1 TITLE PAGE

CLINICAL STUDY PROTOCOL

A 24-Week Open-Label Study Evaluating the Efficacy and Safety of OPN-375 186 µg Twice a Day (BID) in Adults with Bilateral Nasal Polyps using Nasoendoscopic Video

Sponsor:	OptiNose US, Inc.
Protocol Number:	OPN-FLU-NP-3104
Name of Study:	VISUALIZE
EudraCT Number	N/A
Development Phase:	IIIb
Protocol Version/Date:	Amendment 1, Version 1, dated 30 Jan 2018

STATEMENT OF CONFIDENTIALITY:

This document contains scientific and commercial information proprietary to OptiNose US, Inc. that is privileged or confidential and is intended solely for the purpose of this clinical investigation. It should be kept secure and its contents should not be disclosed to any third party without the prior written consent of OptiNose.

VERSION HISTORY

Version	Explanation of Change(s) and Reason/Justification for Changes	Date
0	Original Protocol	16 Jan 2018
1	Updated Title Page to reflect "Protocol Version/Date" Added Version History Section 3 and 13.3 added Urine Pregnancy Test to Visit 2 Section 6.1 and 10.1 - Removed the word "well" from "shake well" to ensure consistency with Instructions for Use Corrected minor formatting issues	30 Jan 2018

Signature Page for Sponsor:

Protocol No. OPN-FLU-NP-3104

Title: A 24-Week Open-Label Study Evaluating the Efficacy and Safety of OPN-375 186 µg Twice a Day (BID) in Adults with Bilateral Nasal Polyps using Nasoendoscopic Video

Name of Study: VISUALIZE

The study will be conducted in compliance with the clinical study protocol, international good clinical practice principles (International Conference on Harmonization [ICH]-Good Clinical Practice [GCP]), and regulatory authority requirements.

Approved by the following:

30 Jan 2018

John Messina, Sr. Vice President Clinical Research & Medical Affairs

30JAN 2018

Jennifer Carothers, Vice President Global Clinical Operations & Outsourcing

Signature Page for Principal Investigator:

Protocol No. OPN-FLU-NP-3104

Title: A 24-Week Open-Label Study Evaluating the Efficacy and Safety of OPN-375 186 µg Twice a Day (BID) in Adults with Bilateral Nasal Polyps using Nasoendoscopic Video

Name of Study: VISUALIZE

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with the accepted version of the Declaration of Helsinki.

Principal Investigator Name: (Printed)	Signature:	Date:

2 SYNOPSIS

TITLE OF STUDY: A 24-Week Open-Label Study Evaluating the Efficacy and Safety of OPN-375 186 µg Twice a Day (BID) in Adults with Bilateral Nasal Polyps using Nasoendoscopic Video

Name of Study: VISUALIZE

SPONSOR: OptiNose US, Inc.

DEVELOPMENT PHASE: 3b

EudraCT Number: N/A

STUDY OBJECTIVES:

Primary: The primary objective of this study is to document the changes in polyp burden over time using nasoendoscopic video.

Secondary: Secondary objectives of this study include:

- Evaluate the safety of OPN-375 via adverse event (AE) reports, vital signs and nasal examination
- Change from Visit 1 (Day 1/Baseline) to each time point in subject symptoms and functioning, as measured by Sinonasal Outcome Test - 22 (SNOT-22)
- Change in the sense of smell as measured by Sniffin' Sticks n-butanol (Extended test)
- Patient's global impression of change (PGIC)
- Percentage of subjects with polyp grade of 0 on at least one side of the nose at each timepoint
- Percentage of subjects with a change of ≥1 point in bilateral polyp grade at each timepoint

STUDY DESIGN: This is a 24-week, open-label, multi-center study designed to assess the efficacy and safety of OPN-375 186 µg BID in subjects with nasal polyps using Nasoendoscopic Video.

STUDY POPULATION: The total planned number of subjects is approximately 10. Each subject receives OPN-375 186 µg BID.

DIAGNOSIS AND MAIN CRITERIA FOR ENROLLMENT:

Potential subjects must meet the following criteria to enter this study:

1. Men or women aged 18 years and older at Visit 1 (Baseline/Day1)
2. Women of child bearing potential must be abstinent, or if sexually active,
   a. be practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [e.g., condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel], or male partner sterilization) before entry and throughout the study, or
   b. be surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or
   c. be postmenopausal (amenorrhea for at least 1 year).
3. Women of child-bearing potential must have a negative urine pregnancy test at Visit 1 (Day 1/Baseline)
4. Must have bilateral nasal polyposis with a grade of 2 or 3 in at least one side of the nasal cavity as determined by a nasal polyp grading scale score measured by nasoendoscopy (see Section 12, Efficacy Assessments) at Visit 1 (Day 1/Baseline)
5. Must have a SNOT-22 score of ≥20 at Visit 1(Baseline/Day 1) (as defined in Section 12, Efficacy Assessments)

6. Must have been on an adequate dose of an intranasal corticosteroid (e.g. fluticasone propionate, fluticasone furoate, mometasone, triamcinolone, ciclosenide, budesonide, budesonide respules, beclomethasone) for at least 1 month, in the previous 3 months prior to Visit 1 (Day 1/Baseline)
7. Subjects with comorbid asthma or chronic obstructive pulmonary disease (COPD) must be stable with no exacerbations (e.g., no emergency room visits, hospitalization, or oral or parenteral steroid use) within the 3 months before the screening visit. Inhaled corticosteroid use must be limited to stable doses of no more than 1,000 μg/day of beclomethasone (or equivalent) for at least 3 months before screening with plans to continue use throughout the study
8. Must be able to cease treatment with oral steroids, intranasal steroids, inhaled corticosteroids (except permitted doses listed above for asthma and COPD) at Visit 1 (Day 1/Baseline)
9. Must demonstrate correct use of the demo EDS
10. Ability to read and speak English
11. Must be capable, in the opinion of the investigator, of providing informed consent to participate in the study. Subjects must sign an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study

The key exclusion criteria are:

1. Women who are pregnant or lactating
2. Inability to have each nasal cavity examined for any reason, including nasal septum deviation
3. Have used XHANCE™ (fluticasone propionate) nasal spray within the past 2 months
4. Nasal septum perforation
5. Has had more than 1 episode of epistaxis with frank bleeding in the month before Visit 1 (Day 1/Baseline)
6. Have evidence of significant mucosal injury or ulceration (e.g. exposed cartilage) on Visit 1 (Day 1/Baseline) nasal examination/nasoendoscopy
7. History of sinus or nasal surgery within 3 months before Visit 1 (Day 1/Baseline). If >3 months subject should be fully recovered from surgery
8. Current, ongoing rhinitis medicamentosa (rebound rhinitis)
9. Have significant oral structural abnormalities, e.g., a cleft palate
10. Diagnosis of cystic fibrosis
11. History of Churg–Strauss syndrome or dyskinetic ciliary syndromes
12. Purulent nasal infection, acute sinusitis, or upper respiratory tract infection within 2 weeks before Visit 1 (Day 1/Baseline). Potential subjects presenting with any of these infections may be rescreened 4 weeks after symptom resolution
13. Planned sinonasal surgery during the period of the study
14. Allergy, hypersensitivity, or contraindication to corticosteroids, steroids, or to any excipients in OPN-375
15. Exposure to any glucocorticoid treatment with potential for systemic effects (e.g., oral, parenteral, intra-articular, or epidural steroids, high dose topical steroids) within 1 month before Visit 1 (Day 1/Baseline); except as noted in inclusion criteria for subjects with comorbid asthma or COPD
16. Have nasal candidiasis at Visit 1 (Day 1/Baseline)
17. History or current diagnosis of any form of glaucoma, ocular hypertension, or intraocular pressure elevation on any form of steroid therapy
18. History or current diagnosis of the presence (in either eye) of a sub-capsular cataract
19. Any serious or unstable concurrent disease, psychiatric disorder, or any significant condition that, in the opinion of the investigator could confound the results of the study or could interfere with the subject's participation or compliance in the study

20. Recent (within 1 year of Visit 1 (Day 1/Baseline)) history of drug or alcohol abuse, or dependence that, in the opinion of the investigator could interfere with the subject's participation or compliance in the study
21. Have participated in an investigational drug clinical trial within 30 days of Visit 1 (Day 1/Baseline)
22. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION:

Subjects will be instructed to administer one spray of OPN-375 per nostril approximately every 12 hours. The active treatment will contain a formulation of fluticasone propionate that delivers 93 µg per spray.

REFERENCE THERAPY, DOSE, AND METHOD OF ADMINISTRATION

N/A – Open Label

ASSESSMENTS:

Efficacy:

The nasal examination and nasoendoscopy with video capture, should be performed by the same physician on each subject. If there are multiple physicians performing these assessments, the same physician should perform these procedures for the same subject throughout the study.

The following efficacy evaluations will be performed at the time points specified in Schedule of Study Procedures and Evaluations:

- Nasoendoscopy will be performed using a rigid endoscope and the exam will be captured on video. The size and type of scope used in an individual subject should remain consistent throughout the study. The examiner must be able to visualize the middle meatus with the scope. Decongestants and/or local anesthetics may be used for the nasoendoscopic procedure, however, if used at Visit 1 (Day 1/Baseline) in a subject, they must be used consistently at all scheduled nasoendoscopic evaluations that follow.
- Polyp grading determined by a nasal polyp grading scale score measured by nasoendoscopy. The baseline assessment of polyp grading is performed at Visit 1 (Day 1/Baseline) by the examining physician to determine study eligibility. Assessment of polyp grade will be performed by an independent reviewer using the videos from the examination. Subjects and visits will be de-identified for this review.
- SNOT-22 is a subject-completed questionnaire that consists of 22 symptoms and social/emotional consequences of their nasal disorder. Each item is rated as follows: 0=no problem, 1=very mild problem, 2=mild or slight problem, 3=moderate problem, 4=severe problem, 5=problem as bad as it can be. The recall period is the past 2 weeks. The SNOT-22 is validated in chronic rhinosinusitis. The SNOT-22 takes approximately 5 minutes to complete.
- The Sniffin' Sticks n-butanol (Extended test) are used to investigate human olfactory performance by use of odor pens. The Extended Test consists of 3 different subtests: Threshold, Discrimination and Identification. The Threshold test is used to ascertain the patient's olfactory threshold. The Discrimination test requires the patient to differentiate smells. The Identification Test requires the patient to identify everyday smells by means of a card with different choices. The test will take approximately 30-40 minutes. All substances contained in the test are non-toxic and not harmful in the used concentrations. The result of this test is expressed as the sum of the results of the 3 subtests, the so called TDI score (threshold, discrimination, identification). Here a score of more than 30 rates as normal, a score of 30 or less indicates hyposmia and a score of 15 and below points to functional anosmia in form of a complete loss of the sense of smell or an extremely weakened smell ability.

- Subject global impression of change will be assessed using a subject-completed PGIC scale, with a single question rated from 1=very much improved to 7=very much worse. The PGIC takes less than 1 minute to complete.

Safety: Safety will be assessed by monitoring of AEs throughout the study, nasal examinations and measuring vital signs (i.e., blood pressure, pulse), and through collection of information for concomitant medications

ENDPOINTS:

Primary:

- Change from Visit 1 (Day 1/Baseline) at end of study in bilateral nasal polyp grade

Secondary:

- Assessment of safety through adverse events (AEs) and AEs of special interest (e.g., epistaxis, nasal septal ulceration, etc.), nasal examinations, vital signs, and concomitant medication usage
- Change from Visit 1 (Day 1/Baseline) to each visit in bilateral polyp grade
- Number of subjects with a change of ≥1 point in bilateral polyp grade at each visit
- Number of subjects with a polyp grade of 0 on at least one side of the nose at each visit
- Change from Visit 1 (Day 1/Baseline) to each visit in average SNOT-22 score
- Average score on the Sniffin Sticks n-butanol (Extended Test) - Threshold test, Discrimination test, and Identification test at Visit 1 (Day 1/Baseline) and Visit 3 (Week 24/End of Study/Early Termination)
- PGIC score at each visit

DURATION OF THE STUDY:

The duration of each subject's enrollment is expected to be approximately 24 weeks.

Open-Label Treatment Phase: 24 weeks

STATISTICAL ANALYSIS:

Sample Size Determination

No statistical sample size calculation was performed for this study. An empiric sample size of 10 subjects is considered to be adequate to assess changes in polyp size and mucosal edema as assessed by nasoendoscopic video, as well as for symptomatic endpoints.

Efficacy Analysis:

Nasal polyp grade score, SNOT-22 (item and total), Sniffin' Sticks n-butanol (Extended test) TDI scores, and PCIG for each timepoint will be listed for each subject.

Safety Analysis:

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 or higher. All AEs during the study period for each subject will be listed and the listing will include the verbatim term, System Organ Class [SOC], preferred term, AE start date, AE end date, severity, serious categorization, causality, action taken if any, and outcome.

Vital signs will be listed for each subject.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug), Version December 2010 or later, and listed by subject.

3 SCHEDULE OF STUDY PROCEDURES AND EVALUATIONS

Visit(s)	1			2			3
	Day 1/ Baseline	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 End of Study / Early Termination**
Procedures and assessments		**(+/-7 days)**	**(+/-7 days)**	**(+/-7 days)**	**(+/-7 days)**	**(+/-7 days)**	**(+/-7 days)**
Informed consent	X						
Medical history	X						
Prior medication history	X						
Inclusion and exclusion criteria	X						
Confirm ability to use demo EDS[a]	X						
Urine pregnancy test[b]	X			X			X
Blood pressure, pulse measurements	X			X			X
SNOT-22	X			X			X
PGIC				X			X
Sniffin Sticks n-butanol (Extended test)	X						X
Nasal examination[c]	X			X			X
Record polyp grade score from nasal polyp grading scale[c]	X						
Endoscopic video uploaded	X			X			X
Review proper use of OPN-375 EDS	X			X			
Treatment compliance		X	X	X	X	X	X
Adverse event collection[d]		X	X	X	X	X	X
Record concomitant medication		X	X	X	X	X	X
Contact with subject[e]		X	X		X	X	

Note: Screening and Baseline visits are combined. All visits should be scheduled based on the date of the Visit 1 (Day 1/Baseline). If necessary, visits may be performed within the time window shown, however, subsequent visits should be scheduled based on the date of the Visit 1 (Day 1/Baseline).

[a] The study staff will dispense a demo EDS (which will be empty) and record in the Accountability Log. This demo EDS is only used at the site at Visit 1 (Day 1/Baseline) and subject should not leave the site with the demo EDS.

[b] Women of child-bearing potential only; a urine pregnancy test will be performed at the site during each office visit.

[c] The nasal examination, nasoendoscopy (including nasal polyp grade), should all be performed by the same physician. If possible, the same physician should perform these procedures for the same subject throughout the study. Nasal polyps will be graded by an Independent Reviewer during Visit 2 (Week12) and Visit 3 (Week 24/End of Study/Early Termination).

[d] The period of observation for collection of adverse events extends from the time the subject gives informed consent until completion of the Visit 3 (Week 24/End of Study/Early Termination). Serious adverse events will be reported through 30 days after the last dose of OPN-375 administration.

[e] Subjects will be contacted approximately every 4 weeks between site visits to have information on treatment compliance, adverse events and concomitant medications collected

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IN-TEXT TABLES

IN-TEXT FIGURES

5 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AE	Adverse Event
BID	Two times a day
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DCF	Data Clarification Form
EDS	Exhalation Delivery System
GCP	Good Clinical Practice
GI	Gastrointestinal
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NARES	Nonallergic Rhinitis with Eosinophilia Syndrome
NSAID	Nonsteroidal Anti-inflammatory Drug
OMC	Ostiomeatal Complex
PGIC	Patient Global Impression of Change
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNOT-22	Sinonasal Outcome Test
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
US	United States
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary

6 INTRODUCTION

OptiNose is developing OPN-375 (XHANCE™ (fluticasone propionate) nasal spray) as an intranasal drug delivery system with the intention to improve the performance of fluticasone propionate in the treatment of nasal inflammatory diseases by facilitating deposition of the topical steroid in regions affected by local inflammation that lead to chronic nasal symptoms (e.g., the ostiomeatal complex). Delivery of drug, using an Exhalation Delivery System (EDS), is intended to improve reproducibility of nasal delivery, particularly deposition of the topical steroid in the region where many polyps originate (producing physical obstruction and inflammatory mediators) and where polyp obstruction threatens normal physiologic ventilation and drainage of the paranasal sinuses. OPN-375 is also intended to address user preference associated with reduced drip-out (posterior and anterior) and taste, and to improve tolerability and efficiency by significantly reducing loss of drug to nontarget sites such as the gastrointestinal (GI) tract and lungs.

Fluticasone propionate is an androstane glucocorticoid with high lipophilicity, high selectivity and affinity for the glucocorticoid receptor, low oral and nasal systemic absorption, and rapid metabolic clearance (Crim 2001). It is approved in many countries for use in the treatment of dermatosis (topical), rhinitis (intranasal), and asthma and chronic obstructive pulmonary disease (COPD) (inhaled), and is one of the most well studied and characterized glucocorticoids in clinical use today.

Information on OPN-375 for treatment of nasal polyposis is summarized in the following sections. For the most comprehensive information on the safety and efficacy of OPN-375 refer to the most recent version of the Investigator's Brochure (IB).

The terms "Sponsor" or "designee" used throughout this document refers to those companies or individuals listed on the Contact Information page(s), which will be provided as a separate document.

6.1 Background

A clinical development program for OPN-375 (XHANCE™) in adults with nasal polyposis has been completed. XHANCE™ is currently approved for the treatment of nasal polyps in

patients 18 years of age or older. OptiNose is intending to gather additional information on the impact of OPN-375 on the signs and symptoms associated with nasal polyposis.

Nasal polyps are benign lesions arising from the mucosa of the nasal sinuses or from the mucosa of the nasal cavity. The clinical symptoms associated with nasal polyposis often depends on the size and location of the polyp. Small nasal polyps are generally asymptomatic but when located in areas such as the middle meatus, they may produce symptoms. Patients with multiple and/or larger polyps may suffer partial or complete obstruction of the nasal passages and/or sinus ostia, which may result in chronic or recurrent acute sinusitis symptoms. Thus, signs and symptoms of nasal polyps may include rhinorrhea, persistent stuffiness, post-nasal drip, decreased or absent sense of smell, loss of taste, facial pain, or headache (Meltzer 2004, Fokkens 2012). Anterior polyps may be visualized on nasal examination or rhinoscopy with an otoscope. Nasoendoscopy is usually required to visualize posterior polyps.

The development of nasal polyps has been associated with chronic inflammation, autonomic nervous system dysfunction and genetic predisposition. Nasal polyps have been associated with allergic rhinitis, asthma, chronic rhinosinusitis, allergic fungal sinusitis; genetic diseases such as cystic fibrosis, primary ciliary dyskinesia, and Young syndrome; clinical syndromes such as Churg-Strauss syndrome, and other hypereosinophilic conditions such as aspirin or alcohol intolerance and nonallergic rhinitis with eosinophilia syndrome (NARES) (Chaaban 2013).

The prevalence of nasal polyps has been estimated to be 1-4%. Nasal polyps can be removed surgically or treated with steroid medication, given orally, by intrapolyp injection, or topically by nasal sprays or drops. None of these methods have proven entirely curative and people often require multiple surgical procedures. Oral steroids may reduce the need for surgery but there are concerns about significant side effects with long-term oral steroid use. Among the intranasal glucocorticoids available in the U.S., beclomethasone (Beconase AQ®) has been approved for prophylaxis of nasal polyps post-surgical resection, and mometasone (Nasonex®) and fluticasone (XHANCE™) have been approved for the treatment of nasal polyps; both of these indications are only in adults (Prescribing Information for Beconase AQ [2005] and Nasonex [2013], and XHANCE™ [2017]).

OPN-375

OPN-375 contains a liquid suspension of fluticasone propionate that it delivers to the nasal mucosa with a drug delivery system designed to deposit the drug aerosol high and deep into the nasal cavity. Fluticasone propionate is a synthetic corticosteroid that has long been commercially available in the US. It is currently approved as monotherapy and in various combinations, and in multiple formulations for multiple indications including creams (for inflammatory dermatoses and other dermatological conditions), inhalers (for asthma and other respiratory conditions), and nasal sprays (for rhinitis and nasal polyposis).

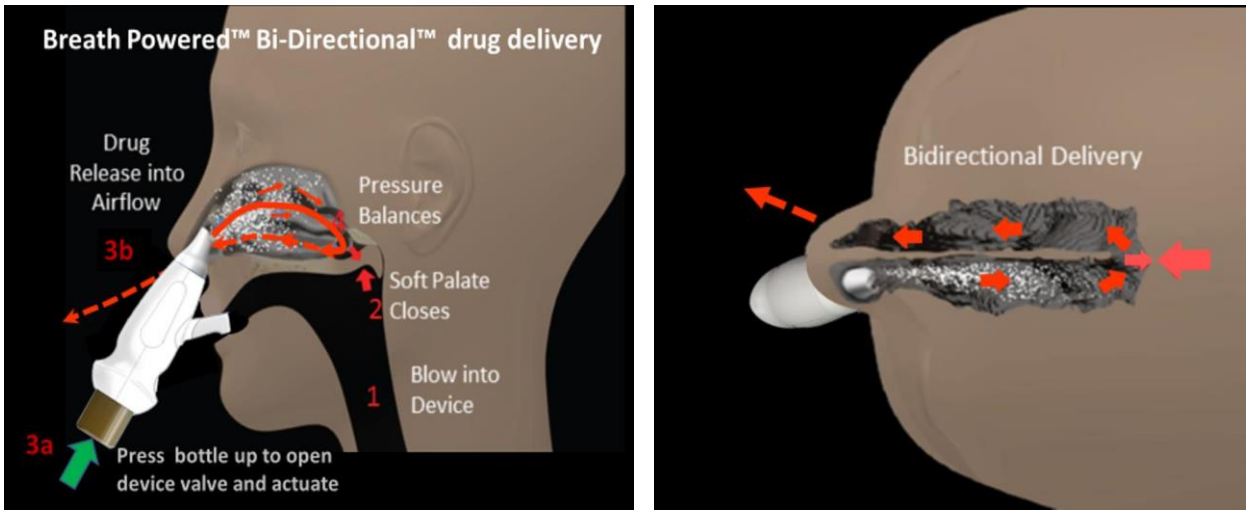
OPN-375 delivers active medication using an EDS. It is composed of a pharmaceutical industry standard amber glass vial containing a suspension of fluticasone propionate, a standard metering spray pump, and plastic casework with an asymmetrically shaped sealing nosepiece and a flexible mouthpiece. The casework defines the drug delivery system's outer shape and includes the moveable mouthpiece and sealing nosepiece. The user inserts the sealing nosepiece into one nostril, so it seals well with the flexible nasal tissues, and inserts the mouthpiece between the lips. After taking a deep breath, the user closes the lips around the mouthpiece and blows into the OPN-375 mouthpiece. Static positive pressure is created and subsequently released through the actuation of the spray by pressing the vial, which concurrently releases the orally-generated pressure/airflow. Blowing through the mouth against a resistance also causes the soft palate to seal closed, separating the oral cavity from the nasal cavities. A nasal spray applicator extends from the metering pump to the tip of the nosepiece. Upon actuation, the design of the EDS allows for air to be channeled from the mouthpiece to the sealing nosepiece when the pump is actuated. Under these conditions, exhaled air creates a positive intranasal pressure, accompanies the aerosol expelled by the spray pump applicator beyond the nasal valve, and places at least 50% of the initially deposited metered spray beyond the head of the inferior turbinate and at least 30% of the initially deposited dose in the upper posterior region of the nasal cavity beyond the head of the inferior turbinate and above the inferior meatus, including the ostiomeatal complex (OMC) (middle meatus). This pattern of delivery produced by OPN-375 is intended to place topical steroid in the region of the nasal cavity where many polyps originate (producing physical obstruction and releasing inflammatory mediators), and where polyp obstruction threatens normal

physiologic ventilation and drainage of the paranasal sinuses. OPN-375 EDS is also intended to address user preference associated with reduced drip-out (posterior and anterior) and taste, and to improve tolerability and efficiency by significantly reducing loss of drug to non-target sites inside the body such as the gastrointestinal tract and lungs.

Figure 1 presents a schematic view of closed palate Breath Powered™ Bi-Directional™ delivery and an image of OPN-375.

Figure 1. Closed Palate Bi-directional Delivery Concept

Schematic A **Schematic B**



Closed palate bi-directional Delivery Concept

A = Cross-sectional view from the left side.

B = Cross-sectional view from the top.

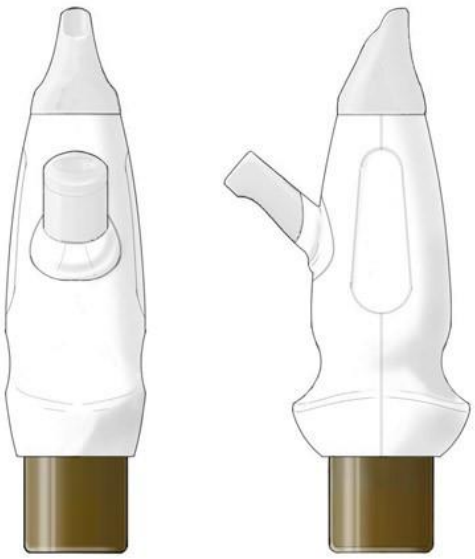
The EDS has a flexible mouthpiece and a sealing nosepiece. The nosepiece is shaped to transfer pressure from the mouth, avoid obstruction by compression of soft tissue, and expand the upper part of the nasal valve. Exhalation through the EDS: 1) creates an airtight seal of the soft-palate, isolating the nose from the mouth and lungs, 2) transfers proportional pressure into the nose, and 3) helps "float" medication around obstructions to deposit in high/deep sites in the nasal labyrinth, such as the OMC. The transferred pressure is proportional to varying

exhalation force, counterbalanced by the pressure on the soft palate. This assures a patent communication behind the nasal septum, allowing air to escape through the opposite nostril. “Positive-pressure” expands passages narrowed by inflammation (versus negative pressure delivery, “sniffing”).

Use is simple and quick. A patient inserts the nosepiece into one nostril and starts blowing through the mouthpiece. This elevates and seals the soft palate, as with inflating a balloon, separating the oral and nasal cavities. The patient completes use by pressing the bottle to actuate. This causes a coordination-reducing valve to release the exhaled breath concurrently with aerosol spray in a “burst” of naturally humidified air.

OPN-375 is shown pictorially in Figure 2.

Figure 2. OPN-375



Before OPN-375 is used for the first time, it is necessary to prime the unit. To prime the unit, shake, then actuate and spray into the air 7 times or until a fine mist appears.

6.2 Clinical Experience

XHANCE™ (fluticasone propionate) nasal spray was approved in September 2017 on the basis of a clinical program demonstrating safety and efficacy. There were two Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies (OPN-FLU-NP-3101 and OPN-FLU-NP-3102) conducted to assess the efficacy and safety of 3 doses of OPN-375 (93, 186, and 372 μg BID) compared with placebo in adult subjects with bilateral nasal polyposis followed by an 8-week open-label extension phase (372 μg BID) to assess safety. The clinical studies were identical in design.

In these studies, all three OPN-375 doses produced statistically significant greater reductions than placebo on the co-primary measures of nasal congestion/obstruction and total polyp grade. Sensitivity analyses conducted on the co-primary outcome variables, including a tipping point analysis, indicated that the results obtained were robust. Results from the co-primary analyses conducted with the integrated data were consistent with the results of the individual pivotal studies. The 186 μg and 372 μg groups had numerically larger magnitudes of effect compared with the 93 μg group.

Results obtained from secondary measures in the pivotal studies were generally consistent with the primary efficacy results. In the open-label phases of the pivotal trials, the improvements from baseline in efficacy assessments seen at the end of the double-blind phases generally continued to increase through week 24. Data from responder analyses demonstrate that OPN-375 substantially reduces polyp grade and the magnitude of reduction continues to increase with longer-term treatment within the period studied.

Clinically meaningful improvements with OPN-375 treatment were also observed broadly in other signs and symptoms of the disease and in physical and emotional parameters relevant to quality of life. Analyses of the Patient Global Impression of Change (PGIC) indicated that treatment with OPN-375 not only produced statistically significant benefits but that the magnitude of change perceived by the subject was clinically meaningful.

There were two Phase 3, open-label, multicenter studies (OPN-FLU-CS-3203, 12-month; OPN-FLU-CS-3204, 3-month) designed to assess the safety and efficacy of OPN-375 372 µg BID in subjects with or without nasal polyps.

Subjects in the open-label studies also had considerable improvement in symptoms and in objectively observed local signs of disease. A substantial proportion of subjects with intranasal edema at study entry no longer had evidence of edema on examination at study completion, a finding consistent with an intranasal deposition profile that places topically-acting fluticasone propionate in the areas beyond the nasal valve including the area of the middle meatus/ostiomeatal complex. In subjects with polyps, extensive reductions in polyp grade were observed and polyps were eliminated from at least 1 side of the nose in approximately 50%. In the 12-month study the improvement in polyp grade increased over time, suggesting benefit with continued treatment over the observed period.

Safety

The most commonly reported adverse events (AEs) in the active treatment groups were associated with local effects at the site of administration in the nasal cavity (epistaxis, nasal congestion, nasal mucosal disorder [primarily erythema], and nasal septum ulceration) or associated with the underlying disease (acute sinusitis or nasopharyngitis). Most local AEs were identified as a result of intensive active monitoring of all subjects at scheduled intervals by skilled nasoendoscopic examination at each visit and were not spontaneously reported. The majority of these AEs were mild and importantly, are known to have resolved with continued use of study drug. No deaths were reported, 18 subjects receiving OPN-375 reported serious adverse events (SAEs) during the placebo controlled and open-label studies. One placebo-treated subject reported a treatment-related SAE, and the overall rate of discontinuations due to AEs was approximately 4% among all subjects who received OPN-375.

Epistaxis was the most common AE reported in clinical trials. The AEs coded to epistaxis were either spontaneously reported clinical events or were observations of mucosal bleeding (active or nonactive bleeding) made during a nasoendoscopic examination. The epistaxis coded AEs were primarily mild, and most were observed on the nasal endoscopic

examination rather than being captured in a spontaneous report by the subject. The majority of bleeding events identified via nasal examination were categorized as nonactive (evidence of clots or previous bleeding). Over 90% of AEs coded to epistaxis in these studies resolved with continued use of study drug. The incidence of epistaxis appeared to have been highest in the first months of study participation when nasal examinations were more frequent.

6.3 Rationale for the Study

Current nasal steroid treatments are suboptimal in reliably reaching target sites beyond the nasal valve (Aggarwal 2004). In order to reduce inflammation and polyp size the drug must reach the polyps in sufficient quantities. The EDS, with its unique mechanism of delivery, provides specific benefits over current nasal drug delivery systems including increased reliability of delivery of topical medication to the anatomical sites which are central to the pathology of nasal polyps.

The results from phase 3 clinical studies in adults with nasal polyposis have demonstrated that OPN-375 is both safe and effective. This study is being conducted to provide nasoendoscopic video evidence of the changes that occur with OPN-375 treatment.

7 STUDY OBJECTIVES

7.1 Primary Objective

The primary objective of this study is to document the changes in polyp burden over time using nasoendoscopic video.

7.2 Secondary Objectives

Secondary objectives of this study include:

- Evaluate the safety of OPN-375 via adverse event (AE) reports, vital signs and nasal examination
- Change from baseline to each time point in subject symptoms and functioning, as measured by Sinonasal Outcome Test - 22 (SNOT-22)
- Change in the sense of smell as measured by Sniffin' Sticks n-butanol (Extended test)
- Patient's global impression of change (PGIC)

- Percentage of subjects with polyp grade of 0 on at least one side of the nose at each timepoint
- Percentage of subjects with a change of ≥1 point in bilateral polyp grade at each timepoint

7.3 Number of subjects and duration of study

The total planned number of subjects is approximately 10. Each subject will receive OPN-375 186 µg BID.

The expected participation period for a subject is approximately 24 weeks.

7.4 Termination of Study

Premature termination of the trial may occur because of a regulatory authority decision, change in opinion of the Institutional Review Board (IRB), drug safety problems, or at the discretion of the Sponsor or their designee. If the study is prematurely terminated, the Sponsor or their designee will promptly notify the investigators.

8 STUDY DESIGN

8.1 Study Overview

This is an open-label, multi-center study designed to assess the efficacy and safety of OPN-375 186 µg BID delivered in subjects with nasal polyps. Approximately 10 subjects will be enrolled.

This study consists of 24 Weeks of open-label treatment. All visit procedures will be performed at the time points indicated on the Time and Events Schedule.

Subjects will undergo screening during the Visit 1 (Day 1/Baseline) visit to determine study eligibility.

Subjects who continue to meet eligibility criteria at Visit 1 (Day 1/Baseline) will be instructed on the use of OPN-375, including dosing instructions, and will receive a 3-month supply of OPN-375.

During the 24 Week open-label treatment, subjects will return to the study site at Visit 2 (Week 12), and then Visit 3 (Week 24/End of Study/Early Termination) for efficacy and safety

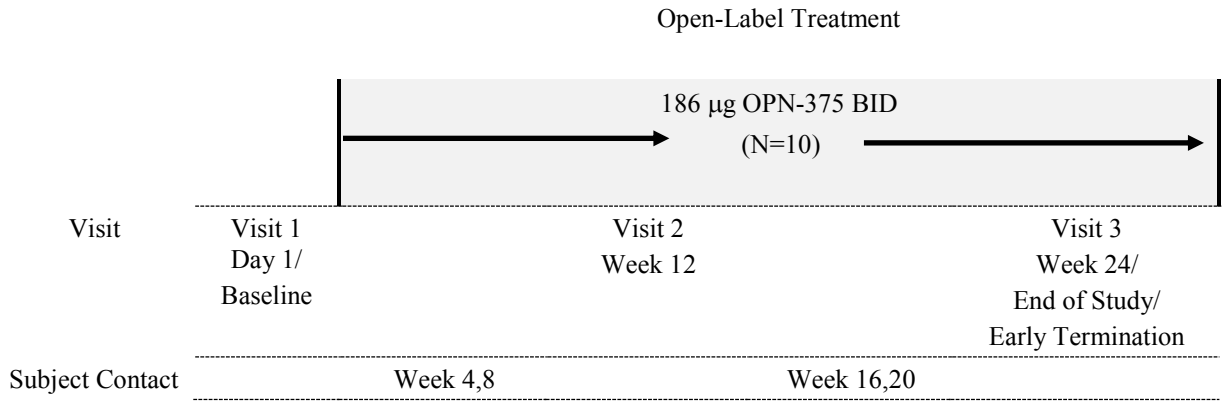
evaluations. At each visit nasoendoscopy will be performed with the examination being captured on video. The investigator will complete the nasal examination. The investigator will utilize appropriate video capturing equipment and will follow the standardized procedure outlined in the nasal examination procedure document.

Subjects will be contacted approximately every 4 weeks between site visits to have information on treatment compliance, adverse events and concomitant medications collected.

At Visit 3 (Week 24/End of Study/Early Termination), or if a subject discontinues study drug before the end of study, an end of study/early termination visit should be performed.

A study flow diagram is shown in Figure 3.

Figure 3: Study Flow Diagram



8.2 Endpoints

8.2.1 Primary Endpoint

Primary Endpoint

- Change from Visit 1 (Day 1/Baseline) at end of study in bilateral nasal polyp grading using nasoendoscopic video

8.2.2 Secondary Endpoints

Secondary Endpoint

- Assessment of safety through adverse events (AEs) and AEs of special interest (e.g., epistaxis, septal ulceration, etc.), nasal examinations, vital signs, and concomitant medication usage
- Change from Visit 1 (Day 1/Baseline) to each visit in bilateral polyp grade
- Number of subjects with a change of ≥1 point in bilateral polyp grade at each visit
- Number of subjects with a polyp grade of 0 on at least one side of the nose at each visit
- Change from Visit 1 (Day 1/Baseline) to each visit in average SNOT-22 score
- Average score on the Sniffin' Sticks n-butanol (Extended test) - Threshold test, Discrimination test, and Identification at Visit 1 (Day 1/Baseline) and Visit 3 (Week 24/End of Study/Early Termination).
- PGIC score at each visit

8.3 Method of Treatment Assignment or Randomization

Following completion of all Visit 1 (Day 1/Baseline) evaluations, subjects who meet all eligibility requirements will be provided with OPN-375 186 µg BID.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Inclusion Criteria

Potential subjects must meet the following criteria to enter this study:

1. Men or women aged 18 years and older at Visit 1 (Day 1/Baseline) visit
2. Women of child bearing potential must be abstinent, or if sexually active,
    a. be practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [e.g., condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel], or male partner sterilization) before entry and throughout the study, or
    b. be surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or
    c. be postmenopausal (amenorrhea for at least 1 year).
3. Women of child-bearing potential must have a negative urine pregnancy test at the baseline visit

4. Must have bilateral nasal polyposis with a grade of 2 or 3 in at least one side of the nasal cavity as determined by a nasal polyp grading scale score measured by nasoendoscopy (see Section 12, Efficacy Assessments) at Visit 1 (Day 1/Baseline)
5. Must have a SNOT-22 score of ≥20 at Visit 1(Baseline/Day 1) (as defined in Section 12, Efficacy Assessments)
6. Must have been on an adequate dose of an intranasal corticosteroid (e.g. fluticasone propionate, fluticasone furoate, mometasone, triamcinolone, ciclosenide, budesonide, budesonide respules, beclomethasone) for at least 1 month, in the previous 3 months prior to Visit 1 (Day 1/Baseline)
7. Subjects with comorbid asthma or chronic obstructive pulmonary disease (COPD) must be stable with no exacerbations (e.g., no emergency room visits, hospitalization, or oral or parenteral steroid use) within the 3 months before the screening visit. Inhaled corticosteroid use must be limited to stable doses of no more than 1,000 μg/day of beclomethasone (or equivalent) for at least 3 months before screening with plans to continue use throughout the study
8. Must be able to cease treatment with oral steroids, intranasal steroids, inhaled corticosteroids (except permitted doses listed above for asthma and COPD) at Visit 1 (Day 1/Baseline).
9. Must demonstrate correct use of the demo EDS
10. Ability to read and speak English
11. Must be capable, in the opinion of the investigator, of providing informed consent to participate in the study. Subjects must sign an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.

9.2 Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from entering this study:

1. Women who are pregnant or lactating
2. Inability to have each nasal cavity examined for any reason, including nasal septum deviation
3. Have used XHANCE™ (fluticasone propionate) nasal spray within the past 2 months
4. Nasal septum perforation
5. Has had more than 1 episode of epistaxis with frank bleeding in the month before Visit 1 (Day 1/Baseline)
6. Have evidence of significant mucosal injury or ulceration (e.g. exposed cartilage) on Visit 1 (Day 1/Baseline) nasal examination/nasoendoscopy

7. History of sinus or nasal surgery within 3 months before Visit 1 (Day 1/Baseline). If ≥3 months subject should be fully recovered from surgery
8. Current, ongoing rhinitis medicamentosa (rebound rhinitis)
9. Have significant oral structural abnormalities, e.g., a cleft palate
10. Diagnosis of cystic fibrosis
11. History of Churg–Strauss syndrome or dyskinetic ciliary syndromes
12. Purulent nasal infection, acute sinusitis, or upper respiratory tract infection within 2 weeks before Visit 1 (Day 1/Baseline). Potential subjects presenting with any of these infections may be rescreened 4 weeks after symptom resolution
13. Planned sinonasal surgery during the period of the study
14. Allergy, hypersensitivity, or contraindication to corticosteroids, or to any excipients in OPN-375
15. Exposure to any glucocorticoid treatment with potential for systemic effects (e.g., oral, parenteral, intra-articular, or epidural steroids, high dose topical steroids) within 1 month before Visit 1 (Day 1/Baseline); except as noted in inclusion criteria for subjects with comorbid asthma or COPD
16. Have nasal candidiasis at Visit 1 (Day 1/Baseline)
17. History or current diagnosis of any form of glaucoma, ocular hypertension, or intraocular pressure elevation on any form of steroid therapy
18. History or current diagnosis of the presence (in either eye) of a sub-capsular cataract
19. Any serious or unstable concurrent disease, psychiatric disorder, or any significant condition that, in the opinion of the investigator could confound the results of the study or could interfere with the subject's participation or compliance in the study
20. A recent (within 1 year of Visit 1 (Day 1/Baseline)) history of drug or alcohol abuse, or dependence that, in the opinion of the investigator could interfere with the subject's participation or compliance in the study
21. Have participated in an investigational drug clinical trial within 30 days of Visit 1 (Day 1/Baseline)
22. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

9.3 Withdrawal, Removal, and Replacement of Subjects

Subjects will be informed that they are free to withdraw from the study at any time at their own request without prejudice to their future medical care, or that they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety, non-adherence to protocol requirements, or administrative reasons (e.g., termination of study by Sponsor).

A subject must be withdrawn for the following reasons:

- Withdrawal of consent
- The subject becomes pregnant
- Discontinuation of study treatment. A subject's study treatment will be discontinued if the investigator or Sponsor considers it in the subject's best interest to stop treatment, (e.g., for safety or significant tolerability reasons such as an AE)
- Termination of the study

A subject may also be withdrawn for the following reasons:

- Lost to follow-up
- Lack of efficacy
- Protocol violation

If a subject withdraws from the study after starting study treatment, appropriate follow-up must be conducted wherever possible.

9.4 Follow-Up for Drug Discontinuation/Subject Withdrawal from Study

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the subject's outcome, if possible. The investigator should inquire about the reason for withdrawal, request the return of all investigational product, and request the subject return for a final study visit and examination.

The date and the reason for subject withdrawal from the study must be recorded on the Case Report Form (CRF).

10 STUDY DRUG

10.1 Study Drug Treatment and Dosing

As shown in Table 1, the study drug dosage will be 186 µg OPN-375 BID. Each spray delivers 93 µg of fluticasone propionate per actuation.

Table 1: Study Drug Dosing

Dosage	Times of administration
186 µg BID	1 spray each nostril every morning 93 µg per spray 1 spray each nostril every evening 93 µg per spray

During this open-label treatment study, all subjects will receive 186 µg of fluticasone propionate BID, and the same dosing procedure will be followed for both the AM and PM doses on each day. The study staff will instruct the subject to shake OPN-375 before use, and then administer 1 spray to the right nostril and 1 spray to the left nostril.

At Visit 1 (Day 1/Baseline), subjects will be provided with a demo EDS to practice administration of a dose and to assure that they can correctly use the EDS (e.g., able to obtain a seal, aim the EDS appropriately, correctly sequence steps). The study staff will record in the accountability log. This demo EDS is only to be used at the site at Visit 1 (Day 1/Baseline) and subject should not leave the site with the demo EDS.

Open-label study drug will be dispensed to subjects at Visit 1 (Day 1/Baseline) and at Visit 2 (Week 12):

- Visit 1 (Day 1/Baseline): 3 kits (Each kit contains 1 bottle)
- Visit 2 (Week 12): 3 kits (Each kit contains 1 bottle)

Throughout the study, subjects will be instructed to shake OPN-375 before use. They will also be instructed that it is only necessary to prime OPN-375 before it is used for the first time as follows:

- To prime OPN-375, shake, then actuate and spray into the air 7 times or until a fine mist appears. Note that it is not necessary to prime OPN-375 before every administration when OPN-375 is being used regularly each day.

The first dose of study drug should be administered in the evening (PM) on Day 1. Throughout the study, subjects will be instructed to administer study drug approximately every 12 hours. If a subject misses a dose, the dose should be taken as soon as remembered, but not within 2 hours of the next scheduled dose. In such cases the subject should wait until the next scheduled dosing time to administer a dose.

The study staff will instruct subjects to report OPN-375 they perceive to be broken or malfunctioning and to return any such OPN-375 to the study site for evaluation and identification of the problem. Study staff will return the malfunctioning OPN-375 to the Sponsor for evaluation and identification of the issue.

An instruction sheet on the use of OPN-375 will be provided by the Sponsor or their designee to be given to the subjects.

10.2 Clinical Supplies

The fluticasone propionate formulation is a milky, white suspension contained in an amber glass bottle crimp sealed by the nasal spray pump. Each actuation delivers 93 µg of fluticasone propionate through the nasal sealing nozzle. The number of deliveries per OPN-375 (after priming) is not less than 120.

10.3 Packaging and Labeling

The demo EDS is only to be used only at Visit 1 (Day 1/Baseline) to confirm subject's ability to use the EDS. The demo EDS will be packaged containing one demo EDS.

Open-label study drug will be packaged in a kit and will consist of one OPN-375 containing 93 µg per spray of study drug.

Labeling will contain all information required by local regulations.

10.4 Dispensing and Return of Study Drug

The investigator or designee at each site will maintain accurate records of open-label OPN-375 and demo EDS units received, including to whom study drug has been dispensed, dates and quantity. All demo and OPN-375 units should be returned to storage, and accounted for, including dates and quantity (subject by subject accounting). Any open-label OPN-375 or demo EDS accidentally or deliberately destroyed will also be documented.

10.5 Storage and Reconciliation of Supplies

All study drug will be supplied by the Sponsor and should be stored securely in a locked facility.

All study drug must be stored at room temperature (between 15°C and 25°C: 59°F and 77°F, with excursions permitted from 15°C and 30°C: 59°F and 86°F). Avoid exposure to extreme heat, cold or light. Shake OPN-375 before each use. Keep all study drug in the manufacturer's packaging.

The shelf life of the product will be supported by ongoing stability studies.

All used and unused OPN-375 will be returned to the Sponsor or designee at the end of the study. Reasons for departure from the expected dispensing or return of OPN-375 must be recorded.

10.6 Concomitant Medication

All pre-study medications used within 1 month before Visit 1 (Day 1/Baseline) must be recorded in the CRF. For subjects with comorbid asthma or COPD, pre-study inhaled steroid (beclomethasone or equivalent) use within the 3 months before Visit 1 (Day 1/Baseline) must be recorded in the CRF.

Concomitant medications include all medications and other treatments taken by the subject during the study, including those treatments initiated prior to the start of the study. All concomitant medications must be recorded on the CRF.

Allowed Concomitant Medications

In subjects with comorbid asthma at study entry (i.e., Visit 1 (Day 1/Baseline)), inhaled corticosteroid use must be limited to stable doses of no more than 1,000 μg/day of beclomethasone HFA (or equivalent; see Attachment 1). Subjects must be on a stable dose for at least 1 month before Visit 1 (Day 1/Baseline) with plans to continue use throughout the study.

Other concomitant medications allowed include:

- Antibiotic medications will be permitted for bacterial infections that develop during the study.
- Intranasal saline spray may be used with the exception of use within 2 hours before or after study drug administration.
- Saline lavage will be permitted only for those subjects regularly using it before study entry; subjects may not initiate use during the study. Saline lavage must not be performed within 2 hours before or after study drug administration.
- Intranasal antibiotics are permitted, but must not be given without 2 hours before or after study drug administration.
- Stable doses (within 2 weeks of the Visit 1 (Day 1/Baseline)) of leukotriene receptor antagonists, beta-blockers, and neuroleptics
- Low to medium strength topical corticosteroids for dermatologic purposes

Other concomitant medications are allowed, if not specially listed below as prohibited.

Prohibited Medications

- Exposure to any glucocorticoid treatment with potential for systemic effects (e.g., oral or parenteral steroids, high dose topical steroids) within 1 month before the screening visit through completion of the study; except as noted for subjects with comorbid asthma or COPD.
- Any systemic, inhaled, intranasal and topical corticosteroids (except low to medium strength topical corticosteroids as noted above)
- XHANCE™ (fluticasone propionate) nasal spray
- Nucala (mepolizumab), Cinquair (reslizumab), Dupixent (dupilumab), or Omalizumab (Xolair®)
- Strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin, conivaptan, lopinavir, voriconazole) with OPN-375 is prohibited because increased systemic corticosteroid adverse effects may occur.

10.7 Treatment Compliance

At each visit after Visit 1 (Day 1/Baseline), subjects will be instructed to bring their partially used/empty OPN-375 units back to the study site at each study visit. At each study visit, all subjects will be reminded of the importance of compliance with their assigned regimen with an emphasis on correct use of OPN-375 and the administration of and timing of doses.

11 VISIT SCHEDULE SUMMARY

Procedures to be performed at each study visit, and the visit time windows, are indicated in Section 3, Schedule of Study Procedures and Evaluations. Additional information related to the individual study visits is presented in the subsections that follow.

The different visits and allowable timing for the nasoendoscopic-related procedures are as presented below and in Section 3, Schedule of Study Procedures and Evaluations:

- The Visit 1 (Day 1/Baseline) nasal examination and nasoendoscopy, are the baseline assessments for these procedures.
- For Visit 2 (Week 12) and Visit 3 (Week 24/End of Study/Early Termination) study visits, if the nasal examination and nasoendoscopic assessments cannot be performed on the same day as the study visit, they may be performed *before or after the study visit*, but must be performed within the same ±7-day window around the expected study visit date (i.e., visit date calculated based on Day 1).

11.1 Visit 1 (Day 1/Baseline)

Subjects will be provided with an informed consent form that will explain the objectives of the study and its potential risks and benefits. The subject should have adequate time to read the informed consent and to ask the investigator any questions. The investigator must be satisfied that the subject has understood the information provided before written consent is obtained. If there is any doubt as to whether the subject has understood the written and verbal information, the subject should not enter the study. A copy of the signed informed consent form will be given to the subject and the original filed in the site file.

After informed consent has been obtained, subjects will undergo all Visit 1 (Day 1/Baseline) procedures indicated in the Schedule of Study Procedures and Evaluations in Section 3, to determine study eligibility.

Subjects will be instructed on the use of OPN-375. They will then be provided with a demo EDS to practice and to assure that they can correctly use the EDS (e.g., able to obtain a seal between the nosepiece and the nostril, sequence). The study staff will dispense a demo EDS and record in the accountability log. This demo EDS is only to be used at the site at Visit 1 (Day 1/Baseline) and subject should not leave the site with the demo EDS. The subject must be able to correctly use the demo EDS prior to entering the study.

Subjects who then meet all eligibility criteria at Visit 1 (Day 1/Baseline), will enter the study and receive 186 µg of OPN-375 BID. OPN-375 will be administered as described in Section 10.1, Study Drug Treatment and Dosing. Subjects will be given 3 kits (each containing 1 OPN-375 unit). Subjects will be instructed to bring the OPN-375 unit with them to their next visit.

11.2 Visit 2 (Week 12)

During the study, subjects will return to the study site at Visit 2 (Week 12), to have efficacy evaluations performed and safety assessed as detailed in Section 3, Schedule of Study Procedures and Evaluations.

11.3 Visit 3 (Week 24/End-of-Study/Early Termination)

Subjects who complete 24-weeks of study treatment, and those who prematurely withdraw from the study for any other reason during this phase should return to the study site and have the end-of-study/early termination visit performed.

12 EFFICACY ASSESSMENTS

The Schedule of Study Procedures and Evaluations in Section 3 indicates the timing of all assessments; further information on each evaluation is provided below.

The nasal examination and nasoendoscopic video, should be performed by the same physician on each subject. If there are multiple physicians performing these assessments, the same physician should perform these procedures for the same subject throughout the study. The Schedule of Study Procedures and Evaluations in Section 3 and Section 11, Visit Schedule Summary, indicates the visits, as well as various visit time windows, at which these

assessments will be performed. Additional information on the nasal examination can be found in Section 13, Safety Assessments.

The following efficacy evaluations will be performed at the time points specified in Section 3, Schedule of Study Procedures and Evaluations:

- Nasoendoscopy will be performed using a rigid endoscope and the exam will be captured on video. The size and type of scope used in an individual subject should remain consistent throughout the study. The examiner must be able to visualize the middle meatus with the scope. Decongestants and/or local anesthetics may be used for the nasoendoscopic procedure, however, if used at Visit 1 (Day 1/Baseline) in a subject, they must be used consistently at all scheduled nasoendoscopic evaluations that follow.
- Polyp grading of each nasal cavity determined by a nasal polyp grading scale score measured by nasoendoscopy (Lildholdt 1995, 1997) as presented in Table 2. The baseline assessment of polyp grading is performed at Visit 1 (Day 1/Baseline) by the examining physician to determine study eligibility. Assessment of polyp grade will be performed by an independent reviewer using the videos from the examination. Subjects and visits will be de-identified for this review.

Table 2: 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

- SNOT-22 is a subject-completed questionnaire that consists of 22 symptoms and social/emotional consequences of their nasal disorder. Each item is rated as follows: 0=no problem, 1=very mild problem, 2=mild or slight problem, 3=moderate problem, 4=severe problem, 5=problem as bad as it can be. The recall period is the past 2 weeks. The SNOT-22 is validated in chronic rhinosinusitis (Hopkins 2009). The SNOT-22 takes approximately 5 minutes to complete.

- The Sniffin' Sticks n-butanol (Extended test) are used to investigate human olfactory performance by use of odor pens. It consists of 3 different subtests- Threshold, Discrimination and Identification. The Threshold test is used to ascertain the patient's olfactory threshold. The Discrimination test requires the

patient to differentiate smells. The Identification Test requires the patient to identify everyday smells by means of a card with different choices. The test will take approximately 30-40 minutes. All substances contained in the test are non-toxic and not harmful in the used concentrations. The result of this test is expressed as the sum of the results of the 3 subtests, the so called TDI score (threshold, discrimination, identification). Here a score of more than 30 rates as normal, a score of 30 or less indicates hyposmia and a score of 15 and below points to functional anosmia in the form of a complete loss of the sense of smell or an extremely weakened smell ability.

- Subject global impression of change will be assessed using a subject-completed PGIC scale as shown in Table 3. The PGIC takes less than 1 minute to complete.

Table 3: Patient Global Impression of Change (PGIC) Scale

Since starting the study drug, how would you rate the change in your symptoms?	
Score	**Description**
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Minimally worse
6	Much worse
7	Very much worse

13 SAFETY ASSESSMENTS

Refer to Section 3, Schedule of Study Procedures and Evaluations, for the timing of all safety assessments.

Safety will be assessed by monitoring of AEs throughout the study (as described in Section 13.4), nasal examinations and measuring vital signs (i.e., blood pressure, pulse), and through collection of information for concomitant medications.

13.1 Nasal Examination

The nasal examination will be performed via nasoendoscopy. See Section 11, Visit Schedule Summary, regarding completion of this assessment, including visit time windows. A summary of the worksheet key assessments from the nasal examination is provided in Attachment 2.

13.2 Vital Signs

Vital signs include systolic and diastolic blood pressure measurements and pulse rate. Before vital signs are measured, the subject should be at rest for at least 5 minutes.

13.3 Laboratory Tests

Laboratory tests, other than the urine pregnancy tests performed at each office visit, are not scheduled assessments for this study. If any laboratory tests are performed as part of a subject's standard of care after the subject is enrolled into the study, and the laboratory test result is considered by the investigator to be clinically significant, it should be considered an AE if it meets the definition provided in Section 13.4.1.

13.4 Adverse Event Definitions and Reporting

13.4.1 Adverse Events

An AE is any untoward medical occurrence associated with the use of an investigational product in humans, whether or not considered related to the investigational product. This includes any occurrence that was new in onset or aggravated in severity or frequency from the baseline condition.

In this study, polyp grade and symptoms of nasal polyps are collected as part of the primary and secondary endpoints. Changes in polyp grade or worsening of these symptoms should not be reported as AEs. All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Abnormal results of diagnostic procedures, including laboratory test abnormalities, or from the nasal examination are considered AEs if they result in:

- Discontinuation from the study;
- Require treatment or any other therapeutic intervention;
- Require further diagnostic evaluation which confirms a clinical significant abnormality (excluding a repetition of the same procedure that rules out an abnormality); or
- Are associated with clinical signs or symptoms that would have a significant clinical impact, as determined by the investigator.

Subjects are encouraged to report AEs spontaneously or in response to general, non-directed questioning. All non-serious AEs are to be followed until the subject completes the study or is lost to follow-up.

Timely, accurate, and complete reporting and analysis of safety information from clinical studies is crucial for the protection of subjects, is the responsibility of the investigators and the Sponsor, and is mandated by regulatory agencies worldwide.

Each AE is to be documented on the CRF with reference to intensity, date of occurrence, duration, frequency, treatment, action taken regarding study drug, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Additionally, the investigator must assess whether the AE is drug related (adverse drug reaction) or not. Changes of AEs and dates of ending must be documented on the CRF.

Surgical procedures, planned before enrollment of the subject in the study, are not considered AEs if the condition(s) was (were) known before study inclusion. In the latter case, the medical condition should be reported in the subject's medical history.

For the purposes of this study, the period of observation for collection of AEs extends from the time the subject gives informed consent at Visit 1 (Day 1/Baseline) until completion of Visit 3 (Week 24 / End of Study/ Early Termination). SAEs will be reported through 30 days after the last dose of OPN-375 administration.

The maximum severity (intensity) of the AE will be categorized by the investigator as shown in Table 4.

Table 4: Adverse Event Severity

Code	Descriptor	Definition
1	Mild	The subject is aware of the symptom, but easily tolerates it
2	Moderate	The subject has discomfort enough to cause interference with usual activity
3	Severe	The subject is incapacitated to work or perform usual activities

13.4.2 Adverse Reactions

An AE is considered related to study drug (adverse reaction) if there is evidence to suggest a causal relationship between the treatment and the AE.

13.4.3 Suspected Adverse Reactions

"Suspected adverse reactions" means any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A "suspected adverse reaction" implies a lesser degree of certainty about causality than "adverse reaction" which means any AE caused by a drug.

An AE is considered to be a suspected adverse reaction if:

- The AE is a single occurrence of an uncommon AE that is known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- The AE occurs one or more times and is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).
- The AE is part of an aggregate analysis of specific AEs observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those AEs occur more frequently in the drug treatment group than in a concurrent or historical control group.

Suspected adverse reactions are the subset of all AEs for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report them is the need for the Sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the AE.

13.4.4 Unexpected Adverse Reactions or Adverse Events

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The suspected adverse reactions listed in the IB (i.e., "expected") are those observed with the investigational drug and for which a causal relationship between the event and the drug is suspected or confirmed. Thus, AEs that would be anticipated to occur as part of the disease

process are considered *unexpected* for the purposes of reporting because they would not be listed in the IB. Additionally, AEs that are listed in the IB as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation, will be considered *unexpected* until they have been observed with the drug under investigation.

13.4.5 Serious Adverse Events

An AE or suspected adverse reaction is considered "serious" if at any dosage, in the view of either the investigator or Sponsor, it meets one or more of the following criteria:

- Is fatal,
- Is life-threatening,
- Results in inpatient hospitalization or prolongation of existing hospitalization,
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Is a congenital anomaly/birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. Since SAEs are critically important for the identification of significant safety problems, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

All SAEs must be reported to the Sponsor or their designee within 24 hours after the investigator becomes aware of the event, along with a determination as to whether it is associated with the study drug, EDS, or procedure.

13.4.6 Life-Threatening Adverse Events

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. As with the definition of serious, the determination of whether an AE is life-threatening can be based on the opinion of either the investigator or Sponsor. Thus,

if either believes that it meets the definition of life-threatening, it must be considered life-threatening for reporting purposes.

13.4.7 Serious Adverse Event Reporting

All SAEs must be reported within 24 hours to:

Ashfield Safety and Pharmacovigilance

Safety Email: APV.AEOptiNose@ashfieldPV.com

Safety Fax: 1-866-391-0765

> Note: If the contact information above changes during the course of the study, written notification will be provided by the Sponsor or their designee to the investigator, and a protocol amendment will not be required.

It is imperative that Ashfield be informed within 24 hours after the investigator becomes aware of a SAE so that reporting to the Regulatory Agencies can be met within the required time frame (7 or 15 calendar days).

Should the investigator become aware of an SAE (regardless of relationship to study drug) that occurs during the study or within 30 days after stopping the study drug, the SAE must be reported in accordance with the procedures specified in this protocol. All SAEs that are not resolved by the end of the study, or that were not resolved upon discontinuation of the subject's participation in the study, are to be followed until either: the AE resolves, the AE stabilizes, the AE returns to baseline values (if a baseline value is available), or it is shown that the AE is not attributable to the study drug or study conduct.

Medical and scientific judgment is to be exercised in deciding whether expedited reporting is appropriate in other situations, such as for important medical events that were not immediately life-threatening or did not result in death or hospitalization but are jeopardizing the subject or require intervention to prevent one of the outcomes listed above.

13.4.8 Non-Serious Adverse Event Reporting

Non-Serious AEs will be recorded in the clinical data base in a timely manner to permit review by the Sponsor.

13.4.9 Pregnancy

Following administration of study drug, pregnancy cases in any female subject will be reported if known until the subject completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the Sponsor or their designee within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The investigator should notify the Sponsor or their designee of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by phone and by faxing/emailing a completed SAE form to the Sponsor or designee within 24 hours of knowledge of the event. Pregnancy in the partners of research subjects does not need to be reported.

14 STATISTICAL ANALYSIS

Data will be summarized descriptively. Listings will be produced using SAS® Version 9.0 or higher. No inferential statistics will be performed for this study.

14.1 Sample Size Determination

No statistical sample size calculation was performed for this study. An empiric sample size of 10 subjects is considered to be adequate to assess changes in polyp size and mucosal edema as assessed by nasoendoscopic video, as well as for symptomatic endpoints.

14.2 Analysis Datasets

Safety Population

The safety population will include all subjects who receive at least 1 dose of study drug.

14.3 Endpoint Evaluation

Nasal polyp grading score, SNOT-22 (item and total), Sniffin' Sticks n-butanol (Extended test) TDI scores, and PCIG for each timepoint will be listed for each subject.

14.4 Safety Analysis

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 or higher. All AEs during the study period for each subject will be listed and the listing will include the verbatim term, System Organ Class [SOC], preferred term, AE start date, AE end date, severity, serious categorization, causality, action taken if any, and outcome.

Vital signs will be listed for each subject.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug), Version December 2010 or later, and listed by subject.

14.5 Interim Analysis

No interim analysis is planned for this study.

15 DATA HANDLING AND RECORD KEEPING

15.1 Case Report Forms

Clinical data will be entered on case report forms (CRFs) for transmission to the Sponsor or their designee. Data on CRFs must correspond to and be supported by source documentation maintained at the study center. All study forms and records transmitted to the Sponsor or their designee must carry only coded identifiers such that personally identifying information is not transmitted.

Any changes made to data after collection will be made through the use of Data Clarification Forms (DCF). Data reported on the CRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. CRFs will be considered complete when all missing and/or incorrect data have been resolved.

15.2 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

The investigator agrees to allow inspections of the study site and any source documentation, by clinical research and audit personnel from the Sponsor or their designee, and external auditors or representatives of regulatory authorities. Direct access to the subject's medical/clinical records is necessary to verify and corroborate the data recorded on the CRFs.

15.3 Record Retention

Study records and source documents need to be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region which includes the study report, whichever is the longer time period.

16 MONITORING

The study will be monitored to ensure that the study is conducted and documented properly according to the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

On-site visits will be made at appropriate times during the period of the study. Monitors (e.g., Clinical Research Associates) must have direct access to source documentation in order to check the consistency of the data recorded in the CRFs. Additionally, remote monitoring may be conducted.

The investigator will make available to the Monitor source documents, medical records, and source data necessary to complete CRFs. In addition, the investigator will work closely with the Monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

17 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor or their designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Principal Investigator.

The Sponsor may arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, Standard Operating Procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions.

18 PROTOCOL AMENDMENT AND PROTOCOL DEVIATION

18.1 Protocol Amendment

A protocol amendment will be required if changes to a protocol significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study. Protocol amendments must not be implemented without prior IRB approval, except when necessary to eliminate immediate hazards to the subjects. If a protocol change is implemented immediately to protect the subjects, the IRB and regulatory authority must be subsequently notified. Documentation of amendment approval by the investigator and IRB must be provided to the Sponsor or their designee. When the change(s) involves only administrative aspects of the study, the IRB only needs to be notified.

18.2 Protocol Deviations

No deviations from the protocol are anticipated. However, should a protocol deviation occur, the Sponsor or their designee must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the study report. Reporting of protocol deviations to the IRB and in accordance with applicable regulatory authority mandates is an investigator responsibility.

19 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations (CFR), and in compliance with GCP guidelines.

Institutional Review Boards will review and approve this protocol and informed consent. All subjects are required to give written informed consent prior to participation in the study. This study will be performed in accordance with GCP by qualified investigators. The study specifically incorporates the following features:

- Multi-center, open-label, study design;
- Prospectively stated objectives and analytical plan;
- Accepted, pre-specified outcome measures for safety and efficacy;
- Site initiation meeting prior to study start and a detailed protocol to promote consistency across sites; and
- Compliance with GCP, with assessment via regular monitoring.

Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

20 FINANCING AND INSURANCE

Financial aspects of the study are addressed in a separate clinical study agreement.

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

21 PRIVACY OF PERSONAL DATA

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. The Sponsor ensures that the personal data are

- processed fairly and lawfully

- collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- adequate, relevant, and not excessive in relation to said purposes
- accurate and, where necessary, kept up to date

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries. The subject has the right to request through the investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel (or their designee) whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

22 PUBLICATION POLICY

Both the use of data and the publication policy are detailed within the clinical study agreement. The investigator should be aware that intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or their designee will solely own all right and interest in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their Institution or directly to the Sponsor or their designee, as will be set forth in the clinical study agreement.

23 REFERENCES

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24 ATTACHMENT 1: BECLOMETASONE – EQUIVALENT DOSES

Steroid	Equivalent dose to Beclomethasone dipropionate 1000 µg
Beclomethasone	
Beclovent® Inhaler, Beclovent® Rotacaps®, Beclovent® Rotahaler®	1000 µg
Clenil Modulite®	1000 µg
Clickhaler	1000 µg
Aerobec® Autohaler	1000 µg
Asmabec® Clickhaler	1000 µg
Becodisks® Dry Powder	1000 µg
Easyhaler	1000 µg
Pulvinal®	1000 µg
Filair® MDI	1000 µg
Qvar® MDI/Easi-breathe/Autohaler	500-750 µg
Fostair®-BDP/Formoterol MDI	500 µg
Vanceril®	1000 µg
Fluticasone	
Fluticasone HFA MDI	500 µg
Seritide®	500 µg
Advair®	500 µg
Budesonide	
MDI	1000 µg
Turbohaler®	1000 µg
Easyhaler®	1000 µg
Novolizer®	1000 µg
Symbicort® Turbohaler- budesonide/formoterol	1000 µg
Mometasone	
Twisthaler®	500 µg
Ciclesonide®	
MDI	500-750 µg

Adapted from the British Thoracic Society and Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. Updated 2009. Available from http://www.sign.ac.uk/pdf/sign101.pdf.
Reference: Primary Care Respiratory Society UK. PCRS-UK Equivalent Doses of Inhaled Corticosteroids Reference Table. Available at http://www.pcrs-k.org/resources/inhaled_steroid_equiv_doses.pdf.

25 ATTACHMENT 2: KEY ASSESSMENTS FOR NASAL EXAMINATION

The nasal examination worksheet will be provided to the sites as a separate document. The worksheet is formatted as a series of questions with check boxes and fields for narrative text. The nasal examination worksheet will be completed by the physician who performs the examination. If decongestants and/or local anesthetics are administered as preparation for the nasoendoscopy, these will be recorded on the form. Please note that if decongestants and/or local anesthetics are administered for the initial Visit 1 (Day 1/Baseline) nasoendoscopy for a subject, the same must be used for each subsequent examination. A rigid endoscope must be used. The size of the endoscope chosen for the initial Visit 1 (Day 1/Baseline) examination for each subject should be used throughout the study. The investigator will use the information from the nasal examination worksheet to complete the nasal examination, and concomitant medication case report forms (CRFs).

EPISTAXIS

- Non-active bleeding, but evidence of recent bleeding (e.g., darker blood, appearing thicker or 'solid' as clots)
- Active bleeding
  - blood tinged mucus
  - mild bleeding, medical intervention not indicated
  - clinically evident bleeding, medical intervention necessary
- Origin of bleeding
- Is the bleeding related to injury/nasal trauma?

SEPTAL EROSION/PERFORATION

- Location
  - anterior, including the nasal valve area
  - posterior to nasal valve
  - both
- Severity
  - evidence of epithelial erosion
  - evidence of ulceration through the epithelial layer with exposed cartilage
  - perforation
- Is the septal perforation related to injury/trauma?

ULCERATION / EROSION (located in area other than septum)

- Severity
  - epithelial surface abnormally eroded/abraded, but not clinically significant and expected to resolve rapidly
  - deeper than surface abrasion, limited clinical significance but may require monitoring or recommendation for routine care
  - deeper ulcers with possible effect on underlying structures, depth is clinically significant, intervention or specific care may be warranted

LOCAL ANESTHETICS AND / OR DECONGESTANTS ADMINISTERED FOR ENDOSCOPY WILL BE RECORDED