AEs for each of the four demographic subsets.

Age

In the pooled safety population, the only AE reported in two or more OPN-375 subjects ≥65 years of age within a single treatment arm was nasal mucosal disorders. The number of subjects 65 and older limits the ability to draw meaningful comparisons.

Race

Epistaxis occurred more frequently in non-white subjects compared to white subjects across the placebo and OPN-375 arms. However, the small number of subjects in the non-white category makes it difficult to draw meaningful clinical conclusions about the AE incidence.

Gender

More female subjects than male subjects in the placebo and high dose OPN-375 arm reported AEs in the infections and infestations SOC. Both genders showed a small trend towards increased epistaxis with increasing dose, with the dose-response more prominent among men.

Table 51. Adverse event incidence in males and females occurring in ≥3 subjects in any OPN-375 arm, Trials 3101 and 3102, pooled safety population

MedDRA Preferred Term	Placebo		OPN-375					
			93-mcg BID		186-mcg BID		372-mcg BID	
	M N=78	F N=83	M N=82	F N=79	M N=94	F N=66	M N=93	F N=68
Subjects with ≥1 AE	42.3%	56.6%	50.0%	48.1%	51.1%	54.5%	55.9%	64.7%
Epistaxis	3.8%	8.4%	14.6%	16.5%	23.4%	19.7%	25.8%	19.1%
Nasal septum ulceration	3.8%	1.2%	3.7%	6.3%	6.4%	7.6%	8.6%	5.9%
Nasal mucosal erythema (LLT)	6.4%	1.2%	6.1%	8.9%	7.4%	3.0%	5.4%	4.4%
Nasal mucosal ulcer (LLT)	0	1.2%	4.9%	3.8%	4.2%	3.0%	3.2%	1.5%
Nasal congestion	1.3%	6.0%	3.7%	2.5%	3.2%	6.1%	3.2%	8.8%
Nasal septum disorder	3.8%	0	3.7%	6.3%	5.3%	1.5%	5.4%	2.9%
Nasal dryness	0	0	0	0	1.1%	1.5%	2.2%	1.5%
Nasopharyngitis	2.6%	7.2%	2.4%	3.8%	0	4.5%	4.3%	11.8%
Acute sinusitis	0	7.2%	4.9%	1.3%	4.3%	4.5%	4.3%	5.9%
Bronchitis	1.3%	3.6%	0	5.1%	1.1%	4.5%	0	5.9%
Influenza	2.6%	3.6%	1.2%	2.5%	3.2%	1.5%	0	5.9%
Pharyngitis	0	2.4%	1.2%	1.3%	0	3.0%	1.1%	5.9%
Headache	1.3%	4.8%	4.9%	3.8%	5.3%	4.5%	4.3%	2.9%
Increased IOP	1.3%	1.2%	1.2%	1.3%	1.1%	3.0%	1.1%	0
Weight increased	0	0	0	0	0	3.0%	0	0

Incidence calculated as n/N, Subjects counted once in each preferred term category and once for each system organ class category.
Source: NDA 209,022, Module 5.3.5.3. ISS Tables, Summary 14.6.1.2. Reviewer calculated nasal mucosal ulcer and nasal mucosal erythema incidence from ISS ADAE.xpt JMP 12.0: SAFFL(Y), PBOFL(Y), APHASE (DOUBLE-BLIND TREATMENT), TRTEMFL(Y) comparison of AELLT by TRTP, SEX, USUBJID.

Reviewer comment. No safety issue was identified based on gender.

Region

More North American (NA) subjects reported at least 1 AE than non-NA subjects. The largest difference in AEs was seen for epistaxis, nasal mucosal erythema, nasal septum ulceration, nasal septum disorder and acute sinusitis, all occurring more frequently in the NA population than the Non-NA. Table 52 summarizes the AE by region for AEs reported by at least 5% of NA subjects.

Table 52. Adverse event incidence by region occurring in ≥5% North American subjects in any OPN-375 arm, Trials 3101 and 3102, pooled safety population

MedDRA Preferred Term*	Placebo		OPN-375					
			93-mcg BID		186-mcg BID		372-mcg BID	
	NA N=50	Non-NA N=111	NA N=50	Non-NA N=111	NA N=50	Non-NA N=110	NA N=48	Non-NA N=113
Subjects with ≥1 AE	58%	45.9%	64%	42.3%	68%	45.5%	79.2%	51.3%
Epistaxis	14%	2.7%	18%	14.4%	28%	19.1%	37.5%	16.8%
Nasal mucosal erythema (LLT)	8%	1.8%	18%	2.7%	12%	2.7%	16.7%	0
Nasal mucosal ulcer (LLT)	0	0.9%	6.0%	3.6%	2%	4.5%	2.1%	2.6%
Nasal septum ulceration	2%	2.7%	10%	2.7%	14%	3.6%	10.4%	6.2%
Nasal congestion	8%	1.8%	8%	0.9%	6%	3.6%	6.3%	5.3%
Nasal septum disorder	2%	1.8%	6%	4.5%	6%	2.7%	10.4%	1.8%
Oropharyngeal pain	2%	0.9%	0	0	6%	0	0	0
Nasopharyngitis	6%	4.5%	4%	2.7%	2%	1.8%	4.2%	8.8%
Acute sinusitis	4%	3.6%	10%	0%	6%	3.6%	14.6%	0.9%
Bronchitis	2%	2.7%	2%	2.7%	2%	2.7%	6.3%	0.9%

Incidence calculated as n/N, Subjects counted once in each preferred term category and once for each system organ class category.
Source. NDA 209,022, Module 5.3.5.3. ISS Tables, Summary 14.6.1.5. Reviewer calculated nasal mucosal ulcer and nasal mucosal erythema incidence from ISS ADAE.xpt JMP 12.0: SAFFL(Y), PBOFL(Y), APHASE (DOUBLE-BLIND TREATMENT), TRTEMFL(Y) comparison of AELLT by TRTP, REGION, USUBJID.

Reviewer comment. The differences in local nasal effects and epistaxis may reflect differences in baseline treatments such as intranasal corticosteroid use or disease severity. There is no clear biologic basis for suspecting an increased potential for safety issues between the two regions.

7.5.4 Drug-Disease Interactions

The Applicant did not complete formal drug-disease interaction studies. As the active drug, fluticasone propionate, is metabolized by the liver, the Applicant's suggestion to increase monitoring in subjects with liver disease is reasonable because of the potential for the drug to accumulate and also consistent with the RLD.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were included in this submission. The Applicant relies on the RLD to support drug-drug interactions.

The Applicant submitted an analysis of epistaxis in pooled safety population among subjects receiving three categories of concomitant medications: NSAIDS, antiplatelet or anticoagulants, and other intranasal medications. There were too few subjects to make

meaningful comparisons with respect AE incidence in the setting of anticoagulant or antiplatelet medications, NSAIDS or intranasal medications.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant performed no new human carcinogenicity studies for this application.

7.6.2 Human Reproduction and Pregnancy Data

The development program included no additional human reproductive and pregnancy data. However, in support of the PLLR labeling the Applicant submitted a literature search.

7.6.3 Pediatrics and Assessment of Effects on Growth

The submission includes no pediatric subjects and requests a deferral for pediatric studies. The Applicant cross-references the assessment of growth from the RLD.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was no overdose experience reported.

7.7 Additional Submissions / Safety Issues

Study OPTUK RFCP PRO002

OPTUK RFCP PRO002 was a phase 2, 12-week, double-blind, randomized, parallel-group, placebo-controlled study in adults with bilateral nasal polyps (grade 1 or 2) involving administration of 400-mcg OptiNose RFCP BID. The safety population included 54 subjects on active treatment and 55 placebo subjects. There were no deaths or SAEs in the active treatment arm. The most common AE was epistaxis, occurring in 9 (47.4%) of the active treatment arm. A single active treatment subject developed hypertension.

Study OPTUK RFCP PRO003

OPTUK RFCP PRO003 was a phase 2, 12-week, double-blind, randomized, parallel-group, placebo-controlled study in 20 adult subjects with chronic rhinosinusitis involving administration of 400-mcg OptiNose RFCP BID. The study subjects did not have a history of nasal polyps. There were no deaths or SAE in the study. Among the 10 subjects exposed to active treatment, the most common AE was pharyngolaryngeal pain (12.0%). One subject withdrew for itchy eyes, headache, redness and swelling of

the skin. The study reported no clinically meaningful changes in hematology, urinalysis, mean vital signs, or mean morning plasma cortisol concentrations for any subject.

8 Postmarket Experience

As OPN-375 is not marketed in any country, (b) (4)

In the United States, the active ingredient fluticasone propionate is available in multiple formulations. The FDA approved intranasal fluticasone propionate (Flonase®) for allergic rhinitis on October 19, 1994, and approved a partial prescription to over the counter switch on July 23, 2014 (see Section 2.3). Because of the extensive historical experience with intranasal fluticasone propionate and the active ingredient in general, a separate FAERS database search was not deemed necessary for this review.

Appendices

9.1 Literature Review/References

The Applicant completed a literature review of PubMed to assess the safety of fluticasone propionate administered by oral inhalation or intranasal routes and identified 39 full text articles with relevant safety information for the period of January 1, 2014, through October 1, 2015. The submitted summary of literature and references raised no new safety signals. A separate review of literature was not completed as the Sponsor's review was considered adequate, and there were no questions raised by the data.

9.2 Labeling Recommendations

Proposed labeling, submitted in physician's labeling rule (PLLR) format, references the labeling of Flovent® HFA and Flonase®. The negotiations of the final labeling are ongoing at the time of this review.

9.3 Advisory Committee Meeting

An advisory committee meeting is not necessary for this NDA.

9.4 Additional Tables

Table 53. Schedule of assessments, Trials 3101 and 3102

Phase	Pretreatment (Screening/Run-in)	DBP						OL Extension
Visit	1	2	3	4	5	6	7	8
Procedures and Assessments	SB PBO Run-in 7 to up to 14 d	Baseline (R) Day 1	Day 10	Week 4	Week 8	Week 12	End-of-DB or ET Week 16	End-of-OL or ET Week 24
			(± 3 days)				(± 3 days)	(± 3 days)
Informed consent, Medical history, ability to use device	X							
Inclusion and exclusion criteria	X	X						
Serum labs, UA /drug screen, PE	X							
Pregnancy test	X						X	X
Ocular examination[a]	X						X	X
BP, pulse measurements	X	X		X	X	X	X	X
Nasal examination	X			X	X	X	X	X
PNIF	X(training)	X		X	X	X	X	X
Medication evaluation	X			X			X	X
SNOT-22		X		X	X	X	X	X
RSDI		X					X	
SF-36v2, PGIC, surgical assessment		X					X	X
MOS Sleep-R		X		X	X	X	X	
ACT, FEV1 (asthma only)		X		X	X	X	X	
Healthy economic assessment		X		X	X	X	X	X
Review proper use device	X	X	X	X	X	X	X	
Review diary entries		X		X	X	X	X	
AE, concomitant meds, Dispense / collect investigational drug, compliance	X	X	X	X	X	X	X	X

ACT = Asthma Control Test; AE = adverse event; CRF = case report form; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; MOS Sleep-R = Medical Outcomes Study Sleep Scale-Revised; OL = open-label; PGIC = Patient Global Impression of Change; PNIF = peak nasal inspiratory flow; RSDI = Rhinosinusitis Disability Index; SF-36v2 = 36-Item Short Form Health Survey version 2; SNOT-22 = Sinonasal Outcome Test-22.
[a] Initial between Visit 1 (Screening) and Visit 2, Day 1 (baseline). Final examination performed within the 7-days before the expected trial visit date.
Source: Adapted from NDA 209,022, CSR OPN-FLU-NP-3101, Table 2

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

/s/

COURTNEY S MCGUIRE
08/14/2017

ANTHONY G DURMOWICZ
08/14/2017

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 209022	**PROPRIETARY NAME:**	(b) (4)
APPLICANT/SPONSOR:	OptiNose US, Inc.	**USAN NAME:**	fluticasone propionate, OPN-375
MEDICAL OFFICER:	Courtney McGuire, MD		
TEAM LEADER:	Anthony Durmowicz, MD	**CATEGORY:**	corticosteroid
DATE:	1/6/2017	**ROUTE:**	intranasal

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
11/18/2016	11/18/2016	New/NDA	

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

OptiNose US, Inc. has submitted a new NDA for fluticasone propionate nasal spray / OPN-375 (b) (4) for the proposed indication of treatment of nasal (b) (4) in subjects 18 years or older (NDA 209022). The proposed drug will be administered intranasally via the OptiNose Bi-directional™ Breath Powdered™ delivery system. The Application is a 505(b)(2) application relying on the reference listed drug Flovent HFA inhalation aerosol (NDA 21433) to support systemic safety through demonstration of a pharmacokinetic bridge between OPN-375 and Flovent HFA. The proposed dose is 93 mcg per nostril twice daily (372 mcg total daily dose) up to 186 mcg per nostril twice daily (744 mcg total daily dose).

The clinical development program included a single phase 1 comparative PK study and 4 phase 3 studies. The two pivotal phase 3 dose ranging trials were replicate 16-week randomized, double-blind, placebo-controlled, parallel-group, multicenter studies in nasal polyposis investigating 93 mcg, 186 mcg and 372 mcg bid OPN-375 compared to placebo in patients with bilateral nasal polyposis. Two additional open-label safety trials of 3 and 12 month duration studying 372 mcg bid OPN-375 in patients with chronic sinusitis with and without nasal polyposis provide additional safety support (3303, 3304). The development program prospectively followed nasal and ophthalmologic exams to monitor for local nasal toxicity (e.g. nasal perforations, ulceration, etc.), cataracts and increased intraocular pressure.

Based on preliminary review of trials 3101 and 3102, all three doses demonstrated benefit over placebo in reduction of nasal obstruction / congestion at 4 weeks and total nasal polyp grade at 16 weeks. The preliminary review of safety data has not raised any new safety concerns for this product that would be unexpected in an intranasal corticosteroid program.

This submission is adequately indexed, organized, and complete to allow for review. The clinical review will focus on dose selection and local / systemic safety with particular attention placed on evaluation of nasal and ophthalmologic examinations and adverse events. At this time, a Sponsor level OSI site inspection is requested given the small number of total subjects in the pivotal studies and large number of study sites. No major issues have been identified which would limit the review of this application.

The filing checklist and slides from the filing meeting held on 1/5/2017 are attached.

OUTSTANDING ISSUES: none

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: _x_ **FILEABLE** ____ **NOT FILEABLE**

____ **APPROVAL** ____ **APPROVABLE** **NOT APPROVABLE**

CLINICAL FILING CHECKLIST FOR NDA

NDA/BLA Number: 209022 **Applicant:** OptiNose US, Inc. **Stamp Date:** 11/18/2016

Drug Name: (b) (4) (Fluticasone Propionate / OPN-375) **NDA/BLA Type:** original NDA, 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).			x	eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	x			Applicant included summary of literature
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
10.	Has the applicant submitted a benefit-risk analysis for the product?	x			Within Clinical Overview
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	x			505(b)(2) Flovent HFA (NDA 021433)

	Content Parameter	Yes	No	NA	Comment
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?	x			Flovent HFA (fluticasone propionate) inhalation aerosol, 0.22 mg per metered inhalation, 0.11 mg per metered inhalation and 0.044 mg per metered inhalation, NDA 021433 (GlaxoGRP LTD). Flovent is relied upon for systemic safety. Nonclinical program also supported by reference to Flonase nasal spray, 0.05 mg per metered spray (NDA 020121)
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	x			
14.	Describe the scientific bridge (e.g., BA/BE studies)	x			BA/BE study (OPN-FLU-1102) compared systemic exposure of OPN-375 (200 and 400 µg) with Flonase (400 µg, Part 1) and Flovent HFA (440 µg, Part 2). OPN-375 BE parameters for OPN-375 vs Flonase were above the upper limit of 90% CI for ln-transformed PK parameters. BE parameters for 400 mcg OPN-375 lower than 125% for Flovent, justifying reliance on systemic safety findings for Flovent HFA NDA.
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? **Study Number:** OPN-FLU-NP-3101 Sample size: 323 Arms: see attached slides Location in submission: 5.3.5.1 **Study Number:** OPN-FLU-NP-3102 Sample size: 323 Arms: see attached slides Location in submission: 5.3.5.1	x			Two identical phase 3 studies examined 3 doses with the to-be-marketed product.
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	x			Two 16-week, pivotal trials with 8-week open label extension

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1: OPN-FLU-NP-3101 Indication: treatment of nasal (b) (4) in 18 years of age or older Pivotal Study #2: OPN-FLU-NP 3102 Indication: treatment of nasal (b) (4) in 18 years of age or older				
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			Agreement on endpoints under IND 110089 [correspondence 4/10/2015]
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	• QT study not needed • ECGs in study 1102. • Relies on RLD (Flovent HFA) for systemic safety • Applicant includes literature review
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			Summary Clinical Safety Section 2.7.4.7.2 and 2.7.4.7.3
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	x			Any dose: 1518 subjects ≥ 3 months: 1238 subjects ≥ 6 months: 605 subjects ≥ 12 months: 147 subjects
24.	For drugs not chronically administered (intermittent or short course), have the			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
	requisite number of patients been exposed as requested by the Division?				
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?				MedDRA 14.1
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			• Ocular examinations for visual acuity, IOP and cataracts in all studies • Prospectively evaluated for nasal AE of special interest (epistaxis, nasal septal abnormalities, non-septal nasal erosion/ulceration) • Cross-reference to RLD for systemic safety (HPA axis, growth) • Collected data on prior nasal surgery
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			• Complete responder analysis submitted • Human factors engineering report
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Pediatric waiver request for children <6 years (section 1.9.1) and pediatric deferral request ≥6 to < (b) (4) (section 1.9.2)
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant	x			Submitted PubMed literature search.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?				
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
37.	Are all datasets to support the critical safety analyses available and complete?	x			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes_____

If the Application is not fileable from the clinical 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.

None

Reviewing Medical Officer Date

Clinical Team Leader Date

U.S. FOOD & DRUG ADMINISTRATION

NDA 209022

(b) (4) (fluticasone propionate)

OptiNose US, Inc.

Courtney McGuire

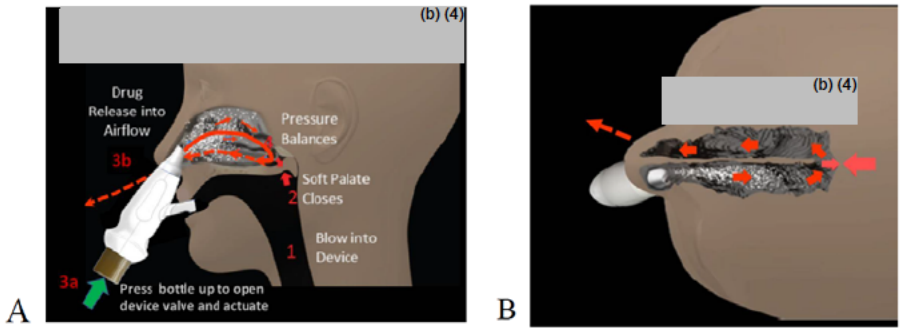
January 5, 2017

Overview

- **Name**: fluticasone propionate Nasal Spray / OPN-375 (b) (4)
- **Class:** corticosteroid
- **Indication:** treatment of nasal (b) (4) in subjects 18 year of age or older
  - Reduced ADS7-IA nasal congestion/ obstruction score over 7 days prior to wk 4
  - Decreased mean total polyp grade at wk 16
- **Dose**: 93 mcg per nostril twice daily (372 mcg total daily dose), up to 186 mcg per nostril twice daily (744 mcg total daily dose)
- **Route:** intranasal via "Breath Powered® exhalation delivery"
- **Application:** 505(b)(2) relying on RLDs: Flonase (NDA 020121) and Flovent HFA (NDA 21433)

Device

- Bi-directional™ Breath Powered™ delivery system
- Patient exhalation causes elevation and sealing of soft palate to facilitate drug delivery to nasal cavity



Source: Figure 3.2.P.1-3, Section 3.2.P.1

Regulatory History Overview

12/20/10	Type B pre-IND meeting	• PK studies may allow RLD use for systemic safety, but not efficacy or local safety • Must complete adequate dose ranging with to-be-marketed device • Long-term safety data of at least 1 year treatment duration is expected
7/16/12	Advice/information request	• CMC, clinical, and clinical pharmacology: comments and recommendations following IND submission
3/9/15 & 4/10/15	Response to request for advice/ comment	• Comments on SAP, including agreement on primary endpoints
11/18/15	Type B pre-NDA meeting	• Dosage form is a "nasal spray" • Nonclinical, drug-interactions, PD from RLD may support 505 (b)(2) application pending review of PK study • Standard nasal (b) (4) indication applies • Safety database and clinical assessments/efficacy database appear adequate for review for the planned NDA indication • Pivotal safety and efficacy trials are studies 3101 and 3102 • SNOT-22 and patient global assessment supportive (b) (4) • OL safety studies are supportive (b) (4) • FDA requested a complete responder analysis for elimination of polyps • Acceptable to model label after RLD but must be PLLR format
11/24/15	Agreed initial pediatric study plan (agreement)	• (b) (4) waiver for <6 years and deferral for children 6 to 17 years.

Phase 1 Trial

Trial	Design	Treatment (mcg)	N	Population	Endpoint
Phase 1 Comparative Bioavailability					
1102	Part 1: OL, R, single-dose, 3-way crossover	• OPN-375 200 • OPN-375 400 • Flonase 400	90	Healthy adults	PK, safety
	Part 2: OL, R, single-dose, 2-way crossover	• OPN-375 400 • Flovent 440	30	Mild to moderate asthma, adults	

Phase 3 trials

Trial	Design	Treatment (mcg)	N	Treatment Duration	Endpoints	Sites (countries)
Pivotal efficacy, safety and dose-ranging trials						
3101	R, DB, PC, PG, MC 16 wk study 8 wk OL extension	100 OPN-375 bid 200 OPN-375 bid 400 OPN-375 bid Placebo bid OL: 400 OPN-375 bid	81 80 80 82 	DBP:16 wk OL ext: 8 wk	*ADS7-IA wk 4 *T. polyp grade wk 16 **SNOT-22 wk 16 **MOS Sleep-R wk 16	US, Canada, CR, Ukraine, South Africa, UK
3102	R, DB, PC, PG, MC 16 wk study 8 wk OL extension	100 OPN-375 bid 200 OPN-375 bid 400 OPN-375 bid Placebo bid OL: 400 OPN-375 bid	81 80 82 80 	DBP, 16 wk OL ext: 8 wk	*ADS7-IA wk 4 *T. polyp grade wk 16	US, Poland, Romania, South Africa, Ukraine
Open Label Safety and Tolerability Studies						
3203	OL, MC	400 OPN-375 bid	224	12 mos	Safety	US
3204	OL, MC	400 OPN-375 bid	706	3 mos	Safety	US

*Co-primary endpoints, ** Key Secondary

Population

	3101 / 3102 (pivotal trials)	3203/ 3204 (OL safety)
Age	≥18 y	
Nasal polyps hx	• Bilateral grade 1 to 3 nasal polyposis per Lildholdt score on nasoendoscopy	• Chronic sinusitis +/- nasal polyposis
Symptoms requirements	• Moderate nasal congestion / obstruction for 7 days prior to screening per protocol grading scale	Subjects without polyps must have 2 or more with at least one of criteria 1 or 2: 1. Nasal blockage/congestion 2. Nasal discharge 3. Facial pain or pressure 4. Reduction or loss of smell
Surgical hx	• No sinus/nasal surgery within 6 mos • < 5 sinus or nasal surgeries (lifetime)	• No sinus/nasal surgery within 6 mos
Key ocular Exclusions:	• No history or current elevated intraocular pressure (>21 mmHg), glaucoma • ≥ grade 1 cataract or < grade 1 cataract with vision changes	
Key nasal exclusions:	• Complete or near-complete nasal cavity obstruction • Epistaxis with frank bleeding (<1 month prior to screening) • Nasal septum perforation • Significant mucosal injury, ulceration, and / or erosion on examination • Purulent nasal infection, acute sinusitis, nasal candidiasis	

Efficacy: Nasal Congestion/Obstruction

Change from baseline ADS7-IA nasal congestion/ obstruction for 7 days prior to wk 4 visit					
Dose (mcg)	**N**	**LS Mean (SE)**	**Difference (active—placebo)**	**95%CI**	**p value**
Study 3101					
Placebo	82	-0.24 (0.07)			
100 OPN-375 BID	81	-0.49 (0.08)	-0.25	-0.43, -0.06	0.010
200 OPN-375 BID	80	-0.54 (0.07)	-0.30	-0.48, -0.11	0.002
400 OPN-375 BID	79	-0.62 (0.07)	-0.38	-0.57, -0.19	< 0.001
Study 3102					
Placebo	79	-0.24 (0.07)			
100 OPN-375 BID	80	-0.59 (0.07)	-0.36	-0.56, -0.16	< 0.001
200 OPN-375 BID	80	-0.68 (0.07)	-0.45	-0.65, -0.25	< 0.001
400 OPN-375 BID	82	-0.62 (0.07)	-0.38	-0.58, -0.18	< 0.001
ADS7-IA = 7-day average instantaneous AM diary symptom score Note- non-sedating antihistamines only allowed after week 4					

Source: Adapted from Tables 2.5-10 and 2 5-11 Clinical Overview Module 2 5

Efficacy: Nasal Polyp Scores

Change from baseline total nasal polyp score (sum both nasal cavities) at end of week 16*				
Dose (mcg)	**N**	**LS Mean (SE)**	**Treatment difference (active-placebo)**	**p value**
Study 3101				
Placebo BID	82	-0.45 (0.135)		
100 OPN-375 BID	81	-0 96 (0.139)	-0.51	< 0.001
200 OPN-375 BID	80	-1 03 (0.138)	-0.59	< 0.001
400 OPN-375 BID	79	-1 06 (0.137)	-0.62	< 0.001
Study 3102				
Placebo BID	79	-0.61 (0.107)		
100 OPN-375 BID	80	-1 31 (0.106)	-0.70	< 0.001
200 OPN-375 BID	80	-1 22 (0.106)	-0.60	< 0.001
400 OPN-375 BID	82	-1.41 (0.104)	-0.80	< 0.001
Measured by nasoendoscopy (using a 0-3 point scale per nostril)				

Source: Adapted from Tables 2.5-10 and 2 5-11 Clinical Overview Module 2 5

Safety- Exposure in Pivotal Studies (DBP)

Variable Statistic	**Placebo BID**	**OPN-375**		
		100 mcg BID	**200 mcg BID**	**400 mcg BID**
	N = 161	**N = 161**	**N = 160**	**N = 161**
Overall (number days exposure)				
Mean (SD)	104.3 (28.36)	111.3 (16.85)	108.0 (23.23)	113.5 (10.82)
SE of mean	2.23	1.33	1.84	0 85
Median	113.0	113 0	113.0	113.0
Min, max	2, 173	8, 143	1, 136	12, 146
Safety analysis set= includes all randomized/enrolled subjects who received ≥1 dose of study treatment, studies 3101 and 3102				

Source: Table 2.7.4-7 Summary Clinical Safety.

Safety- Duration Exposure (All Phase 3)

Variable	Duration of OPN-375 Exposure			
Statistic	Any Exposure	≥3 months	≥6 months	≥12 months*
Duration of treatment (number of days)				
n	1518	1238	605	147
Mean (SD)	136.9 (93.52)	158.2 (90 34)	224.3 (89.25)	375.6 (34 04)
SE of mean	2.40	2.57	3.63	2.81
Median	93.0	155.0	172.0	366.0
Min, max	1, 471	77, 471	165, 471	352, 471
Patient years of exposure				
n	1518	1238	605	147
Total	568.9	536.3	371.5	151.2

*Defined as at least 345 days.
Summary excludes data from site 069 (OPN-FLU-CS-3203) and site 105 (OPN-FLU-CS-3203 and OPNFLU-CS-3204).

Source: Table 2.7.4-10 from Summary of Clinical Safety

Safety- Disposition Pivotal Studies (DBP)

Analysis Group	Placebo BID n (%)	OPN-375		
		100 mcg BID n (%)	200 mcg BID n (%)	400 mcg BID n (%)
ITT analysis set	162 (100)	162 (100)	160 (100)	162 (100)
Safety Analysis Set	161 (99.4)	161 (99.4)	160 (100)	161 (99.4)
Completed DBP	140 (86.4)	153 (94.4)	147 (91.9)	158 (97 5)
Discontinued DBP	22 (13.6)	9 (5.6)	13 (8.1)	4 (2.5)
Lack of efficacy	11 (6 8)	1 (0.6)	3 (1.9)	2 (1.2)
Adverse event	6 (3.7)	3 (1.9)	4 (2.5)	1 (0.6)
Withdrawal by subject	5 (3.1)	2 (1.2)	5 (3.1)	0
Protocol deviation	0	3 (1.9)	0	1 (0.6)
Lost to follow-up	0	0	1 (0.6)	0

TT = intent-to-treat; n (%) = number (percentage) of subjects in the subset.
ncludes 3101/3102
Note: Denominator for calculating all percentages is the number of subjects in the ITT analysis set

Source: Table 2.7.4-11, Summary Clinical Safety

Safety: AEs Pivotal Studies (DBP)

MedDRA Preferred Term	Placebo BID (N = 161) n (%)	OPN-375 100 mcg BID (N = 161) n (%)	OPN-375 200 mcg BID (N = 160) n (%)	OPN-375 400mcg BID (N = 161) n (%)
Deaths	0	0	0	0
SAE	1	1	0	2
Subjects with at least 1 AE	80 (49.7)	79 (49.1)	84 (52 5)	96 (59.6)
Subjects with AE ≥1 leading to DC	7 (4 3)	3 (1.9)	4 (2.5)	1 (0.6)
AE ≥3% and greater than placebo				
Epistaxis	10 (6.2)	25 (15 5)	35 (21 9)	37 (23 0)
Nasal septum ulceration	3 (1 9)	8 (5.0)	11 (6.9)	12 (7.5)
Nasopharyngitis	8 (5 0)	5 (3.1)	3 (1.9)	12 (7.5)
Nasal mucosal disorder (not septum)	8 (5 0)	17 (10.6)	15 (9.4)	11 (6.8)
Nasal congestion	6 (3.7)	5 (3.1)	7 (4.4)	9 (5.6)
Acute sinusitis	6 (3.7)	5 (3.1)	7 (4.4)	8 (5.0)
Nasal septum disorder (erythema)	3 (1 9)	8 (5.0)	6 (3.8)	7 (4.3)
Headache	5 (3.1)	7 (4.3)	8 (5.0)	6 (3.7)
Pharyngitis	2 (1 2)	2 (1.2)	2 (1.3)	5 (3.1)

- 3 DBP SAE: worsening nasal polyps (100 mcg), positional vertigo & menorrhagia (400 mcg)
- 2 additional OL extension SAE : pneumonia and worsening nasal polyp
- Infrequent AE of interest (<3%): cataract, IOP

Label

- Mirrors approved RLD (Flovent and Flonase), but in PLLR format
- Proposal to include two doses:

  "1 (b) (4) spray (93 mcg of fluticasone propionate) (b) (4) nostril twice daily (total daily dose, 372 mcg). (b) (4) 2 (b) (4) (b) (4) sprays (b) (4) (b) (4) nostril twice daily (total daily dose, 744 mcg)."
- Administration instructions for new delivery device
- Warnings and Precautions include local nasal effects and (b) (4)
- Common adverse reactions from pivotal studies ≥ 3%

Preliminary Conclusions

- Fileable
- Advisory Committee Meeting not needed
- No 74-day letter comments
- Potential review issue:
  - Safety
    - Evaluation of ocular and local nasal toxicity
    - Adverse events in subjects with history of recent nasal ulcers, nasal surgery
  - Risk benefit profile of (b) (4) mcg dose relative to (b) (4) mcg

Extra Slides

Summary of Efficacy Assessments

Endpoint	Pivotal Efficacy Studies		Supportive Efficacy Studies	
	OPN-FLU-NP-3101	OPN-FLU-NP-3102	OPN-FLU-CS-3203	OPN-FLU-CS-3204
ADS7-IA and ADS7-IP	√	√	—	—
ADS7-RA and ADS7-RP	√	√	—	—
Nasoendoscopy (polyp score)	√	√	√[a]	√[a]
Nasoendoscopy (Lund-Mackay)[b]	—	—	√	√
SNOT-22	√	√	√	√
MOS Sleep-R	√	√	—	—
PGIC	√	√	√	√
Surgical intervention assessment	√	√	√	√
SF-36v2	√	√	—	—
PNIF	√	√	—	—
RSDI	√	√	—	—
ACT[c]	√	√	—	—
FEV-1[c]	√	√	—	—
Missed work or school	√	√	—	—
Rescue medication use after week 4	√	√	—	—
Medication evaluation questionnaire	√	√	√	√

Source: Table 2.5-9, Clinical Overview

[a] = Evaluated in subjects with nasal polyps.
[b] = An objective clinician-rated assessment used to evaluate changes in common signs associated with chronic sinusitis in the nasal cavity such as edema, discharge, crusting, scarring, adhesions, and nasal polyps.
[c] = Evaluated in subjects with asthma.

Safety- Disposition in Pivotal Trials (OL)

Analysis Group	Placebo n (%)	100 µg OPN-375 n (%)	200 µg OPN-375 n (%)	400 µg OPN-375 n (%)	All OPN-375 n (%)	All Subjects n (%)
TT analysis set	162 (100)	162 (100)	160 (100)	162 (100)	484 (100)	646 (100)
Safety Analysis Set	161 (99 4)	161 (99 4)	160 (100)	161 (99 4)	482 (99 6)	643 (99 5)
Enrolled in OL phase	138 (85 2)	150 (92 6)	139 (86 9)	154 (95 1)	443 (91 5)	581 (89 9)
Not enrolled OL phase	2 (1 2)	3 (1 9)	8 (5 0)	4 (2 5)	15 (3 1)	17 (2 6)
Adverse event	1 (0 6)	0	4 (2 5)	1 (0 6)	5 (1 0)	6 (0 9)
Withdrawal by subject	0	2 (1 2)	1 (0 6)	2 (1 2)	5 (1 0)	5 (0 8)
Lack of efficacy	1 (0 6)	1 (0 6)	2 (1 3)	0	3 (0 6)	4 (0 6)
Other	0	0	1 (0 6)	1 (0 6)	2 (0 4)	2 (0 3)
Completed OL phase	136 (84 0)	146 (90 1)	135 (84 4)	151 (93 2)	432 (89 3)	568 (87 9)
Discontinued OL phase	2 (1 2)	4 (2 5)	4 (2 5)	3 (1 9)	11 (2 3)	13 (2 0)
Adverse event	1 (0 6)	3 (1 9)	1 (0 6)	1 (0 6)	5 (1 0)	6 (0 9)
Lack of efficacy	1 (0 6)	0	3 (1 9)	1 (0 6)	4 (0 8)	5 (0 8)
Withdrawal by subject	0	1 (0 6)	0	1 (0 6)	2 (0 4)	2 (0 3)

Safety- Exposure in OL Studies (3203, 3204)

Variable	OPN-375 400 µg
Statistic	N = 898
Duration of treatment (number of days)	
n	898
Mean (SD)	135.4 (113.79)
SE of mean	3.80
Median	92.0
Min, max	1.0, 471 0
Patient years of exposure	
n	898
Total	332.9

ISS = integrated summary of safety; max = maximum; Min = minimum; N = total number of subjects in
the analysis set; n = number of subjects in the subset.
Safety Analysis Set = All enrolled subjects who received at least 1 dose of study treatment. Data source: Summary Clinical Safety, Table 2.7.4-8

Safety- Exposure in All Phase 3 Studies

Variable Statistic	Double-blind				Open-label	Any Active Exposure
	Placebo	100 µg	200 µg	400 µg	400 µg	
	N = 161	N = 161	N = 160	N = 161	N = 1479	N = 1518
Overall (Number Days Exposure)						
Mean (SD)	152.6 (46.65)	163.4 (28.81)	156.4 (38.99)	167.4 (20.71)	149.1 (90.43)	136 9 (93.52)
SE of mean	3.7	2.3	3.1	1 6	2.4	2.4
Median	169.0	169.0	169.0	169.0	164.0	93.0
Min, max	2, 199	8, 196	1, 213	12, 202	1, 471	1, 471

Abbreviations: OL= open-label, SE= standard error; min=minimum; max=maximum; SD= standard deviation. Includes all randomized/enrolled subjects who received ≥1 dose of study treatment.
Source: adapted from Clinical Overview, Table 2.5-15.

Efficacy- Pivotal Phase 3 Studies

- Co-Primary Endpoints
  - ADS7-IA of nasal congestion/ obstruction for the 7 days immediately prior to wk 4 visit
  - Total polyp grade (sum of scores from both nasal cavities) as determined by a nasal polyp grading scale score measured by nasoendoscopy evaluated at end of wk 16
- Key secondary assessments (3101 only):
  - Change from BL to wk 16 in SNOT-22
  - Change from BL to wk 16 in Sleep Disturbance subscale of the MOS Sleep-R
- Other secondary assessments included:
  - Change from BL at defined time points: ADS7-IA and ADS7-RA nasal symptoms
  - Change from BL in bilateral total polyp grade at defined time points
  - Percentage with a polyp grading score of 0 in ≥ 1 nostril at defined time points
  - Proportion with improvement bilateral polyp grading score (≥ 1 point) at defined time points
  - SNOT-22 change from BL to defined time points in total score and subscale scores
  - Proportion of subjects who no longer qualified for surgical intervention in DB and OL phases
  - PGIC in DB and OL phases

Nasal Symptom Grading Scale 3101/3012

Table 2: Nasal Symptom Scale

Score	Description[a]
0	None
1	Mild – symptoms clearly present, but minimal awareness, and easily tolerated
2	Moderate – definite awareness of symptoms that is bothersome but tolerable
3	Severe – symptoms that are hard to tolerate, cause interference with activities or daily living

[a] Scale will also be used by subjects to score nasal congestion/obstruction symptoms for the 7-day period preceding Visit 1 (Screening).

Source: Protocol OPN-FLU-NP-3101 Amendment 5, table 2

Nasal Polyp Grading Scale 3101/3012

Table 3: Nasal Polyp Grading Scale

Score	Description
0	No polyps
1	Mild polyposis - polyps not reaching below the inferior border of the middle turbinate
2	Moderate polyposis - polyps reaching below the inferior border of the middle concha, but not the inferior border of the inferior turbinate
3	Severe polyposis - large polyps reaching below the lower inferior border of the inferior turbinate

Source: Protocol OPN-FLU-NP-3101 Amendment 5, table 3

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

/s/

COURTNEY S MCGUIRE
01/06/2017

ANTHONY G DURMOWICZ
01/06/2017