CLINICAL STUDY PROTOCOL

A 24-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 186 and 372 µg of OPN-375 Twice a Day (BID) in Subjects with Chronic Rhinosinusitis Without the Presence of Nasal Polyps

Protocol Number:	OPN-FLU-CS-3206
Brief Title:	Re-Open 2
Development Phase:	3b
IND Number:	110089
EudraCT Number	2019-000648-86
Sponsor:	OptiNose US, Inc. 1020 Stony Hill Road, Suite 300 Yardley, PA 19067
Protocol Date:	Amendment 4.0 dated 11May2022

STATEMENT OF CONFIDENTIALITY

VERSION HISTORY

Version	Explanation of Change(s) and Reason/Justification for Changes	Date
0	Original Protocol	06 February 2019
0.1	Synopsis and Sections 2.2, 3.2.1.2, 7.2, and 9.4.2: Key secondary objectives/endpoints at Week 24 for SNOT-22, and performance of computed tomography scans should include mention of early termination (ET) of subjects; "/ET" added where appropriate Synopsis (Primary Efficacy Analysis: Modified for consistency with Section 9.3.2.4 of protocol Schedule of Study Procedures and Evaluations: Removed row with prior medications/procedures/ nondrug therapy history (following "medical/surgical history" row; combined with prior medications and concomitant medications later in table Section 5.1 (last sentence in section): Replaced "OPN-375" with "study drug," as appropriate Section 6.3: Typographical error for Study Visit when subjects are to receive 3 study treatment kits; corrected from "Visit 6" to Visit 5 Other: Minor editorial changes throughout	22 February 2019
1.0	Title page: Added Brief Title "Re-Open 2" Throughout protocol: Replaced "chronic sinusitis" with "chronic **rhino**sinusitis" Synopsis: Updated for consistency with protocol Synopsis and Section 3.1: updated to include the description of a substudy that has been added to evaluate clinical biomarkers to characterize the microbiome and cytokine profiles in a subset of subjects at specified study centers Synopsis and Section 4.1: • Revised Inclusion Criterion 5 to include "bilateral disease on a prior computed tomography (CT) scan performed within 14-days of Visit 1" • Revised Inclusion Criterion 13 regarding cessation of applicable steroid treatment from "baseline" visit to "screening" visit and removed "oral steroids" to address an inconsistency in the protocol. Oral steroids are not allowed within 1 month of screening. Synopsis and Section 4.2: • Added to Exclusion Criterion 8: odontogenic sinusitis • Clarified Exclusion Criterion 17 by adding "eosinophilic granulomatosis with polyangiitis" to describe Churg-Strauss syndrome • Clarified Exclusion Criterion 18: Revised to include "influenza, or SARS-CoV-2 (COVID-19)" to address new concerns related to COVID-19 pandemic. Synopsis, Section 4.2 (Exclusion Criteria 34), and Section 5.6.3: • Revised to include "cobicistat" to examples of cytochrome P450 3A4 inhibitors Schedule of Study Procedures and Evaluations:	10 July 2020

	• Added "SARS-CoV-2 Serology Testing" to Visit 6 to determine if subject carries the antibodies • Added abbreviation for "End of Study (EOS)" to be consistent in use of terminology • Updated superscript comments to be consistent with protocol Schedule of Study Procedures and Evaluations and Section 6.5: • Added clarification to Visit 6 if subject cannot complete EOS CT scan at the Week 24 visit and continues treatment due to issues related to COVID-19 pandemic or due to any upper respiratory infection. Schedule of Study Procedures and Evaluations and Section 7.4.1: Changed physical examination from "full" to "brief" Schedule of Study Procedures and Evaluations and Table 5; • Removed "on site visit" and "office" to clarify urine pregnancy test must be completed at each visit • Added a requirement for subjects who continue treatment past Week 24/Visit 6 to have an additional pregnancy test completed upon returning to site. • Added "Blood Sample for SARS-CoV-2 serology testing" to Week 24/Visit 6 to determine if subject carries the antibodies Sections 2.3, 3.2.1.3, 7.2 (Other Secondary Efficacy Assessments)/7.3 (Health Economics): • Revised the secondary objective relating to the percent of sinus volume occupied by disease, from evaluating "each" maxillary and ethmoid sinus occupied by disease to evaluating the "worst" maxillary and "worst" ethmoid sinus • Added, as part of the Health Economic assessments, the impact of treatment on subjects approved for surgery who no longer elect to undergo surgery Section 5.6.1: • Removed "no more than" from first sentence for clarification • Corrected an inconsistency in the second sentence that subjects must be on a stable dose for at least "3 months" before Visit 1 (Screening) with plans to continue use throughout the study. Section 1.3 Updated language to be more general and not specify countries Section 3.1, 6.0 and 6.1 • Clarified timeline for CT completion at baseline. Section 4.3 • Removed "receives systemic corticosteroids (oral or parenteral)" from reasons as subjects will no longer be withdrawn from the study per FDA request • Added "hospitalized with respiratory symptoms due to SARS-CoV-2 (COVID-19) to address new concerns related to COVID-19 pandemic.	

	Section 5.1 • Included clarification regarding dispensing additional study treatment for subjects that cannot complete the EOS CT scan at week 24 in IWRS due to issues related to COVID-19 pandemic or due to any Upper Respiratory Infection. Section 6 • Bullet 2 - clarified use of CT scan performed within 14 days prior to Visit 1 • Bullet 3 - added influenza, SARS CoV-2 (COVID-19) and "until EOS CT scan can be completed" Section 7.1.1 • Added smoking history data collection for subject medical history Section 7.4.3 Ocular examinations and Attachment 4 • "Ophthalmologist" updated to "Examiner" with definition to allow for additional options to perform the eye exam in the current environment. • Removed "Slit lamp examination" and 'LOCS grading", only visual acuity, cataract assessment and IOP values will be collected to allow for exam to be done by a qualified healthcare provider and providing for assessments as requested by FDA. Attachment 5: Added to provide details of the substudy. List of References • Added the reference to, "The 16-item inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression." List of Abbreviations and Definitions of Terms has been updated as applicable. Minor editorial changes have been made throughout the protocol as appropriate	
2.0	The COVID-19 Pandemic has made it very difficult to schedule and perform the ocular examinations outlined in the protocol. Given the extensive assessment of ocular safety in the previous clinical studies with OPN-375 it was deemed appropriate to remove the scheduled ocular assessments from this protocol. If subjects report visual acuity changes during the study, an ocular exam will be performed. *Details of changes in study protocols* Synopsis: • Removed Early Termination (ET) from objectives • Removed ocular examination from safety objective • Removed "(intraocular pressure [IOP] at screening of > 21 mm Hg)" from Exclusion criteria 26 • Clarified Exclusion criteria 28 • Added Exclusion Criterion 36 (have a recent change in vision). • Removed Early Termination (ET) from endpoints	28 Aug 2020

	• Added clarification "in ethmoid and maxillary sinuses" to co-primary endpoint • Removed ocular examination from safety endpoints. • Removed "ET" from Key Secondary Efficacy Analysis • Updated statistical primary efficacy analysis Schedule of Study Procedures and Evaluations: • Removed ocular examination from procedures and assessments. • Removed superscript "d" explaining previous ocular examination schedule. • Added superscript "j" clarifying SARS-CoV-2 blood draw sample Section 2.1, 2.2 and 2.3: Removed "ET" from objectives Section 2.4: Removed ocular examination from section. Section 3.2: Removed Early Termination (ET) from endpoints Section 3.2.2: Removed ocular examination from section. Section 3.2.1.1: Added clarification "in ethmoid and maxillary sinuses" to co-primary endpoint Section 4.2: • Removed "(intraocular pressure [IOP] at screening of > 21 mm Hg)" from Exclusion criteria 26 • Clarified Exclusion criteria 28 • Added Exclusion Criterion 36 (have a recent change in vision) Section 4.3: • Added sentence, "Subjects wishing to withdraw from study treatment will be encouraged to continue in the study and have all scheduled study procedures performed." • Updated subject withdrawal reasons Section 5.6.1: Clarified use of oxymetazoline or other topical nasal decongestant Section 5.6.2, 6.1 and 6.2: Added "for CRS symptoms" to clarify use of rescue medication Section 6: • Removed ocular examination from section. • Clarified when baseline CT scan should be performed. Section 6.5: • Removed verbiage around subjects who discontinue study drug early during the DB treatment phase. Section 7.4: Removed ocular examination from section. Section 7.4.3: Updated ocular examination performance to be removed per explanation above. Section 8.1: Added, "discontinuation from the study treatment or discontinuation from the study" to what may be considered AEs Section 9.2.1: Replaced modified Intent to Treat Analysis Set (mITT) with "Intent-to-treat Analysis Set" section Section 9.2.3: Replaced "Efficacy Analysis" with "Full Analysis Set (FAS)" section Section 9.3: Clarifications to the Estimands, handling of missing	

	data, and statistical analysis addressing FDA suggestions have been added Section 9.6: Clarifications to the Type 1 Error Control for Multiplicity have been added. Section 9.7.1: Added verbiage "study participation and/or study treatment discontinuation" to be more specific. Section 9.7.2: Removed ocular examination from section. Attachment 4: The eye examination worksheet has been removed Minor editorial changes have been made throughout the protocol as appropriate.	
3.0	The Key Secondary Objectives and the Statistical Analysis Section are amended. The SF-36 Mental and Physical subscale analyses are moved to Secondary Objectives. Additional key secondary objectives evaluating pooled data from this study and an ongoing similarly designed Phase 3 study (Study OPN-FLU-CS-3205) have been added. These analyses will be performed once both studies have completed. In addition, other updates to the Statistical section of this protocol have been made including to the sample size section and a small adjustment to the study power assessment based on interim analysis results from Study OPN-FLU-CS-3205. Details of Changes Synopsis: • Study design updated to remove microbiome and cytokine substudy • SF-36 MCS and PCS was moved from Key Secondary Variables to Secondary Variables • Insertion of Key Secondary Variables from a pooled analysis of studies OPN-FLU-CS-3205 and OPN-FLU-CS-3206 • Updated key secondary endpoints to reflect changes to key secondary objectives • Updated the statistical section to reflect the changes in sample size and key secondary variables Section 2.2: Key Secondary Objectives • Removal of SF-36 MCS and PCS from key secondary objectives • Addition of key secondary objectives from pooled analyses for changes in SNOT-22 in subjects entering study using an intranasal steroid, changes in the Global Pittsburgh Sleep Index score, and moving the assessments of acute exacerbations from study 3205 alone to a pooled analysis Section 2.3: Other Secondary Objectives • Updated secondary objectives where analyses on sub-groups (subjects with and without a history of surgery) will now be performed Section 3.2.1.2: Key Secondary Endpoints	15 October 2021

	• This section was updated to reflect the changes to the Key Secondary Outcome variables to be consistent with the Key Secondary Objectives Section 3.2.1.3: Other Secondary Endpoints • This section was updated to reflect changes to the secondary endpoints to be consistent with the other secondary objectives Section 3.3: Method of Treatment Assignment or Randomization • Section was updated to reflect the new sample size Section 9.1: Sample Size Determination • Sample size calculations and background was updated to reflect changes consistent in the protocol. Section 9.2.3: Full Analysis Set (FAS) • Full analysis set clarifying text was added Section 9.2.4: Per Protocol Analysis Set (PPS) • Per-protocol analysis set was added to clarify additional analyses to be completed Section 9.3.2: Potential Intercurrent Events • Added clarifying text for the intercurrent events were added Section 9.3.3: Primary Estimand • This section was updated to reflect clarification to the intercurrent events consistent with previous sections of the protocol Section 9.3.4: Estimator and Estimation Method – Primary Analysis • Clarifying text for the treatment policy estimand was added to be consistent with changes made to the statistical analysis Section 9.3.5: Supplementary Analysis • Clarifying text for the intercurrent events were added to this section Section 9.4: Sensitivity Analyses • Section was updated to clarify sensitivity analyses being completed on the primary estimand and APOV co-primary endpoints • Clarifying text around the statistical analysis added Section 9.4: Key Secondary Efficacy Analyses • Updated section to match key secondary analyses added to the protocol Section 9.6: Other Secondary Efficacy Analyses • Updated section to match additional secondary analyses added to the protocol Section 9.7: Subgroup Analyses • Section added to clarify sub-group analyses that will be completed in the statistical analysis Section 9.8: Type I Error Multiplicity • Additional clarifying text was added to explain α if unblinded interim analysis does not occur	

	Section 9.8.2: Type I Error Control for Key Secondary Endpoints • Updated key secondary endpoints made in Section 2.2 were updated in this section Section 9.8.3: Key Secondary Endpoints from Pooled Data Studies OPN-FLU-CS-3205 and OPN-FLU-CS-3206 • Added Section 9.8.3 to reflect changes made to the pooled key secondary analyses in Section 2.2 Section 9.10: Interim Analysis • Clarifying text was added to explain planned interim analysis Section 12.4: Future Use of CT Scans • Description of future potential use of data for commercial purposes have been included in the protocol Attachment 4 removed because study design was updated to remove microbiome and cytokine substudy Minor editorial changes have been made throughout the protocol as appropriate.	
4.0	The key secondary objectives/endpoints and the statistical analysis are amended. Key secondary objectives evaluating Study OPN-FLU-CS-3206 have been added. Key secondary objectives evaluating pooled data from this study and a completed study, similarly designed Phase 3 study (Study OPN-FLU-CS-3205), have also been added, as well as pooled analyses evaluating the non-polyp population. These analyses will be performed once both studies have completed. Other updates to the statistical section of have been based on the updates to the objectives and endpoints. Detailed List of Changes Synopsis • Removed SNOT-22 total score from key secondary objectives • Removed change in SNOT-22 total score in subjects on previous INS for treatment of CRS and change in sleep quality using the Global Pittsburgh Sleep Quality Index from baseline to week 24/ET using a pooled study population from Study OPN-FLU-CS-3205 and OPN-FLU-CS-3206 from key secondary objectives o Replaced with change from baseline to Week 4 on CSNS total score in subjects previously on an INS for treatment of CRS within 30 days of Visit 1 and frequency of acute exacerbations of CRS over the 24-week treatment period • Addition of pooled nonpolyp population analysis assessing frequency of acute exacerbations • Addition of assessing 4 separate cardinal CRS symptoms and time to first acute exacerbation of CRS • Updated key secondary endpoints to reflect updated key secondary objectives	11May2022

	• Updated statistical analysis: primary efficacy and key secondary analysis were updated to reflect updated key secondary objectives/endpoints Section 2.2 Key Secondary Objectives • Removed SNOT-22 total score • Removed change in SNOT-22 total score in subjects on previous INS for treatment of CRS and change in sleep quality using the Global Pittsburgh Sleep Quality Index from baseline to week 24/ET using a pooled study population from Study OPN-FLU-CS-3205 and OPN-FLU-CS-3206 from key secondary objectives o Replaced with change from baseline to Week 4 on CSNS total score in subjects previously on an INS for treatment of CRS within 30 days of Visit 1 and frequency of acute exacerbations of CRS over the 24-week treatment period • Addition of pooled nonpolyp population analysis assessing frequency of acute exacerbations • Addition of assessing 4 separate cardinal CRS symptoms and time to first acute exacerbation of CRS Section 2.3 Other Secondary Objectives • Updated where analyses on sub-groups (subjects with and without a history of surgery) will now be performed • Updated other secondary objectives to include previous key secondary objectives listed Section 3.2.1.2 Key Secondary Endpoints • Updated key secondary endpoints to reflect updated key secondary objectives Section 3.2.1.3 Other Secondary Endpoints • Updated other secondary endpoints to include previous key secondary objectives Section 9.2.4 Per-Protocol Analysis Set (PPS) • Per-protocol analysis set definition was updated Section 9.3.4 Estimator and Estimation Method – Primary Analysis • Updated description of time for CSNS from week to days Section 9.4.2 Observed Case Analysis Section was added Section 9.5 Key Secondary Efficacy Analyses • Clarified analyses completed for updated key secondary endpoints Section 9.6 Other Secondary Efficacy Analyses • Clarified analyses completed for secondary endpoints Section 9.7 Subgroup Analyses • Added stratification groups and planned analyses Section 9.8 Type I Error Control for Multiplicity • Updated section to reflect updates to the key secondary endpoints Minor editorial changes have been made throughout the protocol as appropriate.	

Signature Page for Sponsor:

Clinical Study Protocol No. OPN-FLU-CS-3206

Title: A 24-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 186 and 372 µg of OPN-375 Twice a Day (BID) in Subjects with Chronic Rhinosinusitis, Without the Presence of Nasal Polyps

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:

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

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Jennifer Carothers, Vice President Global Clinical Operations & Outsourcing

Signature Page for Principal Investigator:

Protocol No. OPN-FLU-CS-3206

Title: A 24-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 186 and 372 µg of OPN-375 Twice a Day (BID) in Subjects with Chronic Rhinosinusitis, Without the Presence of Nasal Polyps

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:

SYNOPSIS

TITLE OF STUDY: A 24-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 186 and 372 µg of OPN-375 Twice a Day (BID) in Subjects with Chronic Rhinosinusitis, Without the Presence of Nasal Polyps

SPONSOR: OptiNose US, Inc.

DEVELOPMENT PHASE: 3b

IND Number: 110089

EudraCT Number: 2019-000648-86

STUDY OBJECTIVES:

Primary Objectives:

The primary objective of this study is to compare the efficacy of intranasal administration of twice-daily doses of 186 and 372 µg of OPN-375 (fluticasone propionate) with placebo in subjects with chronic rhinosinusitis (CRS) using the following co-primary endpoints:

- change from baseline in symptoms as measured by a composite score of nasal symptoms (CSNS): congestion, facial pain or pressure sensation, and nasal discharge (anterior and/or posterior) at the end of Week 4
  and
- change from baseline to Week 24/ET in the average percent of opacified volume (APOV) in the ethmoid and maxillary sinuses

Key Secondary Objectives:

The following key secondary objectives will compare the efficacy of twice daily doses of 186 and 372 µg of OPN-375 with placebo by pooling the data in subjects from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205, which is a separate study being conducted in parallel to this study.

- change from baseline to Week 4 on CSNS (AM, Instantaneous) score in subjects who were symptomatic at trial entry despite reported use of an intranasal steroid for treatment of CRS within 30 days of Visit 1
- Frequency of acute exacerbations of CRS over the 24-week treatment period, defined as a worsening of symptoms that requires an escalation of treatment

The following key secondary objective will compare the efficacy of twice daily doses of 186 and 372 µg of OPN-375 with placebo by pooling the data in subjects with CRS without nasal polyps, from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205, which is a separate study being conducted in parallel to this study.

- Frequency of acute exacerbations of CRS over the 24-week treatment period, defined as a worsening of symptoms that requires an escalation of treatment

The following key secondary objectives of this study will compare the efficacy twice-daily doses of 186 and 372 µg of OPN-375 with placebo on:

- change from baseline to the end of Week 4 in four separate cardinal CRS symptoms, as measured by a CSNS (AM, Instantaneous): congestion, facial pain or pressure sensation, nasal discharge (anterior and/or posterior), and sense of smell
- time to first acute exacerbation of CRS, defined as a worsening of symptoms that requires escalation of treatment

Safety Objective:

- to evaluate the safety of OPN-375 by monitoring adverse events (AEs) throughout the study; results of nasal examination, vital signs measurements (ie, blood pressure, pulse), and weight; and monitoring concomitant medication usage

STUDY DESIGN: 24-week randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of intranasal administration of 186 and 372 µg of OPN-375 BID in subjects with CRS without nasal polyps.

STUDY POPULATION: Approximately 210 subjects will be randomly assigned to receive OPN-375 186 µg or 372 µg, or placebo (70 subjects in each treatment group); subjects will be randomized using a 1:1:1 ratio.

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 baseline visit
2. women of child-bearing potential must be abstinent, or if sexually active,

   a. be practicing an effective method of birth control (eg, prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [eg, 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 (Screening)
4. must have a history of CRS and be currently experiencing 2 or more of the following symptoms, 1 of which has to be either nasal congestion or nasal discharge (anterior and/or posterior nasal discharge) for equal to or greater than 12 weeks:
   - nasal congestion
   - nasal discharge (anterior and/or posterior nasal discharge)
   - facial pain or pressure
   - reduction or loss of smell
5. endoscopic evidence of nasal mucosal disease, with edema or purulent discharge; or polyps/polypoid tissue <Grade 1 in middle meatus, bilaterally, or presence of bilateral disease on a prior computed tomography (CT) scan performed within 14 days of Visit 1
6. must have confirmatory evidence via a CT scan of bilateral sinus disease (have at least 1 sinus on each side of nose with a Lund-Mackay score of ≥1)
7. baseline CT scan must show a combined ≥25% opacification of the ethmoid sinuses and ≥25% opacification of at least 1 maxillary sinus
8. must have at least moderate symptoms (as defined in protocol) of nasal congestion as reported by the subject, on average, for the 7-day period preceding Visit 1 (Screening) run-in
9. must have an average morning score of at least 1.5 for congestion on the Nasal Symptom Scale (as defined in protocol) recorded on the subject diary over a 7-day period during the first 14 days of the -single-blind run-in period
10. must demonstrate an ability to correctly complete the daily diary during the run-in period to be eligible for randomization
11. subjects with comorbid asthma or chronic obstructive pulmonary disorder (COPD) must be stable with no exacerbations (eg, no emergency room visits, hospitalizations, or oral or parenteral steroid use) within the 3 months before Visit 1 (Screening). 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 Visit 1 (Screening) with plans to continue use throughout the study.
12. subjects with aspirin-exacerbated respiratory disease, who have undergone aspirin desensitization and are receiving daily aspirin therapy, must be receiving therapy for at least 6 months prior to Visit 1
13. must be able to cease treatment with intranasal steroids, inhaled corticosteroids (except permitted doses listed above for asthma and COPD) at the screening visit
14. must be able to cease treatment with oral and nasal decongestants and antihistamines at Visit 1 (Screening)
15. must be able to use the exhalation delivery system (EDS) correctly; all subjects will be required to demonstrate correct use with the practice EDS at Visit 1 (Screening)
16. 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.

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

17. women who are pregnant or lactating
18. inability to have each nasal cavity examined for any reason, including nasal septum deviation
19. inability to achieve bilateral nasal airflow
20. is currently taking XHANCE®
21. have previously used XHANCE for more than 1 month and did not achieve an adequate symptomatic response
22. the nasal/sinus anatomy prevents the accurate assessment of sinus volume via CT scan
23. history of sinus or nasal surgery within 6 months before Visit 1 or has not healed from a prior sinus or nasal surgery

24. have current evidence of odontogenic sinusitis, sinus mucocele (the affected sinus is completely opacified and either the margins are expanded and/or thinned OR there are areas of complete bone resorption resulting in bony defect and extension of the "mass" into adjacent tissues), evidence of allergic fungal sinusitis, or evidence of complicated sinus disease (including, but not limited to, extension of inflammation outside of the sinuses and nasal cavity)
25. have a paranasal sinus or nasal tumor
26. have polyp grade ≥1 (polyp that is free on 5 sides and has a stalk) on either side of the nose as determined by the nasoendoscopy at screening
27. have a nasal septum perforation
28. have had more than 1 episode of epistaxis with frank bleeding in the month before Visit 1 (Screening)
29. have evidence of significant mucosal injury, ulceration (eg, exposed cartilage) on Visit 1 (Screening) nasal examination/nasoendoscopy
30. have current, ongoing rhinitis medicamentosa (rebound rhinitis)
31. have significant oral structural abnormalities (eg, a cleft palate)
32. have a diagnosis of cystic fibrosis
33. history of eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) or dyskinetic ciliary syndromes
34. symptom resolution or last dose of antibiotics for purulent nasal infection, acute sinusitis, upper respiratory tract infection, influenza, or SARS-CoV-2 (COVID-19) has not occurred before Visit 1 or was less than 4 weeks before the CT scan. Potential subjects presenting with any of these infections may be rescreened 4 weeks after symptom resolution.
35. planned sinonasal surgery during the period of the study
36. allergy, hypersensitivity, or contraindication to corticosteroids or steroids
37. has used oral steroids in the past for treatment of CRS and did not experience any relief of symptoms
38. has a steroid eluting sinus stent still in place within 30 days of Visit 1
39. allergy or hypersensitivity to any excipients in study drug
40. exposure to any glucocorticoid treatment with potential for systemic effects (eg, oral, parenteral, intra-articular, or epidural steroids, high dose topical steroids) within 1 month before Visit 1 (Screening); except as noted in inclusion criteria for subjects with comorbid asthma or COPD
41. have nasal candidiasis
42. history or current diagnosis of any form of glaucoma or ocular hypertension
43. history of IOP elevation on any form of steroid therapy
44. history or current diagnosis of the presence (in either eye) of a cataract unless both natural intraocular lenses have been removed
45. history of immunodeficiency
46. 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
47. have a positive drug screen or a recent (within 1 year of Visit 1 [Screening]) 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
48. have participated in an investigational drug clinical trial within 30 days of Visit 1 (Screening)
49. have received mepolizumab (Nucala®), reslizumab (Cinquair®), dupilumab (Dupixent®), omalizumab (Xolair®), or benralizumab (Fasenra™) within 6 months of Visit 1 (Screening)
50. is using strong cytochrome P450 3A4 (CYP3A4) inhibitor (eg, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin, conivaptan, lopinavir, voriconazole, cobicistat)
51. is an employee 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, or is a family member of the employee or the investigator
52. patients who report unexplained worsening of vision within the past 3 months (e.g. difficulty reading or seeing traffic signs from a distance.) A diagnosis of presbyopia established by an eye doctor is not exclusionary.

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION: Twice daily doses of 186 and 372 µg of OPN-375. Subjects will be instructed to administer 2 sprays per nostril approximately every 12 hours for 24 weeks. The active treatment will contain a formulation of fluticasone propionate that delivers 93 µg per spray.

REFERENCE THERAPY, DOSE, AND METHOD OF ADMINISTRATION: Placebo twice daily delivered intranasally by the EDS device for the 7- to up to 21-day single-blind placebo run-in period and the 24-week double-blind treatment phase.

ASSESSMENTS:

Efficacy Assessments: During the double-blind phase, electronic diaries will be completed twice daily by the subject to capture daily nasal symptoms (ie, symptom scores for nasal congestion, nasal discharge [anterior and/or posterior], facial pain or pressure sensation, and sense of smell), and use of approved rescue medication after the Week 4 visit to Week 12. Subject-completed questionnaires will be used to measure the symptoms and social/emotional consequences of the subject's nasal disorder (SNOT-22), health-related quality of life (EuroQol-5 D [EQ-5D] SF-36v2, and Short Form-6 dimension [SF-6D]), sleep quality and disturbances (Pittsburgh Sleep Quality Index [PSQI]), depressive symptoms (Quick Inventory of Depressive Symptomatology [QIDS]), work productivity, and objective smell test (Smell Identification Test [SIT]). Subjects will assess their global impression of change since starting the study drug using the Patient Global Impression of Change (PGIC) scale. Health economic information related to CRS will also be collected using the Health and Work Performance Questionnaire (HPQ). Objective changes in disease severity will be assessed via sinus CT scan.

Safety Assessments: Safety will be assessed by monitoring of AEs throughout the study, nasal examination, vital signs measurements (ie, blood pressure, pulse), weight, and through collection of information for concomitant medications.

ENDPOINTS:

Efficacy

Primary:

Co-Primary Endpoints:

- change from baseline to the end of Week 4 in average instantaneous morning (AM) scores (evaluation of symptom severity immediately preceding the time of scoring) of:
    - nasal congestion
    - nasal discharge (anterior and/or posterior)
    - facial pain/pressure sensation

  The baseline CSNS is the average of the total instantaneous AM scores over the last 7 days of the single blind run-in period, and at the end of Week 4, scores are averaged over 7 days before Week 4.
- change from baseline to Week 24 in the APOV in the ethmoid and maxillary sinuses

Key Secondary Endpoints:

- change from baseline to Week 4 on CSNS score (AM, Instantaneous) in subjects who were symptomatic at trial entry despite reported use of an intranasal steroid for treatment of CRS within 30 days of Visit 1 in subjects from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205 (pooled data)
- Frequency of acute exacerbations of CRS over the 24-week treatment period, defined as a worsening of symptoms that requires an escalation of treatment, in subjects from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205 (pooled data)
- Frequency of acute exacerbations of CRS over the 24-week treatment period, defined as a worsening of symptoms that requires an escalation of treatment in subjects with CRS without NP, from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205 (pooled data)
- change from baseline to the end of Week 4 in four separate cardinal CRS symptoms, as measured by CSNS (AM, Instantaneous): congestion, facial pain or pressure sensation, nasal discharge (anterior and/or posterior), and sense of smell for 3206 alone
- time to first acute exacerbation of CRS, defined as a worsening of symptoms that requires escalation of treatment for 3206 alone

Safety Endpoints:

- monitoring AEs throughout the study; results of nasal examination, vital signs measurements (ie, blood pressure, pulse), and weight; and monitoring concomitant medication usage

DURATION OF THE STUDY:

The duration of each subject's enrollment is expected to be approximately 26 weeks.

STATISTICAL ANALYSIS:

Sample Size Determination: Sample size requirements were based on a previous Phase 3 studies of OPN-375 in subjects with nasal polyposis and data from a study evaluating the change in maxillary and ethmoid opacification in CRS patients treated with an intramuscular dose of triamcinolone. Based on the results for changes from baseline in morning symptoms among subjects with nasal polyps in the previous studies conducted with OPN-375, a sample of 70 subjects per group (210 total subjects) is sufficient to detect a 0.9 scale difference in morning symptoms score between treatments (OPN-375 vs placebo) using a 2-sided test at the 5% significance level with 88% power, and assuming a standard deviation (SD) of 1.7. This sample size is also adequate to detect a 9% difference between treatment groups in average percent opacification using a 2-sided test at the 5% significance level with 88% power, and assuming a SD of 17%.

Primary Efficacy Analysis: For the co-primary endpoint CSNS, the estimator is the mean difference between treatments (active versus placebo) in change from baseline to the end of Week 4 in the 7-day average total CSNS (instantaneous AM). Estimation is based on a mixed model for repeated measures (MMRM), where changes from baseline to Week 2 and Week 4 in the 7-day average total CSNS (instantaneous AM), respectively, are the repeated measures, including categorical effects for previous sinus surgery (Y,N), treatment (OPN-375 186 µg, OPN-375 372 µg, placebo), week (2, 4) treatment-by-week interaction, and the continuous covariate baseline 7-day average total CSNS (instantaneous AM) with baseline-by-week interaction. For the co-primary endpoint APOV, the estimator is the mean difference between treatments (active versus placebo) in the change from baseline to Week 24/ET APOV. Estimation is based on an ANCOVA model including categorical effects for previous sinus surgery (Y,N), treatment (OPN-375 186 µg, OPN-375 372 µg, placebo), and baseline APOV.

Key Secondary Efficacy Analysis:
Change from baseline to Week 4 on CSNS score in subjects who were symptomatic at trial entry despite reported use of an intranasal steroid for treatment of CRS within 30 days of Visit 1 will be analyzed using the same MMRM model described for the co-primary endpoint CSNS, and the model will include a categorical effect term for protocol (OPN-FLU-CS-3205, OPN-FLU-CS-3206). The same model will be used for the analysis of CSNS component scores and sense of smell in the CRS without nasal polyps population.
The frequency of acute sinus exacerbations over 24 weeks will be compared between OPN-375 dose groups and placebo using generalized linear model (GLM) for data from the negative binomial distribution that is commonly referred to as the negative binomial (NB) regression model. The NB model will include the same model terms as the primary models; in additional, the model will include a categorical effect for protocol (OPN-FLU-CS-3205, OPN-FLU-CS-3206), and the logarithm of follow-up time as an offset variable. The same model will be used for the pooled analysis of the frequency of acute sinus exacerbations over 24 weeks in the CRS without nasal polyps population.

The analysis of the following key secondary endpoints are based on the data from Study OPN-FLU-CS-3206 only:

- change from baseline to the end of Week 4 in four separate cardinal CRS symptoms, as measured by CSNS (AM, Instantaneous): congestion, facial pain or pressure sensation, nasal discharge (anterior and/or posterior), and sense of smell will be analyzed using the same MMRM model described above.
- The Kaplan-Meier method and log-rank test will be used to estimate and compare the distributions of time to first acute CRS exacerbation between each OPN-375 dose and placebo.

Safety Analysis:
All safety summaries will be descriptive; no statistical inference procedures will be applied. All safety summaries will be presented by OPN-375 dose level (186 µg and 372 µg) and total OPN-375, and placebo.

SCHEDULE OF STUDY PROCEDURES AND EVALUATIONS

Period	Pretreatment (Screening/ Run-in)	Double-Blind Treatment						
Visit	**1**	**2**	**3**	**4**	**5**	**Subject Contact**		**6****
Procedures and assessments	**Single-Blind Placebo Run-in (7 up to 21 days)**	**Baseline (Randomization) Day 1**	**Week 4[a] ±7 days**	**Week 8[a] ±7 days**	**Week 12[a] ±7 days**	**Week 16 ±7 days**	**Week 20 ±7 days**	**Week 24[a]/ET ±7 days**
Informed consent	X							
Demographics	X							
Medical/surgical/smoking history	X							
Inclusion and exclusion criteria	X	X						
Confirm ability to use EDS[b]	X							
Serum chemistry, hematology, urinalysis	X							
Urine drug screen	X							
Blood Sample for SARS-CoV-2 Serology Testing[j]								X
Brief physical examination	X							
Urine pregnancy test[c]	X	X	X	X	X			X
Vital signs and weight	X	X	X	X	X			X
Nasal and sinus endoscopic assessment	X							
CRS treatment and history	X							
Nasal examination[d]	X							X
CT with Lund-Mackay scoring	X[e]							X[f]
Exacerbation assessment			X	X	X	X	X	X
Surgical intervention assessment		X						X
SNOT-22		X	X	X	X			X
EQ-5D		X						X
SF-36v2		X						X
PSQI		X			X			X
QIDS		X						X
HPQ		X	X	X	X			X
SIT		X						X
PGIC			X					X
Dispense/collect study drug (OPN-375)	X[g]	X	X	X	X			X
Review proper use of EDS	X	X	X	X	X			

Period	Pretreatment (Screening/ Run-in)	Double-Blind Treatment						
Visit	**1**	**2**	**3**	**4**	**5**	**Subject Contact**		**6****
Procedures and assessments	**Single-Blind Placebo Run-in (7 up to 21 days)**	**Baseline (Randomization) Day 1**	**Week 4[a] ±7 days**	**Week 8[a] ±7 days**	**Week 12[a] ±7 days**	**Week 16 ±7 days**	**Week 20 ±7 days**	**Week 24[a]/ET ±7 days**
Treatment compliance		X	X	X	X	X	X	X
Provide/collect subject diary	X				X			
Review subject's diary entries		X	X	X	X			
Contact IWRS[h]	X	X	X	X	X			X
AE collection[i]	X	X	X	X	X	X	X	X
Prior/concomitant medication/procedures/nondrug therapy	X	X	X	X	X	X	X	X
Contact with subject						X	X	

AE=adverse event; CRF=case report form; DB=double-blind; EDS=Exhalation Delivery System; EOS=End of Study; ET=early termination; HPQ=Health and Work Performance Questionnaire; IWRS=interactive web response system; PGIC=Patient Global Impression of Change; EQ-5D=EuroQol-5; SF-36v2=36-Item Short Form Health Survey version 2; SNOT-22=Sinonasal Outcome Test – 22; PSQI = Pittsburgh Sleep Quality Index; QIDS = Quick Inventory of Depressive Symptomatology, SIT = Smell Identification Test.

**If subject cannot complete EOS CT scan at the Week 24 visit, subject should continue treatment until an EOS CT scan can be completed. If subject continues treatment;

- Complete Subject Contacts approximately every 4 weeks to assess safety until subject can complete the EOS CT scan
- When EOS CT scan has been completed and subject returns to study site, perform additional SNOT-22, and urine pregnancy test (women of childbearing potential only)

[a] All visits up to Visit 6 (Week 24) should be scheduled based on the date of the Day 1 visit. If necessary, visits may be performed within the time window shown; however, subsequent visits should be scheduled based on the date of the Day 1 visit.

[b] The assignment of a kit number for the demonstrator model EDS is not performed by IWRS, rather, the study staff will dispense a demonstrator model EDS kit and record the kit number in the drug dispensing log. This practice EDS is only used at the site at Visit 1 (Screening) and is not to be sent home with the subject.

[c] Women of child-bearing potential only; urine pregnancy tests will be performed at each visit, not including subject contacts. Subjects continuing treatment past Week 24/Visit 6 will need an additional pregnancy test completed upon returning to site.

[d] Nasoendoscopy will be performed using a rigid or flexible endoscope. 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.

[e] The CT scan should be performed after diary eligibility is confirmed and prior to Day 21 of the screening run-in period.

[f] For the Week 24 study visit, the CT examination should be performed prior to the on-site visit.

[g] Demonstrator model EDS kit (see footnote b) and single-blind placebo dispensation only.

[h] At Visit 1 (Screening), the IWRS will be contacted to obtain the subject ID number, the identifier for the single-blind kit to be dispensed and to track enrollment. IWRS will be contacted at Visit 2 to randomly assign subjects to treatment. At Visit 2 through – Visit 5, IWRS will be used to assign the study

drug kit(s) to be dispensed. If a subject cannot complete the EOS CT scan at Visit 6 (Week 24), study staff should not complete Visit 6 in IWRS. Subjects should continue study treatment until an EOS CT scan can be completed. Study staff will dispense additional study medication via the "Unscheduled Visit' functionality in IWRS. IWRS will be contacted for each 'Unscheduled Visit,' at which time one treatment kit will be dispensed.

[i] The period of observation for collection of AEs extends from the time the subject gives informed consent until completion of the double-blind treatment period or an early termination visit. Serious adverse events will be reported through 30 days after the last dose of study drug administration.

[j] Blood sample for SARS-CoV-2 serology test at Visit 6 should be completed unless the subject declines testing.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AE	Adverse event
AM	Morning
ANCOVA	Analysis of covariance
APOV	Average percent of opacified volume
BID	Twice a day
BOCF	Baseline Observation Carried Forward
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRS	Chronic rhinosinusitis
CSNS	Composite score of nasal symptoms
CT	Computed tomography
CYP3A4	Cytochrome P450 3A4
DB	Double-blind
DCF	Data Clarification Form
EC	Ethics Committee
ECP	Eosinophil cationic protein
EDS	Exhalation Delivery System
EOS	End of Study
EQ-5D	EuroQol-5
EQ VAS	EQ Visual Analogue Scale
ETDRS	Early Treatment Diabetic Retinopathy Study
EVA	Electronic visual acuity
ET	Early termination
FAS	Full Analysis Set
GCP	Good Clinical Practice
GI	Gastrointestinal
GLM	Generalized linear model
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HPQ	Health and Work Performance Questionnaire
IA	Interim analysis
IASAP	Interim analysis Statistical Analysis Plan
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IFN	Interferon
IL	Interleukin
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive web response system
J2C	Jump to Control
LS	Least-squares
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MCP	Multiple comparison procedure/milk clotting protease
MCS	Mental component score
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MIP	Mycoplasma immunoglobulin protease
mITT	Modified Intent-to-Treat
MMRM	Mixed-effect model for repeated measures
mSv	Millisievert

NB	Negative binomial
OD	Right eye
OMC	Ostiomeatal complex
OS	Left eye
PASS 15	Power Analysis and Sample Size Software
PBO	Placebo
PCS	Physical component score
PGIC	Patient Global Impression of Change
PM	Evening
PMM	Pattern Mixture Model
PPS	Per-Protocol Analysis Set
PSQI	Pittsburgh Sleep Quality Index
QIDS	Quick Inventory of Depressive Symptomatology
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SF-36v2	36-Item Short Form Health Survey Version 2
SF-6D	Short Form-6 dimension
SIT	Smell Identification Test
SNOT-22	Sinonasal Outcome Test-22
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
TSLP	Thymic stromal lymphopoietin
US	United States
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary

1 INTRODUCTION

OptiNose has developed OPN-375 (proprietary name XHANCE®) 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. Delivery of drug using an Exhalation Delivery System (EDS) is intended to improve reproducibility of nasal delivery, particularly deposition of the topical steroid to the middle meatus where the sinuses ventilate and drain (ostiomeatal complex [OMC]). 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 available on OPN-375 for the treatment of chronic rhinosinusitis (CRS) with and without 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.

1.1 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. In the clinical study subject of this protocol, OptiNose intends to study the efficacy and safety of OPN-375 in subjects with CRS.

Sinusitis is defined as symptomatic inflammation of the paranasal sinuses and nasal cavity. If the duration of sinusitis is more than 12 weeks, with or without acute exacerbations, it is deemed to be CRS (Bachert et al, 2014; Fokkens et al, 2012). It is variously estimated that approximately 4% of patients with CRS have concurrent nasal polyps (with estimated prevalence in the low, single digits for the population as a whole). Chronic rhinosinusitis affects approximately 5% to 15% of the general population in Europe and the United States (US) (Hamilos, 2011), and the prevalence of physician-diagnosed CRS was found to be 2% to 4% (Chen et al, 2003; Shashy et al, 2004). Chronic rhinosinusitis has significant impact on healthcare resource utilization and work productivity, with approximately 12 billion dollars in direct medical costs and 20 billion dollars in lost productivity in 2016 (Rudmik 2017). Chronic rhinosinusitis also has a significant impact on health-related quality of life, and patients with this condition scored lower on measures of bodily pain and social functioning than those with serious chronic conditions including angina, back pain, congestive heart failure, and COPD (Gliklich and Metson, 1995).

The etiology and pathogenesis of CRS is multifactorial. Although a number of factors have been found to be associated with CRS, including ciliary impairment, allergy, asthma, aspirin sensitivity,

and an immunocompromised state, there is no clearly delineated single molecular pathway or single antecedent trigger that leads to the development of CRS. Nevertheless, persistent inflammation of the nasal cavity and the paranasal sinuses, progressing from mucosal injury to tissue change, is sine qua non in the pathophysiology of CRS with or without nasal polyps (Akdis et al, 2013). Evidence of inflammation is generally present throughout the nasal cavity, including around the OMC, where the sinuses ventilate and drain into the nasal cavity.

Consistent with the location of the inflammation, the most common symptom associated with CRS is nasal obstruction, followed by facial congestion-pressure/pain-fullness, discolored anterior and posterior nasal discharge, and hyposomia. The presence of 2 or more symptoms, 1 of which should be nasal obstruction/congestion or nasal discharge, persisting beyond 12 weeks, is highly sensitive for the diagnosis of CRS (Meltzer et al, 2004). However, diagnosis based on symptoms alone is relatively nonspecific. Visualization of discharge from the OMC by nasal examination with nasal endoscopy, the presence of polyps in the nasal cavity, or radiographic imaging showing inflammation of the paranasal sinuses is typically needed to confirm the diagnosis (Bhattacharyya and Lee, 2010).

Intranasal topical corticosteroids, though not formally indicated, are first-line pharmacotherapy for CRS with or without nasal polyps (Bachert et al, 2014; Fokkens et al, 2012; Rosenfeld et al, 2015). Qualitative syntheses and meta-analyses have been performed on the reported clinical trials in patients without nasal polyps (10 and 7 trials for qualitative synthesis and meta-analysis, respectively) and in patients with nasal polyps (38 and 26 trials for qualitative synthesis and meta-analysis, respectively) (Fokkens et al, 2012). The studies included patients with prior sinus surgery, without sinus surgery, or a mixed population with regard to sinus surgery. The meta-analyses demonstrated that treatment with intranasal corticosteroids improved symptoms to a greater extent than placebo in CRS patients both with and without nasal polyps. However, the efficacy of intranasal corticosteroids in CRS patients without nasal polyps was modest, with several of the trials failing to demonstrate a significant treatment effect compared with placebo. It is also notable that among the CRS patients without nasal polyps only those who had prior sinus surgery showed symptomatic improvement. Adverse events associated with intranasal corticosteroids generally were local at the site of administration, not serious, and consisted mainly of epistaxis, nasal irritation and headache (Fokkens et al, 2012).

Clinical guidelines suggest that for patients who do not respond to intranasal corticosteroids after 3 months of treatment, a course of systemic antibiotic treatment may be considered.

Endoscopic sinus surgery is generally effective in reducing the symptoms of CRS with or without nasal polyps (Chester et al, 2009); however, the 5-year revision rate for surgery approaches 20%, with the revision rate generally being higher for patients with CRS with nasal polyps (21% vs 16%) than for those without nasal polyps (Hopkins et al, 2009). Furthermore, although surgery is effective, the insufficiency of symptomatic relief with surgery is strongly suggested by the finding that the use of symptomatic medical therapy prior to surgery and after surgery is not meaningfully changed (Bhattacharyya and Lee, 2010).

Clinical guidelines notwithstanding, and despite the large number of clinical trials conducted, it is notable that in the US, no intranasal corticosteroid has been approved for the treatment of CRS. Oral steroids may reduce the need for surgery but there are concerns about significant side effects with long-term oral steroid use.

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

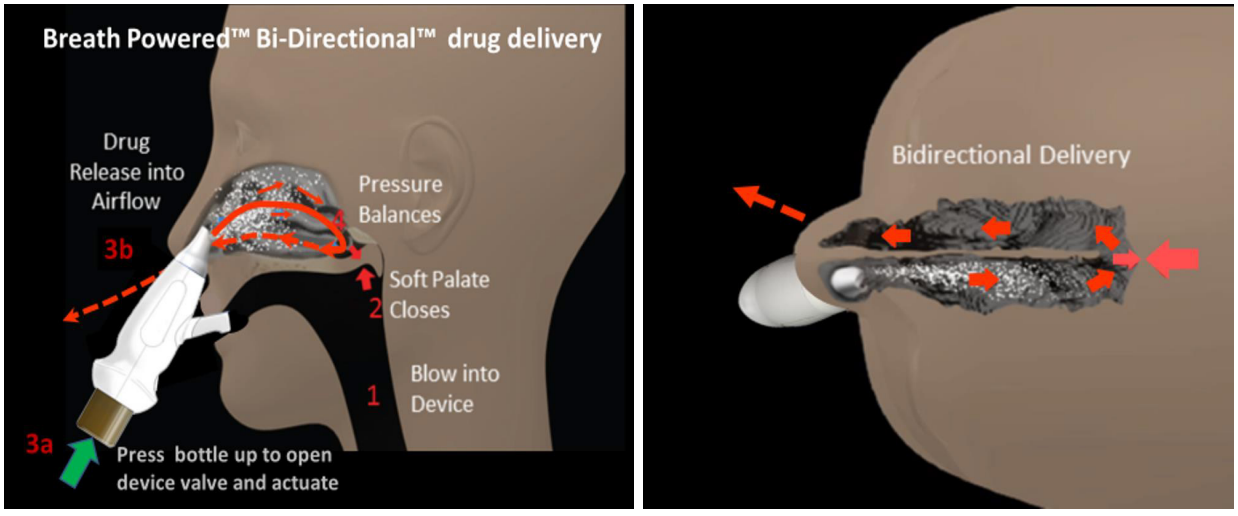
cavity. Fluticasone propionate is a synthetic corticosteroid that has long been commercially available in the US. It is currently approved as monotherapy and in various combinations, and in multiple formulations for multiple indications including creams (for inflammatory dermatoses and other dermatological conditions), inhalers (for asthma and other respiratory conditions), and nasal sprays.

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 1 nostril, so it seals well with the flexible nasal tissues, and inserts the mouthpiece between the lips. After taking a deep breath, the user 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 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 the paranasal sinuses ventilate and drain.

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 System

Schematic A **Schematic B**

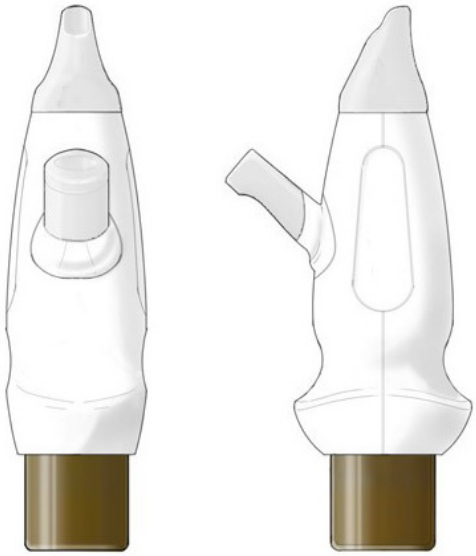


A = Cross-sectional view from the left side.

B = Cross-sectional view from the top.

The OPN-375 EDS is pictured below (Figure 2).

Figure 2: OPN-375 Exhalation Delivery System



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

1.2 Clinical Experience

There were two Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies (OPN-FLU-NP-3101 and OPN-FLU-NP-3102) designed to assess the efficacy and safety of 3 doses of OPN-375 (93, 186, and 372 µg twice a day [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. Both clinical studies were identical in design.

In these studies, all 3 doses of OPN-375 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. 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, mood, and social 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 chronic sinusitis 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/OMC. 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% of subjects. In the 12-month study the improvement in polyp grade, polyp elimination, and edema increased over time, suggesting benefit with continued treatment over the observed period.

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 endoscopic nasal 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 treatment-related SAEs, and the overall rate of discontinuations due to AEs was approximately 4% among all subjects who received OPN–375.

1.3 Rationale for the Study

Patients with CRS currently have limited medical options for treatment. While some symptoms may be reduced, patients are often left with symptoms due to the suboptimal delivery method of current treatments (Fokkens et al, 2012). Standard nasal spray pumps suffer from a number of drawbacks and are considered suboptimal for reliable drug delivery to target sites beyond the nasal valve (Aggarwal et al, 2004). OPN-375, with its breath assisted 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 CRS.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the efficacy of intranasal administration of twice daily doses of 186 and 372 µg of OPN-375 (fluticasone propionate) with placebo in subjects with CRS using the following co-primary endpoints:

- change from baseline in symptoms as measured by a composite score of nasal symptoms (CSNS): congestion, facial pain or pressure sensation, and nasal discharge (anterior and/or posterior) at the end of Week 4

  and

- change from baseline to Week 24/ET in the average percent of opacified volume (APOV) in the ethmoid and maxillary sinuses

2.2 Key Secondary Objectives

The following key secondary objectives will compare the efficacy of twice daily doses of 186 and 372 µg of OPN-375 with placebo by pooling the data in subjects from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205, which is a separate study being conducted in parallel to this study.

- change from baseline to Week 4 on (AM, Instantaneous) CSNS score in subjects who were symptomatic at trial entry despite reported use of an intranasal steroid for treatment of CRS within 30 days of Visit 1
- Frequency of acute exacerbations of CRS over the 24-week treatment period, defined as a worsening of symptoms that requires an escalation of treatment

The following key secondary objective will compare the efficacy of twice daily doses of 186 and 372 µg of OPN-375 with placebo by pooling the data in subjects with CRS without nasal polyps, from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205, which is a separate study being conducted in parallel to this study.

- Frequency of acute exacerbations of CRS over the 24-week treatment period, defined as a worsening of symptoms that requires an escalation of treatment

The following key secondary objectives of this study will compare the efficacy twice-daily doses of 186 and 372 µg of OPN-375 with placebo on:

- change from baseline to the end of Week 4 in four separate cardinal CRS symptoms, as measured by CSNS (AM, Instantaneous): congestion, facial pain or pressure sensation, nasal discharge (anterior and/or posterior), and sense of smell
- time to first acute exacerbation of CRS, defined as a worsening of symptoms that requires escalation of treatment

2.3 Other Secondary Objectives

Secondary objectives of this study are to compare the effect of twice daily doses of 186 and 372 µg of OPN-375 with placebo in:

- change from baseline to Week 24/ET in subject symptoms and functioning, as measured by Sinonasal Outcome Test-22 (SNOT-22) total score for the total population and in patients with and without previous sinus surgery
- change from baseline to Weeks 4, 8, 12, and 24/ET in subject symptoms and functioning, as measured by SNOT-22 total and sub-domain scores for the total population and in patients with and without previous sinus surgery
- change from baseline in symptoms as measured by a CSNS: congestion, facial pain or pressure sensation, and nasal discharge (anterior and/or posterior) to the end of Week 4, 8, and 12 for the total population and in patients with and without previous sinus surgery
- change from baseline to Week 4, 8, and 12 for the total population and patients with and without previous sinus surgery, on facial pain or pressure sensation, nasal discharge (anterior and/or posterior), nasal congestion, and sense of smell as measured by average AM instantaneous symptom scores and PM reflective symptom scores
- change from baseline to Week 24/ET in the APOV in the ethmoid and maxillary sinuses for patients with and without previous sinus surgery
- change from baseline to Week 24/ET in the percent of opacification of the combined volume of the ethmoid and maxillary sinuses
- change from baseline to Week 24/ET in the Lund-Mackay Staging System total score, scores for the maxillary and ethmoid sinuses, and scores for each sinus pair
- change from baseline to Week 24/ET in percent of sinus volume occupied by disease for the worst maxillary sinus (WPOV-M), for the worst ethmoid sinus (WPOV-E), and for the worst sinus between the maxillary and ethmoid sinuses (WPOV) for the total population and in patients with and without previous sinus surgery
- change from baseline to Week 24/ET in the Zinreich modification of Lund-Mackay Staging System total score, scores for the maxillary and ethmoid sinuses combined, and scores for each sinus pair
- change from baseline to Week 24/ET in Zinreich modification of the Lund Mackay Staging System score for the worst sinus between maxillary and ethmoid sinuses in the total population and in subjects with and without previous sinus surgery
- change in patient-reported outcomes from baseline to Week 24/ET as measured by:
  - change in sleep quality from baseline to Weeks 12 and 24/ET, using the PSQI
  - percent of subjects improved as indicated in the Patient Global Impact of Change (PGIC) at Week 4 and Week 24/ET
  - SF-36v2, 8 individual, physically and emotionally based domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) standardized scores
  - change in the severity of depression from baseline to Week 24/ET and severity of depression at Week 24/ET as measured by the Quick Inventory of Depression Symptomatology (QIDS)
  - change in severity of olfactory symptoms from baseline to Week 24/ET as measured by the Smell Identification Test (SIT)

- EuroQol-5 (EQ-5D)
- Short Form-6 dimension (SF-6D) derived scores from the SF-36v2
- assessment of health economic measures during the double-blind treatment phase related to CRS (eg, criteria for surgical intervention for CRS is met [independent of actual surgery performed], subjects who entered the study approved for surgery [with a scheduled surgery date] who no longer elect to undergo surgery, missed work or school days/lost productivity) by Health and Work Performance Questionnaire (HPQ)

The following secondary objectives will compare the efficacy of twice daily doses of 186 and 372 µg of OPN-375 with placebo by pooling the data from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205, which is a separate study being conducted in parallel to this study.

- change from baseline to Week 24/ET in subject symptoms and functioning, as measured by Sinonasal Outcome Test-22 (SNOT-22) total score in subjects who report using an intranasal, topically acting nasal steroid for the treatment of CRS within 30 days of Visit 1
- change in sleep quality from baseline to Week 24/ET, using the Global Pittsburgh Sleep Quality Index (PSQI) Score

2.4 Safety Objectives

to evaluate the safety of OPN-375 by monitoring AEs throughout the study; results of nasal examination, vital signs measurements (ie, blood pressure, pulse), and weight; and monitoring concomitant medication usage

2.5 Number of Subjects and Duration of Study

The total planned number of subjects is approximately 210. Approximately 210 subjects will be randomly assigned to receive 1 of the 2 active treatments or placebo (70 subjects in each group); subjects will be randomized using a 1:1:1 ratio.

The expected participation period for a subject is approximately 26 weeks, including a pretreatment phase consisting of a Screening visit followed by a 7- to up to 21-day single-blind- placebo run-in period and a 24-week double-blind treatment phase.

2.6 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)/Ethics Committee (EC), 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.

3 STUDY DESIGN

3.1 Study Overview

This is a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy and safety of intranasal administration of OPN-375 (186 and 372 µg twice daily) in subjects with CRS without the presence of nasal polyps.

Subjects must sign an informed consent before any study-related procedure is performed. Subjects who meet eligibility criteria at Visit 1 (Screening) will enter a 7- to 21-day -single-blind placebo run-in period to determine disease status and to ensure that they can comply with study procedures. At Visit 1 (Screening), nasoendoscopy-related (nasal examination and assessment of nasal cavity for presence of edema, polypoid tissue/polyps [<Grade 1], or mucopurulence) procedures will be performed for all subjects. During the single-blind- run-in period, subjects will administer morning and evening doses of the study drug (placebo) and will complete a daily diary (electronic) immediately before the morning and evening doses including recording of both instantaneous (evaluation of symptom severity immediately preceding the time of scoring) and reflective (evaluation of symptom severity over the past 12 hours) scores for nasal symptoms.

Subjects determined to meet diary eligibility criteria over a 7-day period during the first 14 days of the single-blind run-in period, will have a sinus computed tomography (CT) scan performed. The CT scan should be performed after diary eligibility is confirmed and prior to Day 21 of the screening run-in period. CT scans performed prior to Day 21 and within 2 weeks prior to Visit 1 as part of routine clinical care may be utilized if the scan meets the CT scan standards outlined in the Imaging Charter for this protocol. The resultant scan will be reviewed centrally to confirm study eligibility prior to randomization.

Those subjects meeting disease severity eligibility criteria (symptom severity and sinus opacification) will be randomly assigned through an interactive web response system (IWRS) to receive 1 of 2 active treatments or placebo: 186 or 372 µg of OPN-375 or placebo BID for the 24-week double-blind treatment phase. During the first 12 weeks of the double-blind phase, electronic diaries will be completed twice daily by the subject to capture symptom scores for nasal congestion, nasal discharge, (anterior and/or posterior), facial pain or pressure sensation, and sense of smell, as well as use of approved rescue medication after the Week 4 visit. Subject-completed questionnaires will be used to measure the symptoms and social/emotional consequences of the subject's nasal disorder (SNOT-22), health-related quality of life (EQ-5D, SF-36v2, and SF-6D), sleep quality and disturbances (PSQI), depressive symptoms (QID), work productivity, and objective smell test (SIT). Subjects will assess their global impression of change since starting the study drug using the PGIC scale. Health economic information related to CRS will also be collected (HPQ). Objective changes in disease severity will be assessed via sinus CT scan.

Safety will be assessed by monitoring of AEs, performing nasal examination, measuring vital signs (ie, blood pressure, pulse) and weight, and through collection of information for concomitant medications.

Refer to the Schedule of Study Procedures and Evaluations, for the timing of all tests, procedures, and assessments that will be performed during the study.

A study flow diagram is shown in Figure 3.

Figure 3: Study Flow Diagram

Single-Blind Lead-In	Double-Blind Treatment						
Pretreatment	**Randomization**						**End of Double-Blind**
	----------186 µg OPN-375 BID (n=70)----------						
	----------372 µg OPN-375 BID (n=70)----------						
	----------Placebo (n=70)----------						
Visit 1 7 up to 21 days Screening /Run-in	**Visit 2** Day 1 /Randomization /Baseline	**Visit 3** Week 4	**Visit 4** Week 8	**Visit 5** Week 12	**Subject Contact** Week 16	**Subject Contact** Week 20	**Visit 6** Week 24 /End of Double-Blind /Early Termination

BID=twice a day.

3.2 Endpoints

3.2.1 Efficacy Endpoints

3.2.1.1 Primary Endpoint

Co-primary Endpoints

- change from baseline to the end of Week 4 in average instantaneous AM scores (evaluation of symptom severity immediately preceding the time of scoring) of:
  - nasal congestion
  - nasal discharge (anterior and/or posterior)
  - facial pain/pressure sensation

The baseline CSNS is the average of the total instantaneous AM scores over the last 7 days of the single-blind run-in period, and the end of Week 4, scores are averaged over the 7 days before Week 4.

- change from baseline to Week 24/ET in the APOV in the ethmoid and maxillary sinuses.

3.2.1.2 Key Secondary Endpoints

Key Secondary Endpoints include:

- change from baseline to Week 4 on CSNS score (AM, Instantaneous) in subjects who were symptomatic at trial entry despite reported use of an intranasal steroid for treatment of CRS within 30 days of Visit 1 in subjects from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205 (pooled data)
- Frequency of acute exacerbations of CRS over the 24-week treatment period, defined as a worsening of symptoms that requires an escalation of treatment, in subjects from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205 (pooled data)
- Frequency of acute exacerbations of CRS over the 24-week treatment period, defined as a worsening of symptoms that requires an escalation of treatment in subjects with CRS without NP, from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205 (pooled data)
- change from baseline to the end of Week 4 in four separate cardinal CRS symptoms, as measured by CSNS (AM, Instantaneous) : congestion, facial pain or pressure sensation, nasal discharge (anterior and/or posterior), and sense of smell
- time to first acute exacerbation of CRS, defined as a worsening of symptoms that requires escalation of treatment

3.2.1.3 Other Secondary Endpoints

- change from baseline to Weeks 4, 8, 12, and Week 24/ET in the SNOT-22 total and sub-domain scores for the total population and in patients with and without previous sinus surgery
- change from baseline in symptoms as measured by a CSNS: congestion, facial pain or pressure sensation, and nasal discharge (anterior and/or posterior) at the end of Week 4, 8, and 12 for the total population and in patients with and without previous sinus surgery
- change from baseline to Weeks 4, 8, and 12 for the total population and in patients with and without previous sinus surgery:
  - in average AM/PM instantaneous (evaluation of symptom severity immediately preceding the time of scoring), (except Week 4 (AM) – key secondary endpoint) and AM/PM reflective (evaluation of symptom severity over the past 12 hours), averages are based on scores recorded in the diary for the 7 days before each time point for:
    - nasal congestion
    - sense of smell score
    - nasal discharge (anterior and/or posterior) score
    - facial pain or pressure sensation score

- change from baseline to Week 24/ET in the APOV in the ethmoid and maxillary sinuses for patients with and without previous sinus surgery
- change from baseline to the Week 24/ET for CT related assessments:
  - Lund-Mackay Staging System total score, scores for ethmoids and maxillary sinuses combined, and scores for each sinus pair (eg, ethmoid, maxillaries, frontal, and sphenoid, and ostiomeatal complex)
  - percent of sinus volume occupied by disease in the worst maxillary sinus (WPOV-M), percent of sinus volume occupied by disease in the worst ethmoid sinus (WPOV-E), and percent of sinus volume occupied by disease in the worst sinus between maxillary and ethmoid sinuses (WPOV) for the total population and in patients with and without previous sinus surgery
  - Zinreich modification of the Lund-Mackay Staging System total score, scores for ethmoids and maxillary sinuses combined, and for each sinus pair (eg, ethmoids, maxillary, frontal, and sphenoid)
  - Zinreich modification of the Lund-Mackay Staging System score for the worst sinus between maxillary and ethmoid sinuses in the total population and in subjects with and without previous sinus surgery
  - change of percent of opacification of the combined volume of the ethmoid and maxillary sinuses
- change from baseline to Week 12 and Week 24/ET in the PSQI global and component scores
- percent of subjects indicating improvement on the PGIC at Week 4 and Week 24/ET
- severity of depression at Week 24/ET as measured by QIDS
- change from baseline to Week 24/ET for:

  - the MCS of the SF36v2
  - the PCS of the SF36v2
  - SF-36v2 individual domains
  - QIDS total score
  - SIT scores
  - EQ-5D VAS and dimensions
  - SF-6D derived scores
- comparison of health economic measures during the double-blind treatment phase related to CRS:
  - percent of subjects indicating that they are willing to consider sinus surgery at baseline and Week 24/ET
  - percent of subjects who meet the minimal objective criteria for surgical intervention (as defined in Section 7.3) at baseline and Week 24/ET
  - percent of subjects approved for surgery who no longer elect to undergo a surgery Week 24/ET
  - number and percentage of missed work days and the percentage of productive hours lost while at work from the HPQ
- change from baseline to Week 24/ET in SNOT-22 total score in subjects who report using an intranasal, topically acting nasal steroid for the treatment of CRS within 30 days of Visit 1 in subjects with CRS without NP, from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205 (pooled data)
- change from baseline to Week 24/ET the Global PSQI Score in subjects with CRS without NP, from studies OPN-FLU-CS-3206 and OPN-FLU-CS-3205 (pooled data)

3.2.2 Safety Endpoints

- assessment of safety through AEs, nasal examination, vital signs measurements, weight, and concomitant medication usage

3.3 Method of Treatment Assignment or Randomization

Subjects will be randomly assigned to treatment according to a computer-generated randomization code. Randomization will be coordinated centrally through an IWRS. The system will provide subject identification numbers at Visit 1 (Screening), which are subsequently linked to the treatment assignments at randomization. Following completion of all baseline evaluations on Day 1, subjects who meet all eligibility requirements will be randomly allocated to 1 of the 3 treatment groups using a 1:1:1 ratio:

- OPN-375 186 µg BID
- OPN-375 372 µg BID
- Placebo BID

Randomization will be stratified by previous sinus surgery (Yes vs No) (previous sinus surgery is defined as evidence of ethmoidectomy [partial or total], or maxillary antrostomy). An IWRS will be used in this study to track enrollment, randomly assign subjects to treatment groups, and manage study drug supplies. At Visit 1 (Screening) and at each double-blind treatment phase study visit through Week 24, site staff will contact the IWRS and provide requested information to uniquely identify the subject. The IWRS will then provide the identifier (kit number) for the single-blind placebo kit at Visit 1 (Screening). The IWRS will then provide the identifier (kit number) for the double-blind study drug kit(s) to be dispensed at the respective double-blind visit.

3.4 Breaking the Blind

This is a double-blind study. During the conduct of the study, the subject, investigator and study personnel at each center, and the Sponsor and/or its designated personnel directly involved in the clinical study will remain blinded to study treatment. The investigator will not be provided with the randomization code. The randomization codes will be maintained within the IWRS, which will allow the investigator to break the blind for an individual subject, if necessary. The investigator should contact the Sponsor or their designee to discuss individual situations before breaking the blind.

If a medical emergency occurs and a decision regarding the subject's condition/treatment requires knowledge of the treatment assignment, the study blind may be broken for the specific subject via the IWRS; the investigator will immediately notify the Medical Monitor of the situation. The date, time, and reason for unblinding must be documented in the source document and in the appropriate section of the case report form (CRF). Additionally, the documentation received from the IWRS indicating the code break must be retained, in a secure manner, in the subject’s source documents.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

1. men or women aged 18 years and older at baseline visit
2. women of child-bearing potential must be abstinent, or if sexually active:
    a. be practicing an effective method of birth control (eg, prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [eg, 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 (Screening)
4. must have a history of CRS and be currently experiencing 2 or more of the following symptoms, one of which has to be either nasal congestion or nasal discharge (anterior and/or posterior nasal discharge) for equal to or greater than 12 weeks:
    - nasal congestion
    - nasal discharge (anterior and/or posterior nasal discharge)
    - facial pain or pressure
    - reduction or loss of smell
5. endoscopic evidence of nasal mucosal disease, with edema, purulent discharge; or polypoid tissue/polyps (<Grade 1) in middle meatus, bilaterally, or presence of bilateral disease on a prior CT scan performed within 14 days of Visit 1
6. must have confirmatory evidence via CT of bilateral sinus disease (have at least 1 sinus on each side of nose with a Lund-Mackay score of ≥1)
7. baseline CT scan must show a combined ≥25% opacification of the ethmoid sinuses and ≥25% opacification of at least 1 maxillary sinus
8. must have at least moderate symptoms (as defined in Section 7.2) of nasal congestion as reported by the subject, on average, for the 7-day period preceding Visit 1 (Screening) run-in
9. must have an average morning score of at least 1.5 for congestion on the Nasal Symptom Scale (as defined in Section 7.2) recorded on the subject diary over a 7-day period during the first 14 days of the single-blind -run-in period
10. must demonstrate an ability to correctly complete the daily diary during the run-in period to be eligible for randomization
11. subjects with comorbid asthma or COPD must be stable with no exacerbations (eg, no emergency room visits, hospitalizations, or oral or parenteral steroid use) within the 3 months before Visit 1 (Screening). Inhaled corticosteroid use must be limited to stable doses of no

more than 1,000 µg/day of beclomethasone (or equivalent, see Attachment 1) for at least 3 months before Visit 1 (Screening) with plans to continue use throughout the study.

12. Subjects with aspirin-exacerbated respiratory disease, who have undergone aspirin desensitization and are receiving daily aspirin therapy, must be receiving therapy for at least 6 months prior to Visit 1.
13. must be able to cease treatment with intranasal steroids, inhaled corticosteroids (except permitted doses listed above for asthma and COPD) at the screening visit
14. must be able to cease treatment with oral and nasal decongestants and antihistamines at Visit 1 (Screening)
15. must be able to use the EDS correctly; all subjects will be required to demonstrate correct use of the practice EDS at Visit 1 (Screening), see Section 6.1
16. 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.

4.2 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. inability to achieve bilateral nasal airflow
4. is currently taking XHANCE
5. have previously used XHANCE for more than 1 month and did not achieve an adequate symptomatic response
6. the nasal/sinus anatomy prevents the accurate assessment of sinus volume via CT scan
7. history of sinus or nasal surgery within 6 months before Visit 1 or has not healed from a prior sinus or nasal surgery
8. have current evidence of odontogenic sinusitis, sinus mucocele (the affected sinus is completely opacified and either the margins are expanded and/or thinned OR there are areas of complete bone resorption resulting in bony defect and extension of the “mass” into adjacent tissues), evidence of allergic fungal sinusitis, or evidence of complicated sinus disease (including, but not limited to, extension of inflammation outside of the sinuses and nasal cavity)
9. have a paranasal sinus or nasal tumor
10. have polyp grade ≥1 (polyp that is free on 5 sides and has a stalk) on either side of the nose as determined by the nasoendoscopy at screening
11. have a nasal septum perforation
12. have had more than 1 episode of epistaxis with frank bleeding in the month before Visit 1 (Screening)

13. have evidence of significant mucosal injury, ulceration (eg, exposed cartilage) on Visit 1 (Screening) nasal examination/nasoendoscopy
14. have current, ongoing rhinitis medicamentosa (rebound rhinitis)
15. have significant oral structural abnormalities (eg, a cleft palate)
16. have a diagnosis of cystic fibrosis
17. history of eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) or dyskinetic ciliary syndromes
18. symptom resolution or last dose of antibiotics for purulent nasal infection, acute sinusitis, upper respiratory tract infection, influenza, or SARS-CoV-2 (COVID-19) has not occurred before Visit 1 or was less than 4 weeks before the CT scan. Potential subjects presenting with any of these infections may be rescreened 4 weeks after symptom resolution
19. planned sinonasal surgery during the period of the study
20. allergy, hypersensitivity, or contraindication to corticosteroids or steroids
21. has used oral steroids in the past for treatment of CRS and did not experience any relief of symptoms
22. has a steroid eluting sinus stent still in place within 30 days of Visit 1
23. allergy or hypersensitivity to any excipients in study drug
24. exposure to any glucocorticoid treatment with potential for systemic effects (eg, oral, parenteral, intra-articular, or epidural steroids, high dose topical steroids) within 1 month before Visit 1 (Screening); except as noted in inclusion criteria for subjects with comorbid asthma or COPD
25. have nasal candidiasis
26. history or current diagnosis of any form of glaucoma or ocular hypertension
27. history of IOP elevation on any form of steroid therapy
28. history or current diagnosis of the presence (in either eye) of a cataract unless both natural intraocular lenses have been removed
29. history of immunodeficiency
30. 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
31. have a positive drug screen or a recent (within 1 year of Visit 1 [Screening]) 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
32. have participated in an investigational drug clinical trial within 30 days of Visit 1 (Screening)
33. have received mepolizumab (Nucala®), reslizumab (Cinquair®), dupilumab (Dupixent®), omalizumab (Xolair®), or benralizumab (Fasenra™) within 6 months of Visit 1 (Screening)
34. is using strong cytochrome P450 3A4 (CYP3A4) inhibitors (eg, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin, conivaptan, lopinavir, voriconazole, cobicistat)

35. is an employee 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, or is a family member of the employee or the investigator
36. patients who report unexplained worsening of vision within the past 3 months (e.g. difficulty reading or seeing traffic signs from a distance). A diagnosis of presbyopia established by an eye care professional is not exclusionary.

4.3 Withdrawal and Removal of Subjects

Subjects will be informed that they are free to withdraw from study treatment and/or 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, nonadherence to protocol requirements, or administrative reasons (eg, termination of study by Sponsor). Subjects wishing to withdraw from study treatment will be strongly encouraged to continue in the study and have all scheduled study procedures performed.

A subject must be withdrawn from treatment for the following reasons:

- subject becomes pregnant
- A subject's study treatment will be discontinued if the investigator or Sponsor considers it in the subject's best interest to stop treatment, (eg, for safety or significant tolerability reasons such as an AE). Subjects who have one of the following AEs must be withdrawn from study treatment.

- IOP of >21 mm Hg
- nasal septal perforation
- new onset or worsening of cataract

A subject may also be withdrawn from study treatment for the following reasons:

- lack of efficacy
- protocol violation

A subject may be withdrawn from the study for the following reasons:

- withdrawal of consent
- adverse event
- protocol violation that makes it unsafe for the subject to continue in the study
- termination of the study
- lost to follow up
- public health measure
- other

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

4.4 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.

The date and the reason for subject withdrawal from the study must be recorded on the CRF.

5 STUDY DRUG

5.1 Study Drug Treatment and Dosing

For the single-blind, run-in period, subjects will be dispensed a single-blind kit at Visit 1 (Screening). Eligible subjects will receive a double-blind study drug kit at Visit 2, Day 1 (Baseline). Thereafter, at scheduled visits (every 4 weeks through Week 8 during the double-blind treatment phase) subjects will receive 1 kit. At Week 12, subjects will receive 3 kits.

If subject cannot complete the EOS CT scan at Week 24, study staff should not complete Visit 6 in IWRS. Subjects should continue study treatment until an EOS CT scan can be completed, study staff will dispense additional study treatment via the "Unscheduled Visit" functionality in IWRS. IWRS will be contacted for each "Unscheduled Visit," at which time one treatment kit will be dispensed.

The IWRS will assign study drug kit numbers as described in Section 3.3. Study drug packaging is described in Section 5.3.

As shown in Table 1, the study drug dosage during the double-blind treatment phase will be 186 or 372 µg of OPN-375 BID or placebo BID.

Table 1: Study Drug Dosing – Double-blind Treatment Phase

	OPN-375 Dosage											
	186 µg BID				372 µg BID				Placebo BID			
Time	AM		PM		AM		PM		AM		PM	
Bottle	1	2	1	2	1	2	1	2	1	2	1	2
Left nostril	PBO	93	PBO	93	93	93	93	93	PBO	PBO	PBO	PBO
Right nostril	PBO	93	PBO	93	93	93	93	93	PBO	PBO	PBO	PBO

BID=twice a day; AM=morning; PBO=placebo; PM=evening.

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

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

During the single-blind run-in and the double-blind treatment phases, the same dosing procedure will be followed for both the AM and PM doses on each day. The study staff will instruct the subject that before the AM and PM doses on each day, they will pick up the unit marked 1, shake it, then administer 1 spray to the right nostril followed by 1 spray to the left nostril, and then to pick up the unit marked 2 and repeat the same procedure.

The first dose of double-blind study drug should be administered in the PM on the day of randomization. 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 study drug they perceive to be broken or malfunctioning and to return to the study site for evaluation and identification of the problem.

An instruction sheet on the use of study drug will be provided by the Sponsor or their designee to be given to the subjects.

5.2 Clinical Supplies

The fluticasone propionate suspension formulation is a milky, pale, white liquid contained within an EDS. Each actuation delivers 93 µg of fluticasone propionate through the sealing nosepiece. Once primed, study drug contains not less than 120 metered sprays.

The placebo used in this investigation will be a formulation identical to the active with the omission of the drug substance fluticasone propionate and will be delivered by an identical delivery system to the active formulation.

5.3 Packaging and Labeling

The practice EDS is to be used only at Visit 1 (Screening) to confirm a subject's ability to use the EDS and will be packaged in a demonstrator model EDS kit containing 1 unit.

Study drug will be packaged identically for each unit of study drug and placebo, and each study drug kit, including the single-blind kit, and will consist of 2 units, 1 marked "1" and 1 marked "2"; each unit will contain either 120 sprays of study drug or placebo as necessary to maintain the blind.

Labeling will contain all information required by local regulations.

5.4 Dispensing and Return of Study Drug

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

5.5 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 study drug 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 study drug units will be returned to the Sponsor or designee at the end of the study. Reasons for departure from the expected dispensing or return of study drug units must be recorded.

5.6 Concomitant Medication

All pre-study medications used within 1 month before Visit 1 (Screening) 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 (Screening) 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.

5.6.1 Allowed Concomitant Medications

In subjects with comorbid asthma at study entry (ie, Visit 1 [Screening]), inhaled corticosteroid use must be limited to stable doses of ≤1000 µg/day of beclomethasone HFA (or equivalent; see Attachment 1). Subjects must be on a stable dose for at least 3 months before Visit 1 (Screening) with plans to continue use throughout the study.

Other concomitant medications allowed include:

- Antibiotic medications for bacterial infections that develop during the study.
- Intranasal saline spray with the exception of use within 2 hours before or after study drug administration.
- Saline lavage *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 or within 48 hours prior to a CT scan)
- Intranasal antibiotics in conjunction with lavage, but must not be given within 2 hours before or after study drug administration.
- Stable doses (within 2 weeks of Visit 1 [Screening]) of leukotriene receptor antagonists, beta-blockers, and neuroleptics.
- Low to medium strength topical corticosteroids for dermatologic purposes
- Montelukast sodium (Singulair) for subjects using it before study entry provided its use is continued throughout the study.
- Aspirin use for desensitization only for those subjects who were receiving therapy prior to study entry and whose symptoms were stable.
- Oxymetazoline or other topical nasal decongestant as part of the nasal examination only but may not be used within 24 hours of CT scan being performed

5.6.2 Rescue Medication

Use of rescue medication for CRS symptoms is not allowed during the single-blind run-in or before the Week 4 visit of the double-blind treatment phase. Subjects will be allowed to use over-the-counter non-sedating antihistamine (eg, cetirizine, levocetirizine, desloratadine) at the label-recommended, usual dose per day as rescue medication following the Week 4 visit.

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

5.6.3 Prohibited Medications

- Exposure to any glucocorticoid treatment with potential for systemic effects (eg, 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), mepolizumab, reslizumab, dupilumab, omalizumab, or benralizumab
- Use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (eg, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir,

ketoconazole, telithromycin, conivaptan, lopinavir, voriconazole, cobicistat) because increased systemic corticosteroid AEs may occur

- Steroid Eluting Sinus Implant (Propel®, SINUVA®)

5.7 Treatment Compliance

At each visit after Visit 1 (Screening), subjects will be instructed to bring their partially used/empty study drug units back to the study site at each study visit where it will be visually inspected. 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 study drug and the administration of and timing of doses.

6 VISIT SCHEDULE SUMMARY

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

- CT scans are required at Baseline and Week 24/ET to evaluate eligibility criteria and primary and secondary endpoints. All CT scans will be sent to a central imaging core lab for review and analysis. The baseline CT scan should be performed after all other screening assessments are completed for subjects who remain eligible (unless utilizing CT scan performed within 14-days prior to Visit 1).
- Subjects who develop an acute upper respiratory tract infection, acute sinusitis, influenza, or SARS-CoV-2 (COVID-19) during the study must be symptom free for at least 28 days prior to undergoing the Week 24/EOS CT scan. Subjects should continue treatment with study medication until EOS CT scan can be completed.
- For the Week 24 study visit, if the nasal examination or CT scan, cannot be performed on the same day as the study visit, they should be performed *before the on-site study visit*.

6.1 Visit 1 (Screening/Single-Blind Placebo Run-in)

After informed consent has been obtained, subjects will undergo all Visit 1 (Screening) procedures to determine study eligibility.

Subjects will be instructed on the use of OPN-375. They will then be provided with an EDS to practice administration of a dose and to assure that they can correctly use OPN-375 (eg, able to obtain a seal, sequence). The assignment of a kit number for the practice EDS is not performed by IWRS; rather, the study staff will dispense a practice EDS kit and record the kit number in the drug dispensing log. This kit is only to be used at the site at Visit 1 (Screening) and is not to be sent home with the subject.

Subjects who meet eligibility criteria at Visit 1 (Screening) will enter a 7- to 21-day, single-blind, placebo run-in period to confirm symptom severity and to ensure that they can comply with study procedures. Subjects will be given a single-blind- placebo drug kit (containing 2 placebo units) assigned through the IWRS and an electronic diary and will be instructed on their use.

During the single-blind run-in period, subjects will administer morning and evening doses of the study drug (placebo) as described in Section 5.1. Subjects will be required to keep a daily diary of nasal symptoms. The electronic diary will be completed immediately before the morning and evening doses and will include recording of both instantaneous (evaluation of symptom severity immediately preceding the time of scoring) and reflective (evaluation of symptom severity over the past 12 hours) scores for nasal symptoms (see Section 7.2). Subjects will be instructed that the use of rescue medication for CRS symptoms is not allowed. Subjects will be instructed to bring the single-blind placebo drug kit and the diary with them to their next visit (Visit 2, Day 1 [Baseline]).

The site staff will monitor the electronic diary transmission reports to ensure that subjects are recording both morning and evening nasal symptoms and that the data are being transmitted to the data base. Site staff should follow-up with subjects as necessary to counsel them on completion of the electronic diaries. The site staff will evaluate the subject's severity scores, entered remotely into the electronic diaries, and will be notified when the subject meets eligibility criteria pertaining

to their symptoms. When a subject reaches an average congestion severity score of at least 1.5 over a 7-day period during the first 14 days of the single-blind run-in period, they will be scheduled to have the CT scan to assess remaining eligibility requirements. The CT scan should be performed after diary eligibility is confirmed and prior to day 21 of the screening run-in period. CT scans performed prior to Day 21 and within 2 weeks before Visit 1, as part of routine clinical care, may be utilized providing the scan meets the CT scan standards outlined in the Imaging Charter for this protocol.

6.2 Visit 2 (Day 1, Baseline; Randomization)

Once it is confirmed that the eligibility criteria based on the CT scan are met, the remainder of study procedures should be performed.

Subjects who then meet all eligibility criteria at Visit 2, Day 1 (Baseline) will be randomly assigned through the IWRS to 1 of 3 arms: 186 or 372 µg of OPN-375 BID, or placebo BID. Study drug will be administered as described in Section 5.1. Subjects will be given 1 double-blind- study drug kit (containing 2 devices) assigned through the IWRS and an electronic diary and will be instructed on their use. Subjects will be instructed to bring the study drug kits and diary with them to their next visit.

Subjects will be required to keep an electronic daily diary of nasal symptoms. The diary will be completed immediately before the morning and evening doses and will include recording of both instantaneous and reflective scores for nasal symptoms (see Section 7.2). Subjects will be instructed that the use rescue medication for CRS symptoms is not allowed.

The site staff will monitor the electronic diary transmission reports to ensure that subjects are recording both morning and evening nasal symptoms and that the data are being transmitted to the data base. Site staff should follow-up with subjects as necessary to counsel them on completion of the electronic diaries.

6.3 Visits 3, 4, and 5 (Weeks 4, 8, and 12)

During the 24-week double-blind treatment phase, subjects will return to the study site at Weeks 4, 8 and 12 to have efficacy and safety assessments performed.

At all visits during the double-blind treatment phase, treatment compliance will be monitored as described in Section 5.7. Subjects will be given a double-blind- study drug kit (containing 2 devices) assigned through the IWRS at Visit 3/Week 4 and Visit 4/Week 8. Subjects will receive 3 kits at Visit 5/Week 12. Subjects will be instructed to bring the study drug kits with them to each visit.

Subjects will be required to keep a daily diary of nasal symptoms through Week 12. The diary will be completed immediately before the morning and evening doses and will include recording of both instantaneous and reflective scores for nasal symptoms (see Section 7.2). Subjects will also be instructed that the use of rescue medication for CRS symptoms is not allowed until after the Week 4 visit; starting at the Week 4 visit, they will be instructed to record use of the approved rescue medication in the electronic diary. Subjects will be instructed to bring the diary with them to all study visits.

The site staff will continue to monitor electronic diary transmission reports throughout the first 12 weeks of double-blind treatment to ensure that subjects are recording both morning and evening

nasal symptoms and rescue medication use and that the data are being transmitted to the data base. Site staff should follow-up with subjects as necessary to counsel them on completion of the electronic diaries.

6.4 Subject Contact (Week 16 and Week 20)

Subjects will be contacted at Weeks 16 and 20 (approximately every 4 weeks after Visit 5 (Week 12) and before Visit 6 (Week 24) to obtain information on treatment compliance, exacerbation assessment, AEs, and concomitant medications.

6.5 Visit 6 (Week 24 End-of-Double-Blind/Early Termination)

Subjects who complete the 24-week double-blind treatment phase, 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/ET from study visit performed, including a CT scan. If a subject could not complete EOS CT scan at the Week 24 visit, subject should have all other scheduled procedures performed and continue on study treatment until an EOS CT scan can be completed. Additional treatment kits can be dispensed via the 'Unscheduled Visit' functionality and the Visit 6 contact should not be completed in IWRS. If subject continues treatment, study staff will complete subject contacts approximately every 4 weeks to assess safety until subject can complete the EOS CT scan. When EOS CT scan has been completed and subject returns to study site, study staff will perform an additional SNOT-22, urine pregnancy test (women of child-bearing potential only), and contact IWRS to complete Visit 6.

6.6 Unscheduled Visits

The Investigator may, at their discretion, arrange for a subject to have an unscheduled assessment(s) at any time, especially in the case of AEs that require follow-up.

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Medical History, Demographics, and Baseline Characteristics

7.1.1 Medical History

A complete medical history will be obtained before randomization to ensure subjects qualify for the study. Data collected will include medical, surgical and smoking history.

7.1.2 Information Pertaining to Chronic Rhinosinusitis

Information pertaining to the subject's CRS, including date of initial diagnosis, number of exacerbations in the previous year, prior treatments for the condition (eg, surgery, medication) will be collected.

7.1.3 Demographic Information and Baseline Characteristics

Demographic information will include age, sex, race, and ethnicity.

7.2 Efficacy Assessments

Electronic diaries will be used by subjects during the single-blind placebo -run-in period and double-blind treatment phase in this study to capture daily nasal symptoms (ie, symptom scores for nasal congestion, nasal discharge [anterior and/or posterior], facial pain or pressure sensation, and sense of smell) and the use of approved rescue medication after the Week 4 visit through Week 12 of the double-blind phase. The Schedule of Study Procedures and Evaluations indicates the timing of all assessments; further information on each evaluation is provided below.

The electronic diaries will be preprogrammed to transmit subject-entered data daily to the electronic diary data base. The site staff will monitor the electronic diary transmission reports to ensure that subjects are recording both morning and evening nasal symptoms and rescue medication use and that the data are being transmitted to the data base. Site staff should follow-up with subjects as necessary to counsel them on completion of the electronic diaries.

Additional information on the nasal examination can be found in Section 7.4.2.

The following efficacy evaluations will be performed:

- At Visit 1 (Screening), study personnel should provide each subject with the description for each symptom severity (ie, mild, moderate, severe) using the definitions provided in Table 2. Each subject will then be asked to provide the severity of their nasal symptoms, on average, over the past 7 days. Subjects must report at least moderate severity of nasal symptoms to enter the study.
- An electronic diary will be provided to each subject. Subjects will be instructed to complete the electronic diary twice daily immediately before dosing (morning and evening) during the single-blind placebo run-in period (for eligibility) and during the first 12 weeks of the double-blind treatment phase. Subjects will report both instantaneous (evaluation of symptom severity immediately preceding the time of scoring) and reflective (evaluation of symptom severity over the past 12 hours) scores for:

- nasal congestion symptoms, nasal discharge (anterior and/or posterior) symptoms, and facial pain or pressure sensation symptoms, scored on the scale in Table 2

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).

Note: Sense of smell, scored as 0=normal, 1=slightly impaired, 2=moderately impaired, 3=absent.

- 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 SNOT-22 is validated in CRS (Hopkins 2009). The recall period is the past 2 weeks. The SNOT-22 takes approximately 5 minutes to complete.
- Recording of each dose of approved rescue medication after the Week 4 visit through Week 12
- The EQ-5D consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The subject is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the subject's health state. The EQ VAS records the subject's self-rated health on a vertical VAS, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the subject's own judgement. The EQ-5D takes 1-2 minutes to complete.
- SF-36v2 is a multipurpose, 36-item subject-completed validated questionnaire that measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The SF-36v2 survey with a 4-week recall will be used. It yields scale scores for each of these 8 health domains, and 2 summary measures of physical and mental health: the PCS and MCS. The SF-36v2 takes approximately 10 minutes to complete. (Optum.com Web site)
- SF-6D is a single health state index derived from the 8 domains from the SF-36v2 (using all but the general health domain and combining role physical and role emotional)
- PSQI is a validated, self-rated questionnaire, which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate 7 "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these 7 components yields 1 global score. The PSQI takes approximately 3-5 minutes to complete

- The 16-item QIDS (Rush et al, 2003) is designed to assess the severity of depressive symptoms. The QIDS is available in a self-rated version and assesses all the criterion symptom domains designated by the American Psychiatry Association Diagnostic and Statistical Manual of Mental Disorders - 5th Edition to diagnose a major depressive episode. The 7-day period prior to assessment is the usual time frame for assessing symptom severity. The psychometric properties of the QIDS, has been established in various study samples. The time required to complete the QIDS is approximately 2-4 minutes.
- SIT is a test comprised of 4 booklets each containing 10 microencapsulated (scratch and sniff) odors. Forced choice response alternatives accompany each test item. The test provides an absolute indication of smell loss (anosmia; mild, moderate or severe hyposomia) as well as an index to detect malingering. The test is self-administered and takes 10-15 minutes.
- Acute exacerbations of CRS are defined as worsening of symptoms requiring antibiotic or corticosteroid use, specifically:
- an event characterized by acute worsening of one or more of the cardinal diagnostic symptoms of CRS (listed below), lasting at least 3 days, that cause the subject to seek medical care:
  - facial pain or pressure
  - nasal congestion/blockage
  - rhinorrhea
  - reduction in sense of smell

    AND
  - escalation of treatment, defined as either initiation of antibiotics or oral steroids, or the escalation of treatment involving an unscheduled acute care visit (eg, emergency room or acute care outpatient clinic) or inpatient care, for increased symptoms of CRS or for acute sinusitis.

  *If an exacerbation start date is less than 7 days after the end date of a previous exacerbation, the entire period will be treated as a single exacerbation.
- Antibiotic use for acute sinusitis during study participation will be captured.
- Assessments from CT scan will be performed for both the baseline CT scan and the Week 24/ET (Visit 6) CT scan
- Lund-Mackay Staging System: Lund-Mackay system (Lund and Mackay, 1993) assigns to each of 10 sinus cavities (left and right maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal) a score of 0 (no opacification), 1 (partial opacification), or 2 (total opacification) based on the extent of mucosal thickening within that sinus, plus a 0-2 score for each OMC. The total Lund-Mackay score for a CT scan ranges from 0-24.
- Zinreich Modification of the Lund-Mackay Staging System (Zinreich 2004): Zinreich modified the Lund-Mackay system by creating subdivisions within "partial opacification" and increasing the range of scores to 0-5 based on percent opacification: 0 = 0%, 1 = 1%-25%, 2 = 26%-50%, 3 = 51%-75%, 4 = 76%-99%, and 5 = 100%

- Percent of sinus volume occupied by disease for the worst maxillary and the worst ethmoid sinus: calculated using the methods outlined in the imaging charter
- 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

Note: Subjects will be considered improved if they have a PGIC of 1, 2, or 3 (very much improved, much improved, or minimally improved). Subjects with missing values will be considered not improved.

7.3 Health Economic Assessments

Health economic information related to bilateral CRS will be collected during the study and will include information on criteria for surgical intervention (independent of actual surgery performed), subjects approved for surgery, who no longer elect to undergo surgery, and missed work or school days/lost productivity. The investigator will ask the subject if he/she would consider surgery and the subject will complete the HPQ (1-2 minutes to complete).

Objective criteria for surgical intervention are as follows:

- used topical intranasal corticosteroid (≥8 weeks duration)
- used either a short course of broad-spectrum/culture-directed systemic antibiotic (2 to 3 weeks duration) or a prolonged course of systemic low-dose -anti-inflammatory antibiotic (ie, macrolide or trimethoprim/sulfamethoxazole) (≥12 weeks duration)
- SNOT-22 total score ≥20
- Lund-Mackay CT score ≥ 1
- subjects who enter the study approved for surgery with a scheduled surgery date, who no longer elect to undergo surgery
- The work productivity questionnaire asks about employment status, work absences, and on-the-job productivity. Subjects will also be asked to provide annual salary and postal code information at screening which will be used to inform overall cost to employers from lost work productivity.

7.4 Safety Assessments

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

Safety will be assessed by performing a physical examination and evaluating clinical laboratory variables at Visit 1 (Screening), and throughout the study based on monitoring of AEs (as

described in Section 8), performing nasal examination, measuring vital signs (ie, blood pressure, pulse) and weight, and through collection of information for concomitant medications.

7.4.1 Physical Examination

A brief physical examination will be performed on all subjects at Visit 1 (Screening). Height will be collected.

7.4.2 Nasal Examination

The nasal examination will be performed via nasoendoscopy; see Section 6, Visit Schedule Summary, regarding completion of this assessment, including visit time windows. The sites will be provided with a nasal examination worksheet. A summary of the key safety assessments from the nasal examination is provided in Attachment 3. Findings from the nasal examination worksheet that are deemed to be clinically significant by the Investigator will be recorded on the AE CRF beginning at Visit 1 (Screening).

7.4.3 Ocular examinations

An ocular examination must promptly be performed if a subject experiences any unexplained worsening in vision during the study (e.g. difficulty reading or seeing traffic signs from a distance). The examiner must be a health care provider with expertise in examination and diagnosis of conditions of the eye. Reports will be forwarded to the investigator.

7.4.4 Vital Signs and Weight

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. Weight will be measured at each visit.

7.4.5 Laboratory Variables

Blood and urine samples will be collected at Visit 1 (Screening) for evaluation of laboratory variables shown in Table 4. The total amount of blood to be taken from each subject for these study specific- measurements is approximately 7 mL.

Table 4: Laboratory Measurements

Hematology	**Serum chemistry**
• hemoglobin concentration • red blood cell count • mean corpuscular volume (MCV) • white blood cells (total and differential) • platelet count • hematocrit	• sodium • potassium • calcium • chloride • urea • creatinine • total bilirubin • alkaline phosphatase • alanine transferase (ALT) • aspartate transferase (AST) • gamma-glutamyltransferase (GGT) • albumin • total protein • glucose
Urinalysis (dipstick)	Urine Drug Screen
• pH • glucose • protein • ketone bodies • indicators of red and white blood cells	• cocaine • phencyclidine • amphetamines class • benzodiazepines class • barbiturates class • opiates class • propoxyphene • methaqualone • methadone
• Women of child-bearing potential only: A urine pregnancy test will be performed at each visit, not including Subject Contacts. Subjects continuing treatment past Week 24/Visit 6 will need an additional pregnancy test completed upon returning to site.	

At Visit 6/Week 24/ET, a blood sample will be obtained for SARS-CoV-2 serology testing.

Blood samples and urine drug screens will be analyzed at a central laboratory facility. Urine samples will be analyzed by dipstick and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with the subject's source documentation.

If any laboratory tests are performed as part of a subject's standard of care after Visit 1 (Screening) and before Visit 2, Day 1 (Baseline), and a change from the Visit 1 (Screening) laboratory test result is considered by the investigator to be clinically significant, the investigator should reassess the subject's eligibility. If any laboratory tests are performed as part of a subject's standard of care after the subject is randomized, and a change from the Visit 1 (Screening) 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 8.1. Significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

8 SAFETY MONITORING AND REPORTING

8.1 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, symptoms of CRS are collected as part of the primary and secondary endpoints. Changes or worsening of symptoms of CRS 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 treatment or discontinuation from the study
- require treatment or any other therapeutic intervention
- require further diagnostic evaluation which confirms a clinically significant abnormality (excluding a repetition of the same procedure that rules out an abnormality)
- 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 has to assess whether the AE is drug related (adverse drug reaction) or not. Changes of AEs and dates of ending have to 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 until completion of the end-of-study visit or an early termination visit. SAEs will be reported through 30 days after the last dose of study drug administration.

The maximum severity (intensity) of the AE will be categorized by the investigator as shown in Table 5.

Table 5: 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 the usual activities

8.2 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.

8.3 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 (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome).
- The AE occurs 1 or more times and is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, 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.

8.4 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 (ie, "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.

8.5 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
- 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, device, or procedure.

8.5.1 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.

8.5.2 Serious Adverse Event Reporting

All SAEs must be reported within 24 hours to:

PPD
Safety Email: safety@optinose.com
Safety Fax: 1-267-521-0750

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 PPD 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).

Because of the need to report to health authorities all SAEs in a timely manner, it is vitally important that an investigator report any AEs that would be considered serious within 24 hours, even if the investigator does not consider the AE to be clinically significant or drug-related.

Should the investigator become aware of an SAE (regardless of relationship to study drug) that occurs within 30 days after stopping the study drug, the SAE must be reported in accordance with the procedures specified in this protocol. There is no time limit on the collection of SAEs that are considered related to study drug.

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.

8.6 Non-Serious Adverse Event Reporting

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

8.7 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 (eg, 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.

9 STATISTICAL ANALYSIS

A detailed Statistical Analysis Plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Statistical analysis principles to address all study objectives are provided below.

9.1 Sample Size Determination

Sample size assumptions were originally generated based on previous Phase 3 studies of OPN-375 in subjects with nasal polyposis and data from a study evaluating the change in maxillary and ethmoid opacification in CRS patients treated with an intramuscular dose of triamcinolone (Pallanch 2013). Updated standard deviation estimates for both co-primary endpoints in this amendment are based on a blinded interim analysis of Protocol OPN-FLU-CS-3205. Based on the results for changes from baseline in morning symptoms among subjects with nasal polyps in the previous studies conducted with OPN-375, a sample of 70 subjects per group (210 total subjects) is sufficient to detect a 0.9 scale difference in 7-day average CSNS (AM instantaneous) between treatments (OPN-375 vs placebo) using a 2-sided test at the 5% significance level with 88% power, and assuming a standard deviation (SD) of 1.7. This sample size is also adequate to detect a 9% difference between treatments in average percent opacification (APOV) using a 2-sided test at the 5% significance level with 88% power, and assuming a SD of 17%. The sample size was estimated for the co-primary efficacy endpoints using Power Analysis and Sample Size Software (PASS 15) (NCSS, 2017).

9.2 Analysis Sets

9.2.1 Intent-to-treat Analysis Set

The intent-to-treat (ITT) analysis set will include all subjects who are randomized regardless of whether they received double-blind treatment.

9.2.2 Safety Analysis Set

The safety analysis set will include all randomized subjects who receive at least one dose of randomized study drug. The treatment group assignment in this population will be defined by the treatment actually received. The safety population will be used for the analysis of safety.

9.2.3 Full Analysis Set (FAS)

The FAS will include all subjects in the ITT set who receive at least one dose of randomized study drug during the double-blinded treatment phase, and have at least one baseline efficacy measure for APOV endpoint, and also have a baseline value and at least one post-baseline value (7-day average AM instantaneous CSNS score) for the CSNS endpoint. Subjects will be included in the treatment group to which they were randomized.

The FAS population will be the primary study population for all efficacy analyses in this study.

9.2.4 Per-Protocol Analysis Set (PPS)

The PPS analysis set excludes subjects from the FAS population that may substantially affect the results of the primary efficacy analysis. The PPS population will be used for a sensitivity analysis for primary and key secondary efficacy endpoints.

Determination of the subjects excluded from the PPS will be made prior to unblinding treatment codes of the database and documented in a separate report.

9.3 Primary Estimand, Intercurrent Events, and Estimation

Primary Objective and Population: The primary objective is to compare the efficacy of intranasal administration of twice-daily doses of 186 and 372 µg of OPN-375 (fluticasone propionate) with placebo in subjects with documented CRS without nasal polyps.

9.3.1 Co-primary Endpoints

- Change from baseline to the end of Week 4 in 7-day average instantaneous AM CSNS (evaluation of symptom severity immediately preceding the time of scoring)
  - nasal congestion
  - nasal discharge (anterior and/or posterior)
  - facial pain or pressure sensation

  The baseline CSNS will be the average of the CSNS over the last 7 days of the placebo run-in period prior to randomization. The CSNS at Week 4 will be the average of the CSNS over the 7 days prior to Day 28.

AND

- The change from baseline to Week 24/ET in the APOV in the ethmoid and maxillary sinuses (APOV is the average percentage of volume opacified across both maxillary and ethmoid sinuses (all 4 sinuses) at each timepoint)

9.3.2 Potential Intercurrent Events

The potential intercurrent events are as follows:

1. Need for systemic corticosteroids for CRS exacerbation or worsening of CRS nasal/sinus symptoms
2. Need for nasal surgery
3. Discontinuation from study treatment

9.3.3 Primary Estimand

The primary efficacy estimand is the difference between each active treatment of twice-daily doses of 186 µg and 372 µg of OPN-375 and placebo for each of the co-primary endpoints.

For the primary estimand, intercurrent events will be addressed as follows:

1. Systemic corticosteroids use for CRS exacerbation or worsening of CRS nasal/sinus symptoms: a composite strategy will be employed with a poor score assigned to this event.

   For CSNS, a value of '9' will be assigned. For APOV, a poor score is defined as follows: for a subject with a baseline APOV ≥ 75%, a value of '100%' will be assigned; if baseline APOV < 75%, a poor score is defined as baseline APOV + 25%. Further detail regarding the definition of a poor score and the handling of a missing within-instrument data in these endpoints is provided in the SAP.

   Systemic corticosteroid use for other indications will be considered a treatment and study discontinuation event (Reference criteria 3).

2. Nasal surgery: composite strategy with worst scores assigned as above.
3. Treatment Discontinuation: treatment policy strategy; subjects may continue in the study until one of the following three mutually exclusive outcomes:
    a) Subject completes Week 24/ET CT scan. In the absence of an intercurrent event (systemic corticosteroids, nasal surgery) use the endpoint value;
    b) An intercurrent event (systemic corticosteroids for CRS exacerbation or worsening of CRS nasal/sinus symptoms, nasal surgery) occurs: Use composite strategy and assign worse score as described above (reference criteria 1, 2);
    c) Subject discontinues the study. Missing data due to study discontinuation following treatment discontinuation will be imputed; further detail on the imputation method is provided in the estimation section for each of the co-primary endpoints.

9.3.4 Estimator and Estimation Method – Primary Analysis

Estimator and estimation method (CSNS)**:** For the co-primary endpoint CSNS, the estimator is the mean difference between treatments (active versus placebo) in change from baseline to the end of Week 4 in the 7-day average total CSNS (instantaneous AM). Estimation is based on a mixed model for repeated measures (MMRM) where changes from baseline to Weeks 2, 4 in the 7-day average total CSNS (instantaneous AM), respectively, are the repeated measures. The MMRM model will employ Restricted Maximum Likelihood (REML) for parameter estimation and the Kenward-Roger method for calculating the denominator degrees of freedom. An unstructured covariance matrix will be used to estimate within-subject error. For the treatment policy estimand, (reference Section 9.3.3, criteria 3c), missing data due to study discontinuation will be estimated within the MMRM model under the assumption that the missing data are missing at random (MAR) and that early discontinuation from the study (prior to Week 4) is unlikely to reflect a treatment effect.

The MMRM model will include categorical effects for previous sinus surgery (Y,N), treatment (OPN-375 186 µg, OPN-375 372 µg, placebo), week (2, 4) treatment-by-week interaction, and the continuous covariate baseline 7-day average total CSNS (instantaneous AM) with baseline-by-week interaction.

Estimator and estimation method (APOV)**:** For the co-primary endpoint APOV, the estimator is the mean difference between treatments (active versus placebo) in the change from baseline to Week 24/ET APOV. Estimation is based on an ANCOVA model including categorical effects for previous sinus surgery (Y,N), treatment (OPN-375 186 µg, OPN-375 372 µg, placebo), and baseline APOV.

For the treatment policy estimand, (reference Section 9.3.3, criteria 3,c), missing data due to study discontinuation will be imputed with a pattern mixture model (PMM) multiple imputation (MI) using the Jump–to-Control (J2C) method. The PMM assumes that the missing data at Week 24/ET on the control arm (placebo) is MAR, and the missing data on the active treatment arms have the profile of the control arm at Week 24/ET.

Multiple imputation using a PMM with J2C method will be conducted using the sequential modeling method as described in (O'Kelly et al, 2014). Further detail on the MI implementation, and statistical analysis and inference is provided in the SAP.

9.3.5 Supplementary Analysis

A supplementary analysis of the primary estimand will be performed.

Supplementary estimand: A supplementary efficacy estimand is the difference between each active treatment of twice-daily doses of 186 µg and 372 µg of OPN-375 and placebo in each of the co-primary endpoints, irrespective of systemic corticosteroid use.

That is, for the supplemental estimand, intercurrent events will be addressed as follows:

1. Systemic corticosteroids use for all indications: treatment policy strategy; consider outcomes irrespective of systemic corticosteroid use; subjects may continue in the study until one of the following two mutually exclusive outcomes:
    a. Subject completes the study, use the endpoint value;
    b. Subject discontinues the study. Missing data due to study discontinuation following treatment discontinuation will be imputed; further detail on the imputation method is provided in the estimation section for each of the co-primary endpoints.
2. Nasal surgery: composite strategy with worst scores assigned.
3. Treatment discontinuation: composite strategy with poor scores assigned.

The estimator and estimation methods for the co-primary endpoints are the same as for the primary estimand described above.

9.4 Sensitivity Analyses

9.4.1 ANCOVA on Ranked APOV Values

A sensitivity analysis of the primary estimand and APOV co-primary endpoint will be performed based on ranked APOV values after modification of the primary estimand as follows. For the composite strategy, a worst score of 100% is assigned; for the treatment policy strategy, baseline APOV is assigned (BOCF). Baseline and endpoint APOV values are then ranked. Ranked APOV values will be analyzed with an ANCOVA model including categorical effects for previous sinus surgery and treatment. Further detail is provided in the SAP.

9.4.2 Observed Cases Analysis

A sensitivity analysis will be performed for both co-primary endpoints based on the FAS, observed cases population. For each co-primary endpoint, the observed cases population is defined to include all subjects who have an observed value for that endpoint, irrespective of an intercurrent event, and the observed value is used in the analysis. For both co-primary endpoints, the estimator and estimation methods are the same as described in Section 9.3.4, with the exception that in the observed cases population there are no missing data; consequently, no imputation is required.

9.4.3 Tipping Point

If the analysis of both co-primary endpoints is statistically significant, then an additional sensitivity analysis will be performed to determine the smallest constant, δ, when applied to the imputed missing data in the active treatment groups, that will yield a mean treatment difference such that the result using the primary analysis model is no longer statistically significant. The constant δ represents a worsening of treatment values and the smallest value, say δ^*, that yields a non-significant result for the primary analysis is called the “Tipping Point.” Further detail on the Tipping Point analysis is provided in the SAP.

9.5 Key Secondary Efficacy Analyses

The analysis of the following key secondary endpoints are based on pooling the data from Study OPN-FLU-CS-3205 and Study OPN-FLU-CS-3206 (pooled data):

- Change from baseline to Week 4 on CSNS score in subjects who were symptomatic at trial entry despite reported use of an intranasal steroid for treatment of CRS within 30 days of Visit 1 will be analyzed using the same MMRM model described for the co-primary endpoint CSNS and the model will include a categorical effect term for protocol (CS-3205, CS-3206).
- The frequency of acute sinus exacerbations over 24 weeks will be compared between OPN-375 dose groups and placebo using generalized linear model (GLM) for data from the negative binomial distribution that is commonly referred to as the negative binomial (NB) regression model. The NB model will include the same model terms as the primary models; in additional, the model will include a categorical effect for protocol (OPN-FLU-CS-3205, OPN-FLU-CS-3206), and the logarithm of follow-up time as an offset variable. The same model will be used for the pooled analysis of the frequency of acute sinus exacerbations over 24 weeks in the CRS without Nasal Polyps population.

The analysis of the following key secondary endpoints are based on the data from Study OPN-FLU-CS-3206 only:

- change from baseline to the end of Week 4 in four separate cardinal CRS symptoms, as measured by (AM, Instantaneous) CSNS: congestion, facial pain or pressure sensation, nasal discharge (anterior and/or posterior), and sense of smell will be analyzed using the same MMRM model described above.
- The Kaplan-Meier method and log-rank test will be used to estimate and compare the distributions of time to first acute CRS exacerbation between each OPN-375 dose and placebo.

9.6 Other Secondary Efficacy Analyses

All statistical analyses in this section that reference the primary MMRM and ANCOVA models described in Section 9.3.4 will include the same factors as their respective primary models, except for the baseline covariate. The baseline covariate for the specific endpoint will be used, unless otherwise specified.

In addition, a combined dose group (OPN-375 186 µg, OPN-375 372 µg) is defined in all models of primary and secondary endpoints by including appropriate model contrasts, assigning equal weight to each dose, to obtain the inferential statistics for combined doses, and for the comparison: combined dose versus placebo.

Intercurrent events for secondary endpoints will be addressed as described in Section 9.3.3 for the primary estimand, unless otherwise indicated, and poor scores assigned to secondary endpoints are defined in the SAP. For the treatment policy estimand, missing data due to study discontinuation will be handled as described in Section 9.3.4 for the primary MMRM and ANCOVA models, respectively.

The following secondary endpoints will be analyzed with MMRM models; further details will be provided in the SAP:

- Change from baseline in average instantaneous and reflective AM and PM CSNS and symptom scores (facial pain or pressure sensation, nasal discharge, sense of smell, and nasal congestion) – (except AM, instantaneous symptom scores – key secondary endpoints)
- Change from baseline SNOT-22 total scores and sub-domain scores
- Change from baseline to Week 24/ET in SNOT-22 total score in subjects from pooling studies OPN-FLU-CS-3205 and OPN-FLU-CS-3206 who report using an intranasal, topically acting nasal steroid for the treatment of CRS within 30 days of Visit 1
- Change from baseline to Week 24/ET PSQI global and component scores
- Change from baseline to Week 24/ET the Global PSQI Score from pooling studies OPN-FLU-CS-3205 and OPN-FLU-CS-3206
- Change from baseline to Week 4, 8, 12, and 24/ET in HPQ endpoints
  - number and percentage of missing work days over the past 4 weeks
  - percentage of productive work hours lost over the past 4 weeks

The following secondary endpoints will be analyzed using an ANCOVA model; further details will be provided in the SAP. Change from baseline to Week 24/ET:

- Lund-Mackay Staging System total score, scores for ethmoids and maxillary sinuses combined, and scores for each sinus pair (e.g., ethmoids, maxillary, frontal, sphenoid, and ostiomeatal complex),
- WPOV-E, WPOV-M, WPOV
- Zinreich modification of the Lund-Mackay Staging System total score, scores for ethmoids and maxillary sinuses combined, and for each sinus pair (e.g., ethmoids, maxillary, frontal, and sphenoid
- Zinreich modification of the Lund-Mackay Staging System score for the worst sinus between maxillary and ethmoid sinuses
- percent of opacification of the combined volume of the ethmoid and maxillary sinuses
- SF36v2 MCS Domain, PCS Domain, and individual health domains
- QIDS total score
- SIT scores

Change from baseline to Week 24/ET for EQ-5D VAS scores will be analyzed with the ANCOVA model described above; EQ-5D dimensions will be summarized. Further details will be provided in the SAP.

The percent of subjects considered improved (ie, subjects with ratings of 1 [very much improved] or 2 [much improved]) based on the PGIC at weeks 4 and 24/ET will be analyzed with a logistic regression MMRM model; further details will be provided in the SAP.

The following endpoints will be analyzed using a logistic regression model; further details will be provided in the SAP:

- QIDS Severity of Depression at Week 24/ET
- The percentage of subjects who meet the eligibility criteria for surgery at Week 24

The percent of subjects indicating that they are willing to consider sinus surgery at baseline and Week 24, and the percent of subjects approved for surgery who no longer elect to undergo a surgery Week 24 within each treatment group will compared with McNemar's test.

Change from baseline to Week 24/ET for SF-6D will be summarized as described in the SAP.

9.7 Subgroup Analyses

The following endpoints will be analyzed according to the primary estimand by subgroup: Subjects with prior sinus surgery versus without prior sinus surgery at baseline. Further detail on the statistical methods will be provided in the SAP.

- Co-primary endpoints (CSNS, APOV)
- All CSNS endpoints other than the primary,
- All individual daily nasal symptoms scores that are components of the CSNS (as well as sense of smell)
- SNOT-22 total score

9.8 Type I Error Control for Multiplicity

9.8.1 Co-primary Efficacy Endpoints

The primary hypothesis of this trial is that OPN-375 high dose (372 µg) group will be superior to the placebo group in both co-primary endpoints.

The familywise Type 1 error probability for the test of the primary hypothesis is α=0.05. The strategy for strong, familywise control of the Type I error is based on closed testing procedure as follows.

1. Test each co-primary endpoint for OPN-375 high dose (372 µg) vs placebo: If $p < 0.05$ for both endpoints, then proceed to key secondary endpoints; otherwise, stop. The order of the testing is as follows:
   a. OPN-375 372 µg versus placebo in the change from baseline in the 7-day average CSNS (instantaneous AM) at the end of Week 4
   b. OPN-375 372 µg versus placebo in the APOV in the ethmoid and maxillary sinuses change from baseline to Week 24/ET

9.8.2 Type I Error Control for Key Secondary Endpoints

The following planned comparisons are defined based on pooled data from Study OPN-FLU-CS-3205 and Study OPN-FLU-CS-3206. Testing will continue based on closed testing procedure, with α=0.05, if the primary hypothesis is met, as follows:

1. OPN-375 372 µg versus placebo in the frequency of acute exacerbations of CRS over 24 weeks
2. OPN-375 372 µg versus placebo in the frequency of acute exacerbations of CRS over 24 weeks in CRS without NP population
3. OPN-375 372 µg versus placebo in change from baseline to Week 4 on CSNS score in subjects who were symptomatic at trial entry despite reported use of an intranasal steroid for treatment of CRS within 30 days of Visit 1

The following planned comparisons are defined based on Study OPN-FLU-CS-3206. Testing will continue based on closed testing procedure, with α=0.05, if the key secondary hypotheses (1-3) are met, as follows:

4. Test each co-primary endpoint for OPN-375 low dose (186 µg) vs placebo: If $p < 0.05$ for both endpoints, then proceed to next endpoints; otherwise, stop. The order of the testing is as follows:
    a. OPN-375 372 µg versus placebo in the change from baseline in the 7-day average CSNS (instantaneous AM) at the end of Week 4
    b. OPN-375 372 µg versus placebo in the APOV in the ethmoid and maxillary sinuses change from baseline to Week 24/ET
5. OPN-375 372 µg versus placebo in change from baseline to the end of Week 4 in nasal congestion
6. OPN-375 372 µg versus placebo in change from baseline to the end of Week 4 in nasal discharge (anterior and/or posterior)
7. OPN-375 372 µg versus placebo in change from baseline to the end of Week 4 in facial pain or pressure sensation
8. OPN-375 372 µg versus placebo in change from baseline to the end of Week 4 in sense of smell
9. OPN-375 372 µg versus placebo in time to first acute exacerbation of CRS

The following planned comparisons are defined based on pooled data from Study OPN-FLU-CS-3205 and Study OPN-FLU-CS-3206. Testing will continue based on closed testing procedure, with α=0.05, if the primary hypothesis is met, as follows:

10. OPN-375 186 µg versus placebo in the frequency of acute exacerbations of CRS over 24
11. OPN-375 186 µg versus placebo in the frequency of acute exacerbations of CRS over 24 weeks in CRS without NP population
12. OPN-375 186 µg versus placebo in change from baseline to Week 4 on CSNS score in subjects who were symptomatic at trial entry despite reported use of an intranasal steroid for treatment of CRS within 30 days of Visit 1

The following planned comparisons are defined based on Study OPN-FLU-CS-3206. Testing will continue based on closed testing procedure, with α=0.05, if the key secondary hypotheses (9-11) are met, as follows:

13. OPN-375 186 µg versus placebo in change from baseline to the end of Week 4 in nasal congestion in CRS without NP population
14. OPN-375 186 µg versus placebo in change from baseline to the end of Week 4 in nasal discharge (anterior and/or posterior)
15. OPN-375 186 µg versus placebo in change from baseline to the end of Week 4 in facial pain or pressure sensation
16. OPN-375 186 µg versus placebo in change from baseline to the end of Week 4 in sense of smell
17. OPN-375 186 µg versus placebo in time to first acute exacerbation of CRS

9.9 Safety Analysis

All safety summaries will be descriptive; no statistical inference procedures will be applied. All safety summaries will be presented by OPN-375 dose level 186 µg, 372 µg, and OPN-375 combined doses and placebo.

9.9.1 Adverse Events (AEs)

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20 or higher. Treatment emergent AEs (TEAEs) are defined as AEs with onset dates on or after the start of double-blind study drug. The incidence of TEAEs during the study period will be tabulated by treatment group and body system (or System Organ Class [SOC] and preferred term) overall, by severity, and by relationship to study drug using subject counts and percent. Those AEs with missing onset dates or missing severity will be included as treatment-emergent. If an AE is reported more than once during the double-blind study phase, the greatest severity and the worst-case attribution will be used for presentation in tables.

Deaths, SAEs, and AEs causing discontinuation of study participation and/or study treatment will be tabulated by treatment group with subject counts and percent. Adverse events for individual subjects will be listed, along with information regarding onset, duration, severity, and relationship to study drug.

9.9.2 Other Safety Endpoints

Baseline physical examination findings and clinical laboratory data will be summarized. Vital signs and weight will be summarized using descriptive statistics including mean values and change from baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point.

Prior/concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug), Version December 2010 or later, and summarized by drug class with subject counts and percent.

9.10 Interim Analysis

A blinded interim analysis is planned for both co-primary endpoints in this study to evaluate the sample size assumptions as follows:

1. Co-primary endpoint change from baseline in the 7-day average CSNS (instantaneous AM) to assess the variance.
2. Co-primary endpoint change from baseline to Week 24/ET APOV to assess variance.

This interim analysis is planned to occur when at least 50% of subjects have reached Week 24/ET endpoint for APOV. At this time it is anticipated that at least 75% of subjects will have reached the Week 4 endpoint for CSNS. The complete details of this interim analysis is provided in the IA-SAP.

10 DATA QUALITY ASSURANCE

10.1 Case Report Forms

Clinical data will be entered on 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.

10.2 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.

10.3 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, whichever is the longer time period.

11 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 investigator generating the data.

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.

12 REGULATORY AND ETHICAL CONSIDERATIONS

12.1 Ethical Conduct of the Study

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 incorporated the following features:

- multi-center, placebo controlled, double-blind, 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.

12.2 Informed Consent Process

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.

12.3 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.

12.4 Future Use of CT Scans

In addition to the main study, subjects will be asked to consent to the release and use of their de-identified CT scans for publications, presentations, training, commercial, and marketing materials. Subjects agreeing to the use of their CT scans for this purpose, will be asked to sign a separate consent form.

The de-identified CT scans will be transferred to the sponsor or its representative. The de-identified CT scans will not be labeled with any patient identifying information. The privacy of personal data will be maintained as described in section 12.3 above.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Monitoring

The study will be monitored to ensure that the study is conducted and documented properly according to the protocol, GCPs, and all applicable regulatory requirements.

On-site visits will be made at appropriate times during the period of the study. Monitors (eg, 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.

13.2 Protocol Amendments and Deviations

13.2.1 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/EC approval, except when necessary to eliminate apparent immediate hazards to the subjects. If a protocol change is implemented immediately to protect the subjects, the IRB/EC 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.

13.2.2 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.

13.3 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.

13.4 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.

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ATTACHMENT 1: BECLOMETHASONE – 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.

ATTACHMENT 2: RADIATION ASSOCIATED WITH CT SCANS

CT scans are required at Baseline and Week 24/ET to evaluate eligibility criteria and primary and secondary endpoints. All CT scans will be sent to a central imaging core lab for review and analysis.

Radiation due to the CT scans required for this study is a risk to the subjects enrolled in this study. The expected dosing for each modality/view is shown below.

MODALITY: VIEW	SCREENING (MSV)	WEEK 24 / DELAYED WEEK 24 (MSV)	TOTAL (MSV)
Thin-Slice CT	2.0	2.0	4.0

The total estimated radiation dose for a subject that undergoes all study-required imaging is expected to be approximately 4 millisievert (mSv) (American Nuclear Society). Based on a large study of cancer risk associated with exposure to radiation, it was estimated that the excess relative risk for cancer is 0.97 per Sv (Cardis et al, 2005). The excess relative risk of the radiation that each subject would receive from participation in this study is therefore 0.97/Sv * 4 mSv * 1 Sv/ 1000 mSv=0.0039. To help place the radiation risk estimate for this study into perspective, a person will be exposed to 0.03 mSv of radiation during a typical coast-to-coast round-trip airplane flight (Radiologyinfo.org), and the public is exposed to approximately 3 - 6.2 mSv / year from background radiation (Huda et al, 2005 and United States Environmental Protection Agency).

ATTACHMENT 3: 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 (Baseline/Day 1) nasoendoscopy for a subject, the same must be used for the Week 24/Visit 6/ET examination. The investigator will use the information from the nasal examination worksheet to complete the nasal examination, and concomitant medication CRFs.

EPISTAXIS

- Non-active bleeding, but evidence of recent bleeding (eg, 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
        - – diameter of perforation
- Is the septal erosion/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

MUCOSAL CANDIDIASIS

- evidence of tightly adhered white material that does not scrape off

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