Anti-Inflammatory Agent in Sinusitis

A Phase IIa, single-center, randomized, placebo-controlled, double-blind study to assess the efficacy of CRTh2 Antagonist AZD1981 in patients with Chronic Rhinosinusitis with Nasal Polyps (CRSwNP).

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PROTOCOL SYNOPSIS

Version	Version 6.0 dated April 5, 2018
Title	A Phase IIa, single-center, randomized, placebo-controlled, double-blind study to assess the efficacy of CRTh2 Antagonist AZD1981 in patients with Chronic Rhinosinusitis with Nasal Polyps (CRSwNP).
Short Title	AZD1981 in CRSwNP
Protocol Number	AP20151107
Study Drug	AZD1981
Clinical Phase	Phase IIa
Principal Investigator	Anju Peters, MD Northwestern University Department of Medicine Division of Allergy-Immunology 211 East Ontario St., Suite 1000 Chicago, IL 60611
Primary Objective	To evaluate the efficacy of AZD1981 compared with placebo in relieving signs and symptoms of disease in patients with Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) poorly controlled on intranasal steroid therapy.
Study Design	This is a Phase IIa, single-center, randomized, placebo-controlled, double-blind study that includes 12 weeks of treatment with AZD1981 (40 mg TID) or placebo TID administered orally as an add-on therapy to intranasal corticosteroids (INS). All subjects will be ≥18 years, have chronic rhinosinusitis with nasal polyps (CRSwNP) with persistent symptoms despite daily treatment over ≥ 6 weeks with intranasal corticosteroid, and have failed one or more courses of oral steroids (typically 0.5mg/kg for one to two weeks). All subjects will have a total nasal polyp score by nasal endoscopy (summation of both nasal cavities) $\geq$ 4 with at least a score of 2 in each nasal cavity. All subjects will have the presence of at least two of the following symptoms prior to screening: nasal blockade/obstruction/congestion; nasal discharge (anterior/posterior nasal drip), facial pain/pressure; reduction or loss of sense of smell.

The study will enroll approximately 60 patients (30 per arm placebo and AZD1981) and will consist of **three phases:**

1. Screening and Run-in (-3 weeks to Day 0)

2. Double-Blinded, Randomized Treatment Period (Day 0 – Week 12)

3. Washout (Week 13-16)

During the **screening period**, each patient's eligibility for the trial will be established. To be eligible at the screening visit (Week 0), patients:

1. Must be ≥18-70 years of age

2. Must have a diagnosis of CRSwNP based on a prior standard of care sinus CT scan and/or endoscopy

3. Must have the presence of at least two of the following symptoms prior to screening: nasal blockade/obstruction/congestion; nasal discharge (anterior/ posterior nasal drip); facial pain/pressure; reduction or loss of sense of smell

4. Must have CRSwNP with persistent symptoms despite daily treatment over ≥ 6 weeks with intranasal corticosteroid spray (fluticasone propionate, fluticasone furoate, mometasone furoate, ciclesonide, budesonide, triamcinolone, or beclomethasone), and have failed one or more courses of oral steroids (typically 0.5mg/kg for one to two weeks)

5. Must have a total nasal polyp score by nasal endoscopy (summation of both nasal cavities) $\geq$ 4 with at least a score of 2 in each nasal cavity during a prior standard of care visit in the 1 month prior to screening.

During the 3 week run-in period (Week-3 to Day 0), patients must remain on a stable dose of INS (fluticasone propionate, fluticasone furoate, mometasone furoate, ciclesonide, budesonide, triamcinolone, or beclomethasone) of 2 actuations in each nostril once a day.

Randomized double blind placebo controlled treatment

At Day 0 of **treatment**, eligible patients will be randomly allocated (in a 1:1 ratio) to receive one of the two treatments: AZD1981 at a dose of 40 mg TID or matched placebo for a total of 12 weeks. Efficacy data will be collected. The primary endpoint will be measured at Weeks 4, 8, 12, and 16.

For the duration of the 12 week treatment period, patients must remain on 2 actuations of their prior standard of care INS (fluticasone

propionate, fluticasone furoate, mometasone furoate, ciclesonide, budesonide, triamcinolone, or beclomethasone) QD.

After completion of the 12 week treatment period, all patients will be followed for an additional 4 weeks during a **wash-out** (Week 13-16) to collect additional efficacy (persistence of cellular and clinical phenotype) data. They will continue their INS during the wash-out phase.

Patients with a clinical diagnosis of co-morbid asthma at screening will be asked to maintain their usual asthma medications, including but not limited to long-acting beta agonists and inhaled corticosteroids. Starting a leukotriene modifier treatment will not be permitted during the randomized period. The treating physicians will manage asthma exacerbations as necessary.

Patients who require oral steroids to treat persistent/worsening disease will be discontinued from the study.

Study Duration

5 months (including recruitment)

Primary Endpoints

1. Change in Total Polyp Score (TPS) from baseline. TPS is the sum of both nostrils as evaluated by nasal endoscopy. Polyp size will be scored for each nasal cavity from 0 to 4 (Total score 0-8) (Table 1).

Secondary Endpoints

1. Change in total nasal symptom (TNSS) score from baseline. Subjective nasal symptoms will be recorded by using visual analog scores (VAS). Scores range from 0 to 10 cm with lower scores indicating milder symptoms (Table 2, page 23).

2. Change in sinus CT score from baseline as assessed by the Lund-Mackay scoring system (Table 3, page 23).

3. Change in Peak Nasal Inspiratory Flow (PNIF) from baseline.

4. Change in sinonasal outcome test (SNOT)-22 from baseline (Appendix 2). SNOT-22 contains 22 questions on sinonasal quality of life related items. Scores range from 0 to 110, with higher scores indicating poorer outcomes and with 8.9 as the minimally clinically important difference between scores.

5. Change in Brief Smell Identification Test (B-SIT) from baseline (Appendix 3). B-SIT will objectively assess olfaction, as smell loss is common and a bothersome in patients with CRSwNP. The B-SIT is a validated 12-item, standardized, quantitative test of olfaction. Higher scores indicate better olfactory function while lower scores represent olfactory dysfunction.

Exploratory Endpoints

1. Change from baseline in soluble inflammatory mediators. Nasal lavage fluid (NLF) will be collected and tested for type 2 inflammatory mediators (eotaxin 3 and periostin), products of T cell activation (e.g. IL-5 and IL-13) and well as products of eosinophil activation and degranulation (e.g. ECP and EPX). Urine will be collected for measurement of LTE_4.

2. Change in Forced Expiratory Volume in 1 second (FEV_1) from baseline.

3. Change in Asthma Control Questionnaire (ACQ5) from baseline (Appendix 4). The questionnaire is comprised of 5 questions that are assessed on a scale from 0-6, where 0 represents good asthma control and 6 represents poor astma control. The overall score is the mean of the responses and the minimal important difference is defined as a change in score of 0.5.

Safety Outcome Measures

The safety of AZD1981 will be assessed using the following outcome measures: incidence and severity of treatment-emergent adverse events and serious adverse events, clinical laboratory measures, and vital signs. In particular we will measure CBC with differential at Week 4, 8, 12, and 16 and liver and renal function tests at Week -3, 2, 4, 8, 12 and 16 based on past trial experience of dose-related toxicity.

Pharmacokinetic Outcome Measures

Plasma samples will be collected for total AZD1981 plasma concentrations and transported to Astra Zeneca at week 8, 12, and 16.

Inclusion Criteria

1. Male or female, age 18-70.

2. Females must be surgically sterile or postmenopausal or using a highly effective form of birth control such as an estrogen containing combined oral contraceptive, progesterone-containing contraception, or double barrier method contraception condom with spermicide or copper banded intrauterine device. Females in certain categories (not sexually active, vasectomized partner, tubal occlusion) will be admitted at the discretion of the investigator on a case-by-case basis.

3. Females must have a negative urine pregnancy test at screening unless documented to have a hysterectomy or be postmenopausal.

4. History of moderate to severe CRSwNP (diagnosed at prior standard of care visit by endoscopy and/or a sinus CT scan) with presence of at least two of the following symptoms: nasal blockade/obstruction/congestion; nasal discharge (anterior/posterior nasal drip), facial pain/pressure; reduction or loss of sense of smell.

5. Poorly controlled by steroidal standard of care at the time of screening, as defined by persistent symptoms despite daily treatment over ≥ 6 weeks with intranasal corticosteroid (fluticasone propionate, fluticasone furoate, mometasone furoate, ciclesonide, budesonide, triamcinolone, or beclomethasone) and having failed one or more courses of oral steroids.

6. Must have a total nasal polyp score by nasal endoscopy (summation of both nasal cavities) ≥ 4 with at least a score of 2 in each nasal cavity in the month prior to V0 (Table 1, page 22).

7. The ability to give informed consent and comply with all study procedures.

Exclusion Criteria

1. Pregnant females or females with plans to become pregnant or breastfeed during the duration of the study.

2. Inability or unwillingness of a participant to give written informed consent or comply with study protocol.

3. Use of any investigational drugs within 30 days of screening.

4. Oral or systemic steroids within 2 weeks of screening or at any time during the screening or run-in. One single course of oral steroids (≤ 0.5mg/kg/day) for up to 5 days will be permitted for asthma exacerbation during the randomization period and the following scheduled visit will be pushed out by 2 weeks.

5. Inability to comply with informed study protocol.

6. Any clinically relevant abnormal findings in clinical chemistry, hematology, urinalysis, physical examination, pulse, blood pressure, at screening which, in the opinion of the investigator, could put the patient at risk because of his/her participation in the study.

7. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with the study requirements or may compromise the quality of the data obtained from the study.

8. Previous anaphylaxis to AZD1981.

9. Acute infection needing antibiotic treatment at screening.

10. Nasal-sinus surgery within the previous 6 months.

11. Use of new leukotriene antagonists/modifier within 2 weeks of screening.

12. SNOT-22 <7 (appendix 2).

13. Patients with asthma are excluded if an exacerbation requiring systemic (oral and/or parenteral) steroid treatment or hospitalization for treatment of asthma has occurred within 2 weeks prior to screening, or are on maintenance doses of oral corticosteroids, or FEV1<50% of predicted or less.

14. Omalizumab within 3 months of visit 1.

15. History of Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis), cystic fibrosis or primary ciliary dyskinesia disorder.

16. On aspirin (>325mg) for Aspirin Exacerbated Respiratory Disease.

17. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy during the study.

18. Recent history of drug or alcohol abuse (within 3 years prior to Visit 1).

19. Contraindications to INS.

Safety Plan

1. Patient will be instructed to recognize the signs and symptoms of any severe hypersensitivity reaction, and to contact a healthcare provider in case of any such symptoms.

2. Individual patient unblinding may be conducted if safety considerations warrant. During the course of the study, a treatment assignment should be unblinded only in the case of a life-threatening medical emergency, or in the event of an unexpected serious event judged by the investigator as related to the study drug. Unblinding will be implemented following agreement by both the investigator and Medical Monitor.

3. Safety data including laboratory tests will be reviewed internally on a periodic basis during the study.

4. Patients with co-morbid asthma may experience serious exacerbations as part of their symptoms and emergent use of systemic corticosteroids maybe indicated. Patients who require treatment with systemic corticosteroids greater than one single course of oral steroids ($\leq$ 0.5mg/kg/day for up to 5 days) will be discontinued from the study and followed for safety assessment for the remainder of the study. Patients will be provided emergency contact information and advised to contact a physician during the entire trial, in case of severe asthma exacerbation.

Investigational Product(s)/Intervention(s), Dosage and Mode of Administration	Patients will receive the study drug (AZD1981 or placebo, supplied by Astra Zeneca), which is administered orally. AZD1981 is a white pill. The placebo contains the same ingredients as the AZD1981 with the exception of the active compound. Study drug will be supplied in a blinded fashion. Three doses will be given daily (40 mg).
Study Procedures	1. Phlebotomy 2. Nasal Endoscopy 3. Sinus CT 4. Peak Nasal Inspiratory Flow 5. Brief Smell Identification Test 6. Spirometry 7. Allergy skin testing
Statistical Considerations	The trial design is a continuous outcome superiority trial with primary efficacy outcome measure of change in Total Polyp Score (TPS) from baseline (V1) to the completion of the treatment phase 1 (V5). Total polyp score is a standardized method for assessing nasal polyp size by endoscopy, based on a scale of 1-4 per side. Inclusion criterion for this study is a TPS of ≥4 with a maximum of 8 and a standard deviation ± 2. A clinically meaningful effect is considered to be a decrease in total polyp score of 1.5 (Table 1, page 22). The analysis of the primary outcome measure will consist of treatment comparisons made using analysis of covariance (ANCOVA); pairwise comparisons for assessing differences between treatment arms will be performed using two treatment groups at a time.

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Glossary of Abbreviations

ACQ	Asthma control Questionnaire
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Amino Transferase
ANCOVA	Analysis of Covariance
AST	Aspartate Amino Transferase
ALP	Alkaline Phosphatase
BUN	Blood Urea Nitrogen
B-SIT	Brief smell identification test
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRSwNP	Chronic rhinosinusitis with nasal polyp
CRTh2	Chemoattractant receptor-homologous molecule on TH2
CTCAE	Common Terminology for Adverse Events
EBV	Epstein Barr Virus
ECP	Eosinophil cationic protein
EPX	Eosinophil peroxidase
FEV1	Forced expiratory volume in 1second
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
IDE	Investigation al Device Exemption
IL-5	Interleukin 5
IL-13	Interleukin 13
IND	Investigational New Drug
INR	International Normalized Ratio
INS	Intranasal steroid
IP	Investigational product
IRB	Institutional Review Board
Kg	Kilogram

LABA	Long acting Beta 2 Agonist
LTE_4	Leukotriene E4
MOP	Manual of Operations
NP	Nasal polyp
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamics
PK	Pharmacokinetic
QD	Once a Day
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvate Transaminase
Th2 cells	Type 2 helper T cells
SNOT-22	Sinonasal outcome test-22
TID	Three Times a Day
TPS	Total polyp score
ULN	Upper limit of Normal
VAS	Visual analog score

1. BACKGROUND AND RATIONALE

1.1 Background

Overview of CRSwNP

Chronic rhinosinusitis (CRS) is an inflammatory disease of the sinuses that affects over 12% of the U.S. population and accounts for almost $10 billion in annual direct healthcare costs (1, 2). In addition, CRS is associated with a significant negative impact on quality of life. Patients with CRS have symptoms including sinus pressure or pain, post nasal drainage, nasal blockage, anosmia or hyposmia and fatigue lasting more than 12 weeks in association with objective evidence of sinus inflammation on computed tomography (CT) scan and/or endoscopy (3). The initial treatment of CRS includes corticosteroids and antibiotics. If medical therapy fails, sinus surgery is recommended. CRS can be further divided into two subgroups based on the presence or absence of nasal polyps, CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP), respectively. CRSwNP has a prevalence of 2-4% in US and Europe and has a greater disease burden as this subgroup of CRS is often refractory to conventional medical treatment with corticosteroids and antibiotics and disease persists despite sinus surgery (4) (5). Interestingly, patients with CRSwNP are more likely to undergo revision sinus surgeries for disease management when compared to patients with CRSsNP. Finally, as many as 40-60% of CRSwNP patients are diagnosed with asthma and, conversely, patients with moderate to severe asthma have a higher prevalence of CRSwNP compared to those with mild asthma (6). Worsening of severe asthma is often related to CRS exacerbations, which adds to the morbidity and costs associated with CRS (7) (8). Taken together, CRSwNP is an aggressive form of CRS with substantial impact on QOL that is often resistant to medical and surgical treatment and, as such, there is an unmet need for novel therapies aimed at improving care of patients with CRSwNP.

Mechanism active in CRSwNP

Nasal polyps (NPs) are characterized by a pronounced tissue eosinophilia and a predominant type 2 inflammatory infiltrate comprised of mast cells, type 2 innate lymphoid cells (ILC2s), T helper type 2 (Th2) cells and basophils (9) (10) (11) (12) (13) (14) (15). These immune cells are capable of producing a variety of type 2 pro-inflammatory mediators that can perpetuate the ongoing inflammatory response observed in NPs. Of note, studies from our lab and others have shown elevations in levels of the classic type 2 cytokines, IL-5 and IL-13, as well as the eosinophilic chemotactic proteins, eotaxin-1, 2, and 3 in the nasal polyps and lavage fluid of patients with CRSwNP compared to sinonasal tissue and nasal lavage fluid from patients with CRSsNP and controls (15) (9). Prostaglandin D2 (PGD2) is another important inflammatory mediator elevated in nasal polyps (16). This arachidonic acid metabolite is produced mostly by mast cells and induces chemotaxis of inflammatory cells including TH2 cells, eosinophils, ILC2s, and basophils (16) (17, 18). PGD2 acts via 2 different receptors, one of which is chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells (CRTH2). This receptor is expressed on Th2 cells, ILC2 cells, eosinophils, and basophils, many of the inflammatory cells implicated in the pathogenesis of nasal polyps (18, 19). Signaling via CRTH2 mediates chemotaxis of the type 2 inflammatory cells, release of type 2 cyokines by ILC2s, and activation of eosinophils and Th2 cells (18) (20) (21). The biological actions of CRTh2 can be reduced via blocking the PGD2 binding site on the CRTh2 (22). Past studies have shown that sinus disease severity and a poor overall disease prognosis are associated with increased eosinophils in the sinonasal tissue (23) (24) (25) (26). Since PGD2, a known inducer of eosinophil chemotaxis and type 2 inflammation, is elevated in nasal polyps, we hypothesize that blocking PGD2 signaling with a CRTh2 antagonist will decrease the type 2 eosinophilic inflammation observed in nasal polyps and result in improved sinonasal symptoms in patients with CRSwNP.

Current approaches to CRSwNP and Unmet needs in CRSwNP-refractory patients

The current medical management of CRSwNP remains a challenge and there is a serious gap of new and effective medical treatment options for CRSwNP. Intranasal and oral corticosteroids are currently utilized to treat nasal polyps. At present, only one INS, Nasonex™ (mometasone furoate), is approved by the FDA for the treatment of nasal polyps, but its efficacy is modest (27). This is due to the fact that it is difficult for INS sprays to penetrate into the polyp mucosa to reduce inflammation, so polyps rarely regress with this treatment alone. Oral corticosteroids, although more effective than INS, offer only transient relief and are associated with serious side effects such as adrenal insufficiency and osteoporosis, limiting their use. Surgery is recommended for patients with CRSwNP who fail medical therapy however, up to 50% of CRSwNP patients with eosinophilia have disease recurrence and almost 12% need revision surgery by 36 months (28). Given that patients are poorly responsive to INS, systemic corticosteroids provide short term benefit with a potential for long term adverse effects, and because surgery is not uniformly effective, there remains an unmet need for a new treatment for CRSwNP. Mucosal-based eosinophilia has been shown to directly correlate with sinus disease severity as observed by sinus CT and endoscopy, and is associated with a poor prognosis after surgery including a significant negative impact on QOL outcomes and higher rates of polyp recurrence (24-26). The lack of a drug that effectively treats the type 2 eosinophilic inflammation in nasal polyps is a critical shortcoming in the treatment of CRSwNP. Understanding the inflammatory pattern of CRSwNP and biomarkers that characterize an effective treatment approach against the type 2 inflammation that includes ILC2s, eosinophils, basophils, and mast cells will represent a substantial development in the targeted pharmacologic management of patients with CRSwNP.

1.2 Rationale for Selection of Study Population

We aim to examine the added effects of a CRTh2 antagonist in CRSwNP subjects with moderate to severe disease not controlled on treatment with steroid-based standard of care due to an unmet medical need in this population.

1.3 Investigational Product(s) (IP) /Intervention(s)

AZD1981 is an oral, potent, selective, reversible antagonist of CRTh2 that has been evaluated by Astra Zeneca in 18 clinical studies, including Phase II trials in asthma.

1.4 Rationale for Selection of Investigational Product(s)/Intervention(s) and Regimen

CRTh2 is expressed on many of the inflammatory cells implicated in allergic airway inflammation such as asthma, including Th2 lymphocytes, eosinophils, and basophils (18, 19). The biological consequences of CRTh2 activation include eosinophil shape change, basophil degranulation, Th2 cytokine production, upregulation of adhesion molecules, and chemotaxis of eosinophils, basophil and Th2 lymphocytes(19) (18). Stimulation of CRTh2 is expected to induce the recruitment of these cells into the site of PGD2 accumulation as well as to induce eosinophil and Th2 cell activation and to inhibit apoptosis of Th2 cells (21) (20).

We propose to use AZD1981 in subjects with CRSwNP who are otherwise uncontrolled on first-line intranasal corticosteroid therapy and have failed at least one course of oral steroids. The nasal polyp pathology of CRSwNP shows elevations in not only the number of mast cells but also the levels of PGD_2 in nasal polyp tissue when compared to healthy controls (12, 16). The

chemotactic effects of PGD2 are mediated through engagement with its receptor CRTh2. This G-protein coupled receptor is expressed on the surface of eosinophils, basophils, ILC2s, and Th2 cells. Through this interaction, studies have shown that PGD_2 can promote eosinophil and Th2 cell accumulation in areas of inflammation. Th2 cells can then become activated and secrete pro-inflammatory cytokines including IL-5 and IL-13. Additionally, recruited eosinophils can activate and degranulate releasing their granular proteins including eosinophil cationic protein (ECP) and eosinophil peroxidase (EPX). Recent studies have also demonstrated that CRTh2 interaction with PGD_2 leads to ILC2 chemotaxis and type 2 cytokine release from ILC2 cells (20). The inflammatory environment in CRSwNP is characterized by a type 2 inflammatory response consisting of elevated eosinophilic chemokines, eosinophils, and eosinophilic degranulation products (ECP and EPX), Th2 lymphocytes and type 2 cytokines such as IL-5, basophils and mast cells (9, 10, 12). In addition, ILC2 cells, the key component in innate immunity that release type 2 cytokines are elevated in NP as well. Furthermore, CRTh2 expression has been observed on eosinophils, Th2 lymphocytes and ILC2s in NP tissue (14, 19). We have recently confirmed the presence of CRTH2 gene expression on NP tissue (unpublished data by A. Kato et al.). These findings suggest that the PGD2/CRTh2 pathway may contribute to the known type 2 inflammatory environment observed in CRSwNP. Functionality of the PGD2/CRTh2 pathway has been demonstrated in a small study using a nasal polyp explant system (17). In this study, incubation of nasal polyp tissue with IgE/anti-IgE led to increased production of PGD2 and enhanced expression of its receptors. The study also showed that the CRTh2 pathway was involved in the chemotaxis of human Th2 cells in the supernatants from nasal polyp tissue.

Our proposed hypothesis is that AZD1981 in CRSwNP will reduce CRTh2-expressing leukocyte recruitment to the nasal polyp and nasal mucosa and will reduce leukocyte activation through CRTh2, thus reducing the signs and symptoms of CRSwNP refractory to control with steroids.

A CRTh2 antagonist has the potential to impact CRSwNP patients in the following ways:

1. The quality of life impairment in CRSwNP is pronounced with higher bodily pain and decreased social function compared to chronic diseases that are considered more serious than CRS such as congestive heart failure, chronic obstructive pulmonary disease (COPD), and angina (27);

2. CRS has significant negative economic impact. With almost 12% of the US population suffering from CRS, it is estimated that the overall annual economic burden of CRS in the United States is about $22 billion (1). A significant portion of this cost is related to medication usage without clear evidence of effective symptom control, leading to the need for sinus surgery, each costing about $8,000 US dollars. It is estimated that over 500,000 sinus surgeries are done annually for refractory CRS, contributed to by the high rate of recurrence in patients after surgery who return to steroid-based medical management that is ineffectual.

3. Current therapy options in uncontrolled patients are off-label and include the use of corticosteroids with greater risks to patients and potential for significant toxicity (diabetes, osteoporosis, cataracts, glaucoma, avascular necrosis of hips).

1.4.1 Preclinical Studies

Relevant preclinical studies of AZD1981 have provided evidence that AZD1981 blocks CRTh2-mediated shape change in human eosinophils and basophils in blood, blocks CRTh2 mediated chemotaxis of human Th2 cells and eosinophils.

1.4.2 Clinical Studies

AZD1981 has undergone extensive clinical trials in subjects with allergic asthma but is not currently FDA approved for this indication. In the 17 clinical studies completed to date, AZD1981 was generally well tolerated (AZ Investigator's Brochure, version 10). The clinical efficacy of AZD1981 in asthma has been evaluated in 3 randomized, double-blind, placebo-controlled studies. Two of the studies were 4-week studies; the third was a 12-week study. The first 4-week study in asthma patients withdrawn from their ordinary low-dose inhaled corticosteroid (ICS) treatment, indicated a positive effect on morning peak expiratory flow (PEF) (primary variable). Differences between treatment groups for secondary variables (lung function, reliever use and asthma symptoms) were small, but generally in favor of AZD1981. The second 4-week dose-finding study, in asthma patients not adequately controlled on their current ICS treatment, found no statistically significant effect of AZD1981 on morning PEF (primary variable). However, secondary efficacy variables measured in the clinic (forced expiratory flow in 1 second [FEV1] and Asthma Control Questionnaire [ACQ] results) showed clinically relevant improvements over placebo. The positive clinical effects of AZD1981 on both lung function and asthma control were almost exclusively seen in the atopic (allergic) subgroup. The 12-week dose-finding study of AZD1981 as add-on therapy in atopic asthma patients uncontrolled on low-dose inhaled corticosteroids (ICS) and long –acting-b2-agonists (LABA) did not significantly change pre-dose, pre-bronchodilator FEV1 (primary variable) or any other efficacy outcome compared t placebo in atopic asthma patients treated with ICS/LABA. AZD1981 has also been tested in COPD. However, neither of the 2 completed 4-week studies in COPD patients showed any indication of clinical efficacy and the current focus in clinical development of AZD1981 at Astra Zeneca has been allergic diseases such as asthma and urticaria.

1.5 Risks

1.5.1 Risks of Investigational Product(s)/Intervention(s)

AZD1981: In studies in healthy volunteers as well as in studies in patients with asthma and COPD, a small number of subjects had transient elevations of hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and/or alkaline phosphatase), abnormal renal function (elevated creatinine and BUN, decreased GFR), abnormal urine routine (presence of blood, elevated WBC, urine protein), raised WBC count, decreased blood albumin, skin eruptions (over back, abdomen and skin folds), fever, dizziness and headache. All the events subsided with stoppage of IMP. There were no other identified safety concerns based on adverse event (AE) reporting, and no consistent clinically relevant changes in safety laboratory variables, vital signs, electrocardiogram (ECG) results, or physical examination findings were observed in the 17 clinical studies completed to date using AZD1981 (AZ investigator's Brochure, version 10). The thorough QT study has confirmed that there are no effects on cardiac repolarization.

1.5.2 Study Procedures and Risks

Phlebotomy: May cause pain, bruising, infection, light-headedness and fainting. The maximum blood that would be drawn in a 2-month period in the primary outcome study is 66 mL (less than 5 tablespoons total) over six blood draws. Liver and renal function tests will be drawn at baseline for safety monitoring and at the end of week 2, 4, 8, 12, and 16. CBC with differential, comprehensive chemistry (renal and liver function) will checked at screening and at V2 (week 2), V3 (week 4), V4 (week 8), V5 (week 12), and V6 (week 16). Plasma will also be sent to Astra Zeneca for PK studies at Week 8, 12, and 16.

Allergy Skin Testing: May experience swelling, itching and redness at the site where the skin is pricked by the needle. There is also a remote possibility of a generalized reaction to the allergy skin tests. Reactions could include hives, hay-fever symptoms, difficulty breathing, and rarely feeling faint or dizzy. Participants will be evaluated for environmental allergies using skin prick tests. The skin prick test consists of putting a drop of the allergen (*e.g.* pollen, animal dander) on the skin (forearm) and pricking the skin lightly with a needle. If the subject is allergic, they will develop a small welt similar to a mosquito bite. For prick skin tests, we use 24 standard allergens. We also include 2 control tests, histamine and saline, which serve as positive and negative controls respectively.

Nasal Endoscopy: May cause sense of pressure or tickling in the nose. In rare instances, subjects may have an allergic reaction to the sprays used before the nasal endoscopy. These reactions usually occur in patients who have had exposure to the spray multiple times in the past. If a reaction occurs, subjects may develop a rash, itching, or have some swelling. This is a routine procedure that allows physicians to evaluate nasal passages and tissues around the sinus openings. An anesthetic spray (tetracine hydrochloride) will be applied to the inside of the subject's nose before the subject is examined. The maximum dose will be no more than 20 mg. This procedure will take approximately 30 minutes to complete.

Sinus CT scan: The radiation dose received from this protocol (2 CT scans), is approximately equal to 50 days of background radiation. A CT scan will be performed at Day 0 and at 12 weeks to evaluate how a participant's sinus disease improves over the course of treatment with AZD1981. This will be performed in the Otolaryngology Clinic using a cone-beam CT scan. The CT scans are important objective measure for assessing disease burden as it is unaffected by subjective symptom reporting. The scanner utilized is a Xoran X-cat open frame scanner and is not an enclosed ring like the traditional CT scan. For research related CT scans, the CT scan will only be interpreted by the investigators (and not a radiologist). We will utilize a protocol, which exposes subjects to the lowest possible dose of radiation in order to obtain a CT scan suitable for assessment of CRS status. Using this protocol, participants will be subjected to radiation exposure of 0.04mSv, which is comparable to a chest X-ray. The cone-beam CT scan enables sinus CT scans to be obtained at a significantly lower radiation dose than a conventional CT scanner. The subject may need further imaging if any unexpected findings are found on the CT scan.

Nasal lavage: This procedure is routinely used as treatment for some patients with chronic rhinosinusitis. Other than the sometimes unpleasant sensation of water in the nose, there are no significant risks to this procedure. Participants will be asked to provide nasal lavage fluid. For this, 5mL of pre-warmed lactated Ringer solution (Kendall McGaw Laboratories, Irvine, CA) will be instilled into each nostrils with a syringe while the head is extended. Then, after approximately 10 seconds, the subject will tilt their head downward expelling the solution into a plastic collecting basin. The specimens will be stored in the Allergy-Immunology Research Laboratories on the McGaw Mezzanine at -80°C for assays per manufacturer's instructions (IL-5, IL-13, eosinophil cationic protein [ECP], eosinophil peroxidase [EPX], periostin, eotaxin 3).

Spirometry: This test may cause a cough or temporary feeling of lightheadedness. These symptoms typically resolve shortly after the test is finished. Participants will be asked to have their pulmonary function measured by spirometry. For this breathing test, subjects will be asked to breathe hard and quickly into a machine, called a spirometer. This machine measures how fast and how much air moves out of the lungs over a period of time. Subjects may be asked to blow into the spirometer several times. This test can take up to 15 minutes to complete.

Peak Nasal Inspiratory Flow*:* May cause temporary feeling of lightheadedness which typically resolves shortly after the test is finished. Participants will be asked to have their nasal inspiratory flow measured. For this upper airway breathing test, subjects will place a mask over their nose and mouth that forms a seal with their face. This mask is connected to a special meter such that when they sniff hard and quickly, the meter will determine their nasal inspiratory flow. Subjects may be asked to sniff into the mask several times for an accurate reading. This test can take up to 10 minutes to complete.

Questionnaires*:* Questionnaires may be perceived as intrusive and/or tedious. Participants will complete sinusitis, asthma, and allergy questionnaires including the Sino-Nasal Outcome Test (SNOT-22) and Asthma Control Questionnaire (ACQ5). These are a series of questions about whether subjects have sinus symptoms, if they have had any previous evaluations or treatments, and how well they feel their asthma is controlled. The questionnaires also include questions on quality of life. Overall, completing a questionnaire usually takes 15 minutes.

Smell tests: Some odors used in the B-SIT may be perceived as unpleasant. Participants will undergo evaluation with a clinically validated. Brief Smell Identification Test (B-SIT). The B-SIT is a validated 12-item, standardized, quantitative test of olfaction with high test-retest reliability and is highly correlated with more sophisticated measures of olfactory dysfunction. Each smell test will take approximately 20 minutes to complete.

1.5.3 Risk of Concomitant Medications, Prophylactic Medications and Rescue Medications

Intranasal steroid (concomitant medication allowed during study) may cause nasal irritation.

1.6 Benefits

1.6.1 Benefits of Investigational Product(s)/Intervention(s)

The patients treated with AZD1981 may experience decreased polyp size and nasal symptoms associated with nasal polyps. The patients may also notice improvement in asthma if they also have asthma in addition to the CRSwNP. It is not known if these benefits will be maintained after treatment. The placebo group has no potential clinical benefits.

1.6.2 Benefits of Study Procedure(s)

There are no known benefits of the study procedures (phlebotomy, nasal endoscopy, nasal lavage, smell test, and spirometry) in the general population or in participants with CRSwNP. The participant may gain knowledge about their disease.

2. OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of AZD1981 compared with placebo in decreasing polyp size as measured by the TPS in patients with intranasal corticosteroid refractory chronic rhinosinusitis with nasal polyps.

2.2 Secondary Objectives

1. To evaluate the clinical efficacy of AZD1981 by measuring improvement in nasal symptoms by visual analog scores (VAS), radiographic improvement in CRSwNP by Sinus CT scan and nasal patency by quantifying nasal peak inspiratory flow.

2. To evaluate the improvement in sinonasal quality of life benefit provided by treatment of refractory CRSwNP with AZD1981 by measuring SNOT-22 (appendix 2). In addition, we will objectively assess olfaction via B-SIT (appendix 3).

2.3 Exploratory Objectives

1. To evaluate the efficacy of AZD1981 in asthma in patients with coexistent CRSwNP and asthma by assessing lung function and asthma control based on ACQ5 (Appendix 4).

2. Measure markers of eosinophilic type 2 inflammation that are targeted by CRTH2 inhibition. We will measure ECP, EPX, IL-5, IL-13, eotaxin 3, and periostin in the nasal lavage fluid. In addition, we will measure urinary LTE4 to assess change in the PGD2 pathway.

3. STUDY DESIGN

This study is a Phase IIa, single-center, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of an orally administered AZD1981 as add-on therapy for the treatment of adult patients (18-70 years old) who have been diagnosed with CRSwNP either by endoscopy and/or sinus CT scan and remain symptomatic despite treatment with therapeutic doses of INS. All participants will have CRSwNP and will have been on INS (fluticasone propionate, fluticasone furoate, mometasone furoate, ciclesonide, budesonide, triamcinolone, or beclomethasone) for at least 6 weeks and failed one or more courses of oral steroids. All participants will have a baseline TPS of 4 or greater with at least a score of 2 in each nasal cavity despite treatment with standard doses of INS during a prior standard care of visit. The TPS measures size of nasal polyps by endoscopy and is the summation of both nasal cavities. In addition, the participants must have at least two of the following symptoms prior to screening: nasal congestion/blockage/obstruction; nasal discharge (anterior/posterior nasal drip); facial pain/pressure or reduction/loss of smell.

This study will enroll 60 patients (30 per arm placebo and AZD1981) and will consist of 3 phases.

1. **Screening and run-in (week -3 to Day 0)**

   During the screening, each patient's eligibility for the trial will be established. To be eligible, patients:

   A. Must have an endoscopy total polyp score (TPS) $\geq$ 4 with at least a score of 2 in each nasal cavity during a prior standard care of visit within the month prior to screening. The TPS measures size of nasal polyps by endoscopy and is the summation of both nasal cavities (Table 1, page 22).

   B. Must have presence of at least two of the following symptoms prior to screening: 1. Nasal congestion/blockage/obstruction; 2. Nasal discharge (anterior/posterior nasal drip); 3. Facial pain/pressure; or 4. Reduction or loss of smell.

   C. Must have been on 2 actuations of INS in each nostril daily for at least 6 weeks prior to the screening visit. Approved agents include: fluticasone furoate, fluticasone propionate, triamcinolone acetonide, mometasone furoate, budesonide, ciclesonide, or beclomethasone.

   D. Must be willing to fill out questionnaires

   E. During the 3 week run-in period (Week-3 to Day 0), patients must remain on their prior standard of care INS (fluticasone furoate, fluticasone propionate, triamcinolone acetonide, mometasone furoate, budesonide, ciclesonide, or beclomethasone) of 2 actuations in each nostril once a day.

2. **Double-Blinded, Randomized Treatment Period (Day 0 to Week 12)**

   At Day 0 of treatment, eligible patients will be randomly allocated (in a 1:1 ratio) to receive one of the two treatments: AZD1981 at a dose of 40 mg TID or matched placebo for a total

of 12 weeks. Efficacy, safety, pharmacokinetic (PK), and pharmacodynamics (PD) data will be collected. The primary end points will be measured at Weeks 4, 8, 12 and 16. For the duration of the 12-week treatment period, patients must continue their prior standard of care INS (fluticasone furoate, fluticasone propionate, triamcinolone acetonide, mometasone furoate, budesonide, ciclesonide, or beclomethasone), 2 actuations each nostril QD and those with asthma will continue their pre-determined asthma treatment.

3. **4 Week Washout**

After completion of the 12 week treatment period, all patients will be followed for an additional 4 weeks during a placebo wash-out to characterize the PK and PD properties of AZD1981 and to collect additional efficacy and safety data. The participants will remain on their INS 2 actuations each nostril QD.

Patients who require treatment for persistent or worsening sinus disease or oral steroids for asthma exacerbation will be discontinued from the study.

3.1 Study Endpoints

3.1.1 Primary Endpoint

The primary endpoint will be change in endoscopic polyp size as measured by the TPS from baseline (Day 0) size to week 12 in the treatment period. The TPS obtained at randomization (V1) will be used as the baseline.

Table 1. Endoscopic Total Polyp Score (TPS)

Polyp score	Polyp size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching the lower border of the middle turbinate or polyp medial to the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity

3.1.2 Secondary Endpoints

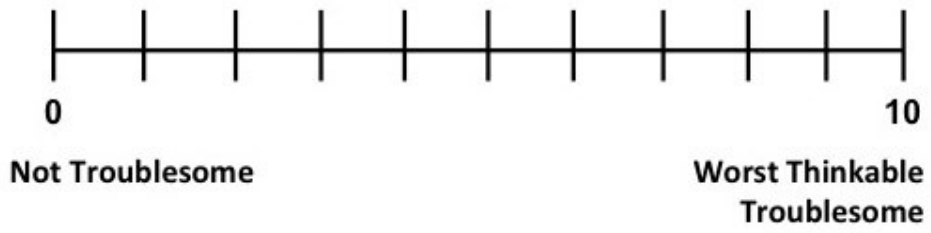
Change from baseline at Week 12 in:

1. Nasal symptoms as measured by visual analog scores (VAS) from baseline to week 12 in the treatment period. The score obtained at randomization will be used as the baseline.

Table 2. Visual analog scores (VAS) for nasal symptoms

VAS score	Severity of symptoms
0-3 cm	Mild
>3-7 cm	Moderate
>7-10 cm	Severe

Visual Analog Scale: How troublesome are your symptoms of rhinosinusitis currently? (Mark on line)



2. Sinus CT scan assessment by Lund-Mackay scoring system.

Table 3. Lund Mackay Sinus CT Staging System (29)

	Right	Left
Maxillary		
Anterior ethmoid		
Posterior ethmoid		
Sphenoid		
Frontal		
Osteomeatal complex		
Total (0-24)		

Scores each sinus: 0-2, osteomeatal complex: 0 or 2
0=Normal, 1=partial opacification, 2=total opacification
Interpretation of total score
1) Normal (score = 0)
2) Equivocal (score = 1 to 4)
3) Abnormal (score = ≥ 5)

3. Nasal patency as measured by PNIF (peak nasal inspiratory flow).

4. Patient reported symptoms as assessed by the 22-item Sinonasal Outcome Test (SNOT-22) (Appendix 2).

5. Smell test (B-SIT) (Appendix 3).

3.1.3 Exploratory Endpoints

1. Change from baseline at 12 weeks in asthma outcomes (lung function as measured by FEV1 and control [ACQ5; Appendix 4] in patients with coexistent CRSwNP and asthma.

2. Measure markers of eosinophilic type 2 inflammation that are targeted by CRTH2 inhibition. We will measure ECP, EPX, IL-5, IL-13, eotaxin 3, and periostin in the nasal

lavage fluid. In addition, we will measure urinary LTE4 to assess change in the PGD2 pathway.

3.2 Study Completion

This study will be considered “complete” when the primary, secondary and/or exploratory objectives have been met. This includes analysis of all the data required to meet the chosen objectives.

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 Inclusion Criteria

1. Male or female, ages 18-70 years old with CRSwNP diagnosed by a sinus CT scan and/or endoscopy during a prior standard of care visit.

2. Females must be surgically sterile or post-menopausal or using a specified acceptable form of birth control throughout the duration of the study, oral contraceptive, (i.e., double barrier method contraception (condom with spermatocide or copper banded intrauterine device)). Females in certain categories (non-sexually active, vasectomized partner, postmenopausal) will be admitted at the discretion of the investigator on a case-by-case basis.

3. Females must have a negative urine pregnancy test at screening unless documented to have a hysterectomy or postmenopausal.

4. A minimal endoscopy total nasal polyp score of 4 out of a maximum score of 8 for both nostrils (with at least a score of 2 for each nostril) during a prior standard care of visit within 1 month of screening despite completion of a prior INS treatment for at least 6 weeks before screening.

5. Presence of at least two of the following symptoms prior to screening: nasal obstruction/congestion; nasal discharge [anterior or posterior]; facial pressure/pain; or reduction or loss of smell.

6. Signed written informed consent.

4.2 Exclusion Criteria

1. Pregnant females or females with plans to become pregnant or breastfeed during the duration of the study.

2. Recent history of drug or alcohol abuse (within 3 years prior to Visit 1).

3. Inability or unwillingness of a participant to give written informed consent or comply with study protocol.

4. Use of any investigational drugs within 30 days of screening.

5. Use of oral corticosteroids (OCS) within 2 weeks before screening or are scheduled to receive OCS during the study period for another condition. One single course of oral steroids ($\leq$ 0.5mg/kg/day) for up to 5 days during the randomization will be permitted for asthma exacerbation and the following scheduled visit will be pushed out by 2 weeks.

6. Monoclonal antibody or immunosuppressive treatment within 3 months of screening.

7. Use of new leukotriene antagonists/modifier within 2 weeks of screening.

8. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy during the Screening Run-in Period or the Randomized Treatment Period.

9. Patients who have undergone any nasal surgery within 6 months before screening.

10. Patients who are on aspirin for desensitization (> 325 mg daily).

11. Acute infection needing antibiotic at the time of screening.

12. Ongoing rhinitis medicamentosa.

13. Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis), Young's syndrome, Kartagener's syndrome or dyskinetic ciliary syndromes, cystic fibrosis.

14. Patients with comorbid asthma are excluded if:
    A. Forced expiratory volume (FEV1) is 50% (of predicted normal) or less.
    B. An exacerbation requiring systemic (oral and/or parenteral) steroid treatment or hospitalization (>24 hour) for treatment of asthma has occurred within 2 weeks prior to screening.
    C. Are on maintenance doses of oral corticosteroids.

15. Uncooperative or any condition that could make the patient potentially non-compliant to the study procedures.

16. Any clinically relevant abnormal findings in clinical chemistry, hematology, urinalysis, physical examination, pulse, blood pressure at screening, which, in the opinion of the investigator, could put the patient at risk because of his/her participation in the study.

17. Contraindications to INS (refer to National Product labeling for all contraindications or warning/precaution of use related to INS).

18. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or may compromise the quality of the data obtained from the study.

19. Previous anaphylaxis to AZD1981

20. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy during the study.

4.3 Participant Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.

2. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.

3. The participant is “lost to follow-up” (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).

4. The participant dies.

5. The participant develops a medical condition or is initiated on new medication (s) not previously mentioned in the list of prohibited medications that, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant’s ability to comply with study requirements or may compromise the quality of the data obtained from the study.

6. The participant meets any of the individual stopping rules as delineated in Section 8.

7. Patient is non-compliant with study protocol in the judgment of the PI.

4.4 Management of Participant Withdrawal

Patients are at any time free to withdraw from study without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. Adverse events will be followed up (See Sections 8.1.4 and 8.1.5); the patient should return all study drugs. If possible, they will be seen and assessed by an investigator.

For patients withdrawn due to incorrect inclusion and for patients for whom the treatment code has been prematurely broken by the investigator, no further assessments will be performed except for the completion of the Follow-up Visit. This is done out of concern for the patients’ safety.

If a patient prematurely discontinues the study after randomization, the patient will be asked to complete Visit 6 at the time of discontinuation. For patient withdrawn due to study specific discontinuation criteria, see Section 4.3.

Withdrawn subjects will not be replaced.

4.5 Recruitment Methods

Potential subjects will be recruited through print advertising (e.g., flyers, posters at Northwestern Memorial Hospital and other affiliates, ads on transit lines), registries (e.g., Research Match, Illinois Women’s Health Registry), online advertising (e.g., social media) and referrals from physicians. Recruitment will continue throughout the trial until 60 patients are randomized into the trial.

Flyers and posters will be placed in the Allergy and Otolaryngology clinics at Northwestern Memorial Hospital.

EPAM is a company which advertises through social media (i.e. Facebook, Twitter, and Reddit) and targets individuals with chronic rhinosinutis or nasal polyps using the iSwarm system. Potential research subjects are sought out as pre-qualified clinical candidates in the iSwarm system by pooling user demographics, locations, and identified on line communities. Digital engagement strategies such Northwestern IRB-approved as banner ads, side panel ads and promoted messaging allows the potential subjects to contact the research team directly by taking a secure, confidential online pre-screening survey.

Research Match is a secure online, national recruitment tool that is maintained by Vanderbilt University. ResearchMatch.org allows researchers to conduct feasibility or recruit potential study participants. Participants who are interested and released their contact information to the study team will be contacted via telephone or email. If participants cannot be reached via telephone, the Research Match follow-up email will be sent to them.

The Illinois Women's Health Registry was established and overseen by Northwestern University's Women's Health Research Institute at the Feinberg School of Medicine to encourage investigator-initiated research targeting women's health. The role of the Registry is to facilitate the recruitment and identification of women who may be eligible to participate in IRB approved research being conducted at Northwestern University and other research institutions across the state of Illinois.

5. INVESTIGATIONAL PRODUCT

5.1 INVESTIGATIONAL PRODUCT(S) / INTERVENTION(S)

AZD1981 (Astra Zeneca) is a sterile, white pill.

AZD1981: Refer to Section 1.5, Section 1.6, and applicable product labeling for product description and for known and potential risks to human participants associated with the investigational product(s)/intervention(s).

Placebo: contains the same ingredients as the AZD1981 with the exception of the active compound.

5.2 Packaging and Labeling

Astra Zeneca will supply AZD1981 and matched placebo for this study in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The tablets will be packaged in child-resistant bottles. The patients will receive a four-week supply of the investigational product (IP) or placebo at dispensing visits. The labels will fulfill GMP Annex 13 requirements for labeling. Booklet labels will be used where applicable and label text will be translated into local languages.

5.3 Preparation, Administration, and Dosage

AZD1981 for oral administration will be available in tablet form. A pharmacist at the research pharmacy (Investigational Pharmacy, Northwestern Memorial Hospital, 251 E. Huron Street, LC700, Chicago, IL 60611) will dispense the study drug or placebo to subjects. Subjects and study team will be blinded to treatment assignment during trial. The drug will be self-administered by the subject.

AZD1981 tablets will be provided in 20mg strengths. All patients will take 2 tablets in the morning, 2 tablets in the afternoon, and 2 tablets in the evening of AZD1981 and/or placebo. The tablets should be swallowed whole with a glass of water.

5.4 Accountability of Investigational Products(s) / Intervention(s)

Under Title 21 of the Code 21 of the Code of Federal Regulations (21CFR§312.62) the investigator will maintain adequate records of the disposition of the investigational product(s)/intervention material(s), including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting, and a detailed accounting of any investigational products(s)/intervention material(s) accidentally or deliberately destroyed.

The study site will maintain records for records for receipt, storage, use, and disposition. A dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of investigational product(s)/intervention material(s) dispensed.

All records regarding the disposition of the investigational product(s)/intervention material(s) will be available for inspection by the FDA. All residual product(s) will be destroyed or retained for future in vitro studies.

5.5 Assessment of Compliance with Investigational Product(s)/Intervention Materials

All study drug supplies will be supplied at treatment facility. The pharmacy will keep records of doses dispensed.

5.6 Discontinuation of Investigational Product(s)/Intervention Material(s)

Refer to Section 4.3 and Section 8.

6. OTHER MEDICATIONS

6.1 Concomitant Medications

Concomitant medications may be used as follows: Leukotriene antagonists/modifier will be permitted during the study, as long as they were started at least 2 weeks prior to screening. Oral and topical antihistamines without decongestants at the current FDA-approved doses. Low dose estrogen containing oral contraception is permitted. Patients taking H2 blockers and proton pump inhibitors for gastroesophageal reflux disease will be permitted to continue their use during the study. Inhaled asthma controllers, including corticosteroids and quick relief inhalers such as albuterol or levoalbuterol are permitted during the study. Antihypertensives and cholesterol agents will be permitted as long as the doses and type of medication were stable for at least 6 weeks prior to screening. These diseases must be recorded as part of the medical history collected during the screening period. All concomitant medication and changes in treatment will be recorded in appropriate section. Normal nasal saline will be allowed during the study. Topical decongestants, e.g. Oxymetazoline hydrochloride (to reduce the swelling and widen the path for the endoscope), as well as a topical anesthetic e.g. Lidocaine are allowed before endoscopy.

6.2 Prophylactic Medications

None

6.3 Rescue Medications

None

6.4 Prohibited Medications

Oral corticosteroids will be prohibited at screening and run-in but may be allowed as a rescue medication. One single course of oral steroids (0.5mg/kg) for up to 5 days will be permitted for asthma exacerbation and the following scheduled visit will be pushed out by 2 weeks.

Starting a new leukotriene antagonists/modifier (e.g. montelukast) will not be allowed within 2 weeks of screening or during the treatment phases.

7. STUDY VISITS AND PROCEDURES

7.1 Enrollment and Randomization

A dedicated clinical study coordinator will be responsible for advertising, screening and consenting the study subjects. This research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any screening study procedures. Participants who are deemed eligible (See Section 4.1, 4.2, and 4.3) will be enrolled and assigned a unique participant number. The study will take place in the Department of Otolaryngology (675 North St. Clair, Galter 15, Chicago, IL 60611) and/or Division of Allergy-Immunology (675 North St. Clair, Galter 18-250, Chicago, IL 60611)

The clinical trial consists of three periods, using an add-on therapy approach to INS:

1. Screening and Run in period (3 weeks)
2. Randomized treatment period (12 weeks; Visits 1-5)
3. Post-treatment period (4 weeks; Visit 6)

The study visits occur on the planned dates (relative to the first dose), as scheduled. The visit schedule should be adhered to within the ± 4 day visit window.

If a patient is prematurely discontinued from treatment, all assessments planned at the End of Treatment visit should be performed.

Prior to all screening assessments, after discussion of participation in the study, the written consent form must be signed and dated.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than 1 site visit if necessary, as long as the screening visit window prior to Day 0 (V1) is respected. Patients that fail screening for exclusion criteria, for example concomitant medications, acute illness (upper respiratory tract infection), required drug-specific discontinuation periods or laboratory tests may be rescreened for study eligibility 1 additional time.

7.2 Screening

Visit 0 (D-21); Screening Run-in

1. Obtain informed consent document signed by participant and assign number.

2. Review inclusion and exclusion checklist.

3. Interview to collect patient demographic information, nasal polyposis information, other medical history (including asthma history, number of asthma exacerbations in the previous year, hypersensitivity to aspirin or NSAID), surgical history (including number and dates of previous surgery for nasal polyps), and prior and concomitant medications (including background therapy for NP and asthma).

4. Measure vital signs [blood pressure, heart rate, respiration rate, body temperature, weight (kg), height (cm)].

5. Perform physical examination (nose, heart, and lung).

6. Perform spirometry, within the time period between V0 and V1, for all patients and ensure that patients with co-morbid asthma are stable (with a FEV1>50% (of predicted normal) and has not experienced any exacerbation requiring treatment with > 1 systemic (oral or parenteral) steroids bursts for worsening asthma and/or hospitalization or an emergency/urgent medical care visit for worsening asthma in the previous 2 weeks.

7. Obtain safety labs: Complete blood count (including platelet count) with differential, IgE, comprehensive chemistry [glucose, BUN, sodium, potassium, bicarbonate, creatinine, total and direct bilirubin, alkaline phosphatase (ALP), total protein, albumin, SGOT (AST), SGPT (ALT)] and calcium (8 mL blood total).

8. Obtain urine for urinalysis (dipstick).

9. Urine pregnancy test for all females unless surgically sterile or postmenopausal.

10. Remind participant to continue their standard of care INS (fluticasone furoate, fluticasone propionate, triamcinolone acetonide, mometasone furoate, budesonide, ciclesonide, or beclomethasone), 2 actuations each nostril as mandatory background therapy throughout the study.

11. Assessment of adverse events during study visit.

12. Schedule appointment for the next visit.

7.3 Main Study Visits

Visit 1, (DAY 0): Randomization

1. Record all medication use with start date and dose in CRF; inquire about AEs/SAEs and background therapy tolerability.

2. Perform nasal endoscopy.

3. Record physical.

4. Reconfirm eligibility based on review of Inclusion/Exclusion Criteria and the V1 endoscopy local reading.

5. Obtain spirometry and record result in the CRF.

6. Check compliance with background use of the mandatory background INS therapy as defined as:

   ≥80% of total number of prescribed “stable dose” sprays taken during the screening period.

7. Check for use of prohibited medications.

8. Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).

9. Perform allergy skin testing. The participant will not have to be skin tested if testing was done in the Division of Allergy-Immunology at Northwestern Medical Group during a prior standard care of visit.

10. Administer SNOT-22.

11. Perform sinus CT scan (within the time period between V0 and V1) if one was not done within a 4 month window of V0.

12. Nasal lavage with 10 cc of normal saline for mechanistic studies (as described in Section 1.5.2): ECP, EPX, eotaxin 3, IL-5, IL-13, periostin.

13. Urine for LTE_4.

14. Administer VAS for nasal symptoms.

15. Administer the smell test (B-SIT)

16. Administer the ACQ5 in patients with asthma.

17. Check PNIF.

18. Randomize subjects (1:1) to receive either study drug or placebo per research pharmacist.

19. Dispense study drug or placebo from pharmacy to patient (4 week supply).

20. Remind participant to continue their standard of care INS (fluticasone furoate, fluticasone propionate, triamcinolone acetonide, mometasone furoate, budesonide, ciclesonide, or beclomethasone), 2 actuations each nostril as mandatory background therapy throughout the study.

21. Schedule appointment for next visit.

Visit 2, (Week 2)

1. Obtain blood for liver and renal function test: AST, ALT, ALP, total bilirubin, BUN and creatinine (5 mL total).

Visit 3, (Week 4)

1. Record all medication use with start date and dose in CRF; inquire about AEs/SAEs and background therapy tolerability.

2. Check compliance with background use of the mandatory background INS therapy as defined as:

≥80% of total number of prescribed “stable dose” sprays taken during the screening period.

3. Obtain spirometry and record result in the CRF.

4. Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
5. Perform extended physical examination.

6. Perform nasal endoscopy.

7. Administer VAS for nasal symptoms

8. Nasal lavage with 10 cc of normal saline for mechanistic studies (as described in Section 1.5.2): ECP, EPX, eotaxin 3, IL-5, IL-13, periostin.

9. Urine for LTE_4.

10. Check PNIF.

11. Perform SNOT-22.

12. Perform ACQ5 in those with asthma.

13. Obtain safety labs: Complete blood count (including platelet count) with differential, sodium, potassium, glucose, BUN, bicarbonate, phosphorus, creatinine, total and direct bilirubin, alkaline phosphatase, total protein, albumin, SGOT (AST), SGPT (ALT) and calcium (8 mL total).

14. Urine for urinalysis.

15. Dispense study drug or placebo from pharmacy to patient (4 weeks).

16. Remind participant to continue their standard of care INS (fluticasone furoate, fluticasone propionate, triamcinolone acetonide, mometasone furoate, budesonide, ciclesonide, or beclomethasone), 2 actuations each nostril as mandatory background therapy throughout the study.

17. Schedule appointment for next visit.

Visit 4, (Week 8)

1. Record all medication use with start date and dose in CRF; inquire about AEs/SAEs and background therapy tolerability.

2. Check compliance with background use of the mandatory background INS therapy, as defined as:

≥80% of total number of prescribed “stable dose” sprays taken during the screening period.

3. Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).

4. Perform focused physical examination of nose, heart, skin and lungs.

5. Administer VAS for nasal symptoms.

6. Nasal lavage with 10 cc of normal saline for mechanistic studies (as described in Section1.5.2): ECP, EPX, eotaxin 3, IL-5, IL-13, periostin.

7. Check PNIF.

8. Perform nasal endoscopy.

9. Administer SNOT-22.

10. Obtain urine for LTE_4.

11. Obtain safety labs: Complete blood count (including platelet count) with differential, glucose, BUN, bicarbonate, phosphorus, creatinine, total and direct bilirubin, alkaline phosphatase, total protein, albumin, SGOT (AST), SGPT (ALT) and calcium. Also, obtain blood for PK studies that will be stored frozen and sent to Astra Zeneca (15 mL blood total).

12. Urine for urinalysis.

13. Dispense study drug or placebo from pharmacy to patient (4 weeks).

14. Remind participant to continue their standard of care INS (fluticasone furoate, fluticasone propionate, triamcinolone acetonide, mometasone furoate, budesonide, ciclesonide, or beclomethasone), 2 actuations each nostril as mandatory background therapy throughout the study.

15. Schedule appointment for next visit.

Visit 5, (Week 12)

1. Record all medication use with start date and dose in CRF; inquire about AEs/SAEs and background therapy tolerability.

2. Check compliance with background use of the mandatory background INS therapy as defined as:

   $\geq$80% of total number of prescribed “stable dose” sprays taken during the screening period.

3. Obtain spirometry and record result in the CRF.

4. Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).

5. Perform extended physical examination including head and neck, heart, lungs, abdomen, and skin exam.

6. Administer VAS for nasal symptoms.

7. Nasal lavage with 10 cc of normal saline for mechanistic studies (as described in Section 1.5.2): ECP, EPX, eotaxin 3, IL-5, IL-13, periostin.

8. Check PNIF.

9. Perform nasal endoscopy.

10. Administer SNOT-22.

11. Perform ACQ5.

12. Perform smell test (B-SIT).

13. Obtain urine for LTE_4.

14. Obtain safety labs: Complete blood count (including platelet count) with differential, glucose, BUN, bicarbonate, phosphorus, creatinine, total and direct bilirubin, alkaline phosphatase, total protein, albumin, SGOT (AST), SGPT (ALT) and calcium. Also, obtain blood for PK studies that will be stored frozen and sent to Astra Zeneca (15 mL blood total).

15. Urine for urinalysis.

16. Obtain a sinus CT scan.

17. Remind participant to continue their standard of care INS (fluticasone furoate, fluticasone propionate, triamcinolone acetonide, mometasone furoate, budesonide, ciclesonide, or beclomethasone), 2 actuations each nostril as mandatory background therapy throughout the study.

18. Schedule appointment for next visit.

7.4 Follow-up Visit(s)

Visit 6, (Washout)

1. Record all medication use with start date and dose in CRF; inquire about AEs/SAEs and background therapy tolerability.

2. Comprehensive physical exam of the head and neck, heart, lungs, abdomen, and skin including height, weight, and vital signs.

3. Check compliance with background use of the mandatory background INS therapy as defined as:

≥80% of total number of prescribed “stable dose” sprays taken during the screening period.

4. Nasal lavage with 10 cc of normal saline for mechanistic studies (as described in Section 1.5.2): ECP, EPX, eotaxin 3, IL-5, IL-13, periostin.

5. Urine for urinalysis.

6. Obtain Safety labs: CBC with differential, comprehensive chemistry [glucose, BUN, bicarbonate, phosphorus, creatinine, total and direct bilirubin, alkaline phosphatase, total protein, albumin, SGOT (AST), SGPT (ALT)]. Also, obtain blood for PK studies that will be stored frozen and sent to Astra Zeneca (15 mL blood total).

   If abnormal, the patient will be contacted and approached as outlined in Section 8.1.2.

As needed visits

1. Subjects may come in at any time at the discretion of the investigator or the subject for follow up.

Early discontinued patients will be required to report for safety follow-up visit within a month of study discontinuation.

7.5 Visit Windows

Study visits should take place within the time limits below:

1. As detailed above, most visits have ± 4 day window for 4 week visits.

7.6 Study Procedures

1. Phlebotomy
2. Nasal endoscopy
3. Spirometry
4. Peak nasal inspiratory flow
5. Nasal lavage
6. Smell test (B-SIT)
7. Allergy skin testing

7.7 Study Arm Assignment Procedures

7.7.1 Blinding and Randomization

Individual investigational product(s)/intervention(s) assignments for this blinded study will be on occluded labels (provided by the site pharmacist) in 3 blocks of 4 weeks for the 12-week study.

7.7.2 Securing Blinding and Randomization Information

Randomization lists will be maintained in a secured area by the pharmacist(s) responsible for maintaining the blind. During site visits, the pharmacist will check the occluded labels to ensure that they are intact and in a secure, yet accessible, location for study personnel.

7.7.3 Requirements for Unblinding

This study may be unblinded only for safety reasons or only if the study information is needed for an interim or final analysis as described below. If a clinically significant event occurs and knowledge of treatment assignment is required, the blind may be broken. Unblinding must be approved by the study Medical Monitor unless an immediate life threatening condition has developed and the Medical Monitor is not accessible.

7.7.4 Documenting an Unblinding

Any unblinding (opening of a label or disclosure envelope) will require a full written account of the event(s) that necessitated the unblinding of the treatment assignment for an individual participant. This account will be made in the participant study file and in the final study report and will include the reason(s) for the unblinding, the name of the Medical Monitor who was notified and approved the unblinding, the names of the individuals unblinded, and the date and time the unblinding occurred.

8. SAFETY PROCEDURES

8.1 Stopping Rules

8.1.1 Study stopping Rules

Study enrollment and ongoing study procedures will be suspended pending expedited review of all pertinent data by the institutional review board (IRB), medical monitor and the FDA if any one of the following occurs:

1. A serious adverse event (Section 8.2.2).

8.1.2 Individual Stopping Rules

A study participant will be discharged from the study if he/she suffers:

1. A severe adverse event (Section 8.2.2)
2. A severe, unanticipated, drug-related event (Section 8.3.3.1)
3. Pregnancy (Section 8.4.2.1)
4. Any of the following liver function test abnormalities

   A. ALT or AST > 8 x ULN

   B. ALT or AST > 5 x ULN for more than 2 weeks

   C. ALT or AST >3 x ULN and total bilirubin > 2 x ULN or prothrombin INR > 1.5

   D. ALT or AST > 3x ULN and with appearance of or worsening of fatigue, nausea, (eosinophils > 5% of leukocytes)

   E. If the above liver abnormalities occur, scheduled study visits should no longer be performed, but should be replaced with the assessments described below in “Additional Study Procedures,” before the patient is withdrawn from the study. Patients should not be withdrawn from the study until liver enzymes are back to normal.

8.1.3 Additional Study Procedures

If a patient reach a limit of ALT or AST > 3 times ULN, the patient could continue with the study treatment and the scheduled study visits as planned. In addition, additional assessments as described below should be performed.

1. Repeat liver enzymes (AST, ALT and ALP), eosinophil count, prothrombin time, INR and total serum bilirubin every 48 hours until values begin to decrease. The frequency of monitoring can then be reduced until the lab parameters return to the normal range. Samples will be analyzed locally to assure immediate access of laboratory results to the site.

2. Obtain full medical history including alcohol use, medicines, recreational drug use, surgery, blood transfusions, excessive physical exercise and special diets.
3. Screen for acute viral hepatitis A, B, C, D and E, EBV, CMV, and autoimmune hepatitis (antinuclear antibodies). Perform clinical examination looking for evidence for other acute or chronic liver diseases such as alcoholic hepatitis, nonalcoholic steatohepatitis, ischemic hepatitis and biliary tract disease.

4. Request an ultrasound investigation of the liver and biliary tract and consider gastroenterology or hepatology consultation.

8.1.4 Premature Discontinuation of Investigational Product(s)/Intervention(s) with continued study participation/follow-up

Continued follow up if the investigation products were discontinued for safety reasons would be based on the visit number in the protocol at the time of drug discontinuation and the possibility of evaluating outcome.

8.1.5 Premature Termination Follow-up

Participants who are prematurely terminated from the study will be followed to monitor safety for a minimum of 30 days or until resolution of the disqualifying event whichever is longer or until the Medical Monitor and the Principal Investigator determine that the follow-up is complete.

8.1.6 Participant Replacement

Participants who prematurely terminate from this study will not be replaced.

8.2 Adverse Events

This section defines the types of adverse events and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and ICH E6: Guideline for Good Clinical Practice, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events version 3.0 (Aug. 9, 2006). The investigators conducting this trial have reviewed these criteria and consider them appropriate for this subject population.

8.2.1 Adverse Event Definition

An adverse event is any occurrence or worsening of an undesirable or unintended sign, symptom, abnormal laboratory finding, or disease that is temporally associated with participation in this study whether considered related to the study or not.

Any adverse event that occurs from the moment the subject has signed the consent form will be recorded and is reportable. An adverse event will be followed until any of the following takes place: a) it is resolved, b) participant is stable, c) a minimal of 30 days after participant is terminated from the study or d) the Medical Monitor and the Principal Investigator determine that follow-up is complete.

8.2.2 Serious Adverse Event (SAE) Definitions

An SAE is defined as "any adverse event occurring at any dose that suggest a significant hazard, contraindication, side effect, or precaution." This includes but is not limited to any of the following events:

1. Death. A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up after the completion of study will be reported whether it is considered to be study-related or not.

2. A life-threatening event. A life-threatening event is any adverse experience that, in the view of the investigator, places the study participant at immediate risk of death from the reaction as it occurred.

3. An inpatient hospitalization or prolongation of existing hospitalization.

4. Persistent or significant disability.

5. An event that required intervention to prevent permanent impairment or damage.

6. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

7. Congenital anomaly or birth defect.

Regardless of the relationship of the adverse event to the study, the event will be reported as an SAE if it meets any of the above definitions.

8.2.3 "Expected" verses "Unexpected" Adverse Event Definition

A suspected adverse reaction is considered "expected" when it is listed in the investigator brochure, the package insert or the protocol. An adverse event is considered "unexpected" when its nature or severity is not consistent with the information that is provided in the Package insert, and/or this protocol (Section 1.5).

8.3 Management of Adverse Events

8.3.1 Collecting Procedure

Adverse events may be discovered through any of these methods:

1. Observing the participant.

2. Questioning the participant, with standardized questions at the beginning (except Visit 0) and the end of study visits.

3. Receiving an unsolicited complaint from the participant.

4. An abnormal value or result from a clinical or laboratory evaluation (e.g., a radiograph, an ultrasound, or an electrocardiogram) can also indicate an adverse event.

8.3.2 Recording and Reporting Procedure

Throughout the study the Principal Investigator will record all adverse events on appropriate adverse event case report forms regardless of their severity or relation to the study.

8.3.2.1 NOTIFYING THE MEDICAL MONITOR

The Principal Investigator will ensure the timely dissemination of AE information to the Medical Monitor.

8.3.2.2 NOTIFYING THE INSTITUTIONAL REVIEW BOARD

The Principal Investigator will ensure the timely dissemination of AE information to the IRB in accordance with the applicable regulations and guidelines.

8.3.2.3 NOTIFYING THE FDA

The IND Sponsor will file all adverse events in the IND Annual Report to the FDA. The Principal Investigator will be responsible for compiling the IND Annual Report.

8.3.3 Grading and Attribution

8.3.3.1 GRADING CRITERIA

In addition to determining whether an adverse event fulfills criteria for a serious adverse event or not, the severity of adverse events experienced by study participants will be graded according to the criteria set forth in the National Cancer Institute's *Common Terminology Criteria for Adverse Events Version 3.0* (published Aug. 9, 2006). This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.

- Adverse events listed in the NCI-CTCAE will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

  Grade 1 = Mild adverse event.

  Grade 2 = Moderate adverse event.

  Grade 3 = Severe and undesirable adverse event

  Grade 4 = Life-threatening or disabling adverse event.

  Grade 5 = Death.

- Adverse events not included in the NCI-CTCAE listing, which have relative specificity for the protocol will be recorded and graded 1 to 5 according to the grade definition provided below.

  For anaphylaxis:

  Grade 1 = Oral urticarial or erythema

Grade 2 = Flushing, urticarial, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and /or emesis.

Grade 3 = Marked dysphagia, hoarseness, and /or stridor; shortness of breath, wheezing & retractions; crampy abdominal pain, recurrent vomiting and / or diarrhea; and /or mild dizziness

Grade 4 = Cyanosis or SpO_2 < 92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

Grade 5 = Death.

- Other adverse events not included in the NCI-CTCAE listing, will be recorded and graded 1 to 5 according to the General Grade Definition provided in the Table below:

Grade 1	**Mild**	Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	**Moderate**	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
Grade 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required hospitalization or hospice care probable.
Grade 5	**Death**	Death.

8.3.3.2 DEFINITION OF ATTRIBUTION

The relationship, or attribution, of an adverse event to the study will be determined by the Principal Investigator or designee by using the descriptors provided in the following table. The Principal Investigator or designee by using the descriptors provided in the following table. The Principal Investigator or designee will record the determination of attribution on the appropriate adverse event or serious adverse event form. The relationship of an adverse event to the

investigational drug(s)/intervention(s)/procedure(s) or other study drug will be furthered determined.

NCI-CTCAE attribution of adverse events

Code	Descriptor	Definition
	UNRELATED CATEGORY	
1	Unrelated	The adverse event is clearly not related to study
	RELATED CATEGORIES	
2	Unlikely	The adverse event is doubtfully related to study
3	Possible	The adverse event may be related to study
4	Probable	The adverse event is likely related to study
5	Definite	The adverse event is clearly related to study

(For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE website: http://ctep.cancer.gov/reporting/ctc.html)

8.4 Management of Serious Adverse Events

8.4.1 SAE Collecting Procedure

Serious adverse events will be collected described for adverse events in Section 8.3.1.

8.4.2 SAE Recording and Reporting Procedure

Serious adverse events will be recorded on the **serious adverse event case report form** (Appendix 6) and will include a narrative of the event signed and dated by the Principal Investigator and the site Medical Monitor. In addition, the FDA MedWatch 3500A form will be filled out.

8.4.2.1 REPORTING PREGNANCY

The Principal Investigator or a physician designee will counsel the participant and discuss the risks of continuing with the pregnancy ad the possible effects of the fetus. Monitoring of the participant will continue until the conclusion of the pregnancy, and follow-up adverse event case report form detailing the outcome of the pregnancy will be submitted. Follow-up information detailing the outcome of the pregnancy should be reported to the Medical Monitor as it becomes available. Any premature termination of the pregnancy will be reported. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE.

8.4.2.2 UNEXPECTED, NON-SERIOUS ADVERSE EVENTS

An unexpected, non-serious adverse event that is of Grade 2 severity or higher and study related will be recorded and reported to the site Medical Monitor under the serious adverse event reporting procedure outlined below in Sections 8.4.2.3, 8.4.2.4, and 8.4.2.6.

8.4.2.3 SAE REPORTING CRITERIA AND PROCEDURES

- The Principal Investigator will be notified by the staff no later than 24 hours after a staff member becomes aware of a SAE.
- The site Medical Monitor will be notified by the Principal Investigator no later than 24 hours after the Principal Investigator becomes aware of the SAE.
- Within another 24 hours, the site Medical Monitor will discuss with the Principal Investigator the impact of the SAE on the participant and on the study and will decide whether standard or expedited reporting will be applied. A finalized, initial **SAE case report form** and a **MedWatch 3500A form** will be generated by the Principal Investigator.

8.4.2.4 NOTIFYING THE MEDICAL MONITOR

The Principal Investigator will ensure the timely dissemination of SAE information, including expedited reports, to the Medical Monitor.

8.4.2.5 NOTIFYING THE INSTITUTIONAL REVIEW BOARD

The Principal Investigator will ensure the timely dissemination of SAE information, including expedited reports, to the IRB in accordance with IRB regulations and guidelines.

8.4.2.6 NOTIFYING THE FDA

The following process for reporting a serious adverse event ensures compliance with the ICH guidelines, 21 CFR 46 and 21 CFR §312.32. After the SAE has been reported by the principal investigator and assessed by the IND sponsor, the IND sponsor must report the event to the appropriate health authorities using one of the two options:

1. Standard reporting to the FDA (report in the context of an **IND Annual Report**) applies if the adverse event is classified as either:

    A. Serious, related to the study and expected (Section 8.2.1 and 8.2.2) or

    B. Serious and unrelated to the study (Section 8.2.3)

    For standard reporting, the IND Sponsor will file the finalized forms to the FDA together with all other SAE documents in the IND Annual Report. The Principal Investigator will be responsible for compiling the IND Annual Report.

2. **Expedited reporting (IND safety report)** to the FDA applies if the adverse event is considered serious, related to the study and unexpected. SAEs that do not strictly fit the above criteria may be reported to the FDA in an expedited manner if the IND Sponsor chooses to do so. This option applies if the AE is classified as one of the following:

    A. Serious and unexpected suspected adverse reaction

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

i. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome);

ii. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

iii. An aggregate analysis of specific events 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 events occur more frequently in the drug treatment group than in a concurrent or historical control group.

B. Findings from other studies

The sponsor must report any findings from other epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure, or other aspects of the overall conduct of the study.

These events will be reported by the IND Sponsor within 15 calendar days after the IND sponsor becomes aware of the SAE; fatal or life-threatening events will be reported within 7 calendar days. All principal investigators must report SAEs to their respective IRBs as mandated by them.

8.5 Protocol Deviations

The practices below are consistent with Good Clinical Practice (GCP ICH E6) Sections:

- Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- Quality Assurance and Quality Control, section 5.1.1.
- Noncompliance sections 5.20.1, and 5.20.2.

8.5.1 Protocol Deviation Definition

A protocol deviation is any noncompliance with the protocol, Good Clinical Practice (GCP), or the study's Manual of Operations (MOP). Noncompliance may be either on the part of the participant, the investigator, or the study staff.

8.5.2 Management of Protocol Deviations

8.5.2.1 DETECTING PROTOCOL DEVIATIONS

Protocol deviations will be detected by direct questioning of participants and regular review of CRFs to determine if visits take place in appropriate windows.

8.5.2.2 REPORTING PROTOCOL DEVIATIONS

Upon determination that a protocol deviation has occurred, the study staff will a) notify the Principal Investigator and b) and will begin completing the Protocol Deviation Form (Appendix 7). The Principal Investigator will complete and sign the Protocol Deviation form and submit to the site IRB, per IRB regulations. The IND sponsor will be responsible for notifying the FDA.

9. SAMPLE SIZE CALCULATIONS AND STATISTICAL PLAN

9.1 Sample Size and Power Calculations

The sample size estimates were calculated according to the study and primary endpoint parameters for TPS described above powered to either 90% or 80%. From these calculations, the more conservative number of study subjects was 24 per arm. We plan to enroll 30 per arm to be cautious in anticipating a drop-out rate of 20%.

1-Sided alpha	Power	Difference in mean	Standard dev	TOTAL sample size (inclusive of Treatment and Placebo)
0.1	0.90	1.5	2	47
0.1	0.80	1.5	2	33

9.2 Data Analysis

9.2.1 Study Participant Baseline Characteristics and Demographics

Summary descriptive statistics for baseline and demographic characteristics will be provided for all enrolled participants. Demographic data will include age, race, sex, body weight, and height; these data will be presented in the following manner:

- Continuous data (i.e., age, body weight, and height) will be summarized descriptively by mean, standard deviation, median, and range.

- Categorical data (i.e., sex and race) will be presented as enumerations and percentages.

Analyses of primary and secondary outcomes were conducted by intention-to-treat analysis with participants analyzed according to the randomly assigned treatment group irrespective of compliance. The Mann Whitney U test will be used to compare treatment groups if a non-Gaussian distributed data are generated; otherwise, if data are normally distributed, an unpaired t test will be used. Wilcoxon rank-sum tests will be used to compare continuous variables within groups and Fisher's exact tests will be used to compare categorical variables. The level of significance employed will be 0.05. Relationships between the primary efficacy variable and various in vitro and in vivo variables will be explored using Pearson product-moment correlation coefficient or the Spearman rank correlation coefficient, as appropriate.

Summary statistics will be reported for all secondary efficacy variables. Continuous variables will be summarized by sample size, mean, median, standard deviation, minimum, and maximum. Discrete variables will be summarized by frequencies and percentages.

9.2.2 Primary Endpoint Analyses

The analysis of the primary outcome measures will consist of treatment comparisons made using analysis of covariance (ANCOVA); pairwise comparisons for assessing differences between treatment arms will be performed using two treatment groups at a time.

9.2.3 Secondary Endpoint Analyses

This study is not designed or powered to perform hypothesis testing on secondary endpoints. All secondary analyses will be treated as supportive. Treatment comparisons of change from baseline to Week 12 will be made using ANCOVA.

9.2.4 Exploratory Endpoint Analyses

Student t test will be used to analyze continuous variable differences. Mann-Whitney U test will be used to analyze unpaired comparisons.

9.2.5 Safety Analysis

Safety analyses will include AEs SAEs, laboratory abnormalities, and physical examination abnormalities. All participants in the safety sample will be included in all safety analyses. Frequency of AEs will be tabulated by system organ class and preferred term, as well as by seriousness, severity, and treatment relatedness. Frequency of SAEs will be tabulated by system organ class and preferred term. For pertinent laboratory measurements, mean and mean change from baseline values will be presented by treatment group and visit. Frequency of physical examination abnormalities will be tabulated by treatment group.

9.2.6 Pharmacokinetic and Pharmacodynamic Data Analyses

Plasma sample will be collected and stored frozen at week 8, 12, and 16 and transported to Astra Zeneca with coded sample numbers to maintain confidentiality.

9.2.7 Medical History

Medical history within the past 12 months – including the existence of current signs and symptoms – will be collected for each body system.

9.2.8 Medication Use

All medications taken by or administered to study participants beginning 30 days before enrollment and continuing throughout the study will be collected. All medications used will be coded according to the WHO drug dictionary. The number and percentage of participants receiving prior and concomitant medications/therapies will be presented overall and by medication class.

9.2.9 Study Completion

The percent of participants who complete the study, losses to follow-up, times to lost to follow-up, and reasons for discontinuation (e.g., adverse events) will be presented.

9.3 Interim Analyses

Given the small study size, no interim data analysis is planned.

9.4 Deviations from Statistical Plan

The principal features of the study design and of the plan for statistical analysis of the data are outlined in this protocol. Any changes in these principal features will require a protocol amendment.

10. IDENTIFICATION AND ACCESS TO SOURCE DATA

10.1 Identifying Source Data

The investigator will keep accurate records to ensure that the conduct of the study is fully documented. Data derived from source documents will be transferred to protocol-specific CRFs. The results of all clinical and clinical laboratory evaluations will be maintained in the participant's medical records and the data will be transferred to clinical CRFs, as applicable.

10.2 Updating Source Documentation

Documents describing the safety profile of an investigational product(s)/intervention material(s), such as eh investigator's brochure and the package insert, will be amended as needed by the investigational product(s)/intervention material(s) manufacturer to ensure that the description of safety information adequately reflects any new clinical findings.

The Principal Investigator will provide the site Medical Monitor, and the IRB with the most up-to-date versions of the above documents as soon as the Principal Investigator becomes aware of any changes. For purchased investigation product(s)/intervention material(s), the Principal Investigator will confirm that there are no changes to the package insert every 3 months. In case of package insert changes, the Principal Investigator will notify the site Medical Monitor and the IRB.

10.3 Permitting Access to Source Data

The investigational site participating in this study will maintain the highest degree of confidentiality of the clinical and research information obtained from the participants in this clinical trial. Medical and research records will be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational site will permit authorized representatives of the sponsor(s) and health authorities to examine (and when required by applicable law, to copy) clinical records for the purpose of quality assurance reviews, audits, and evaluations of the study safety and progress. Unless required by the laws that permit copying of records, only the coded identity associated with documents or with other participant data may be copied (and all personally identifying information will be removed). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that is linked to identified individuals.

The records will be maintained in locked file cabinets in Allergy-Immunology offices in 211 E. Ontario or Department of Otolaryngology in 675 N. St. Clair and/or password protected computers.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The Principal Investigator will keep accurate records to ensure that the conduct of the study is fully documented. The investigator will ensure that all CRFs are complete, they will be reviewed and signed by the Principal Investigator. All discrepancies identified will be resolved with the Principal Investigator and the CRFs will be amended as needed. They will be stored by the investigator according to Northwestern University and GCP ICH guidelines.

12. ETHICAL CONSIDERATONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

12.1 Statement of Compliance

This study was designed to ensure the protection of subjects according to the ethical principles of the Declaration of Helsinki and amendments concerning medical research in human subjects. This clinical study will be conducted using good clinical practice (GCP), as delineated in Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance, and according to the criteria specified in this study protocol. Before study initiation, the protocol, the informed consent documents will be reviewed and approved by IRB, as well as any other appropriate health authorities. Any amendments to the protocol or to the consent materials will also be approved by the appropriate bodies listed above prior to implementation.

12.2 Informed Consent and Assent

The informed consent will provide information about the study to ta prospective participant to allow for an informed decision about participation in the study. All participants (or their legally acceptable representative) must read, sign, and date a consent form prior to study participation. Consent materials for participants who do not speak or read English will be translated into the participants' appropriate language.

The informed consent form will be revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the informed consent will be given to a prospective participant for review. The Principal Investigator or an approved designee will discuss the consent with the prospective participant and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason.

12.3 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number and these numbers rather than names will be used to collect, store, and report participant information.

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14. Appendices

Appendix 1. Study Design

Visit	V0	V1	V2	V3	V4	V5	V6
Time	screening (-3 weeks)	Day 0[#]	2 week	4 week	8 week	12 week	16 week wash out
Consent	X						
Inclusion/exclusion	X						
History (incl current meds)	X	X		X	X	X	X
Urine Pregnancy	X						
Blood	X[¶]		X[§]	X[$]	X[$¥]	X[$¥]	X[$¥]
Urinalysis	X			X	X	X	X
Questionnaire SNOT-22		X		X	X	X	X
Questionnaire ACQ5		X		X		X	X
VAS		X		X	X	X	X
B-SIT		X				X	
Physical (extended incl nose/lung)		X		X		X	X
Physical (nose/lung)	X				X		
Allergy skin test		X					
Spirometry	X	X		X	X	X	
Peak nasal Inspiratory flow		X		X	X	X	
Nasal endoscopy		X		X	X	X	
Nasal lavage fluid		X		X	X	X	X
Sinus CT scan		X				X	
Vitals	X	X		X	X	X	X
Assess use of INS	X	X		X	X	X	X
Dispensing study drug		X		X	X		
Dispense INS	X	X		X	X	X	
Urine for LTE_4		X		X		X	X

V=Visit; SNOT-22: Sinonasal Outcome Test; B-SIT: Brief Smell Identification Test; VAS: Visual analog scores; ACQ5: Asthma Control Questionnaire 5-item

#: randomization to placebo or drug daily
¶: CBC with diff, comprehensive chemistry, Calcium, IgE
§: AST, ALT, Alk Phos, T bili
$: CBC with differential, Comprehensive chemistry (LFTs and renal function), Calcium
¥: plasma for pharmacokinetic studies
Nasal lavage fluid: IL-5, Il-13, ECP, EPX: Eosinophil peroxidase, periostin, eotaxin 3 INS: Fluticasone propionate, 2 actuations each nostril QD

Appendix 2. Sino-Nasal Outcome Test-22 Questionnaire

1. Sino-Nasal Outcome Test-22 (SNOT-22)
Please rate your problems as they have been OVER THE PAST 2 WEEKS.

Considering how severe the problem is when you experience it and how frequently it happens, please rate each item below on how "bad" it is by selecting the choice that corresponds with how you feel. (0 = No problem, 5 = Problem as bad as it can be)

	No problem (0)	Very mild problem (1)	Mild or slight problem (2)	Moderate problem (3)	Severe problem (4)	Problem as bad as it can be (5)
Need to blow nose	◯	◯	◯	◯	◯	◯
Sneezing	◯	◯	◯	◯	◯	◯
Runny nose	◯	◯	◯	◯	◯	◯
Cough	◯	◯	◯	◯	◯	◯
Post nasal drip	◯	◯	◯	◯	◯	◯
Thick nasal drainage	◯	◯	◯	◯	◯	◯
Ear fullness	◯	◯	◯	◯	◯	◯
Dizziness	◯	◯	◯	◯	◯	◯
Ear pain/pressure	◯	◯	◯	◯	◯	◯
Facial pain/pressure	◯	◯	◯	◯	◯	◯
Difficulty falling asleep	◯	◯	◯	◯	◯	◯
Waking up at night	◯	◯	◯	◯	◯	◯
Lack of a good night's sleep	◯	◯	◯	◯	◯	◯
Waking up tired	◯	◯	◯	◯	◯	◯
Fatigue during the day	◯	◯	◯	◯	◯	◯
Reduced productivity	◯	◯	◯	◯	◯	◯
Reduced concentration	◯	◯	◯	◯	◯	◯
Frustrated/restless/irritable	◯	◯	◯	◯	◯	◯
Sad	◯	◯	◯	◯	◯	◯
Embarrassed	◯	◯	◯	◯	◯	◯
Sense of taste/smell	◯	◯	◯	◯	◯	◯
Blockage/congestion of nose	◯	◯	◯	◯	◯	◯

Appendix 3. B-SIT

The Brief Smell Identification Test™ Administration Manual

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GENERAL INTRODUCTION

The senses of taste and smell monitor the intake into the body of all nutrients and airborne chemicals required for life. Olfaction, in particular, provides an early warning for toxic fumes, smoke, leaking natural gas, spoiled food, and dangerous environments. This sense, more than any other, determines the flavor and palatability of foods and beverages, and provides a vast array of aesthetic delights.

Unlike vision and hearing, olfaction is rarely evaluated by physicians, the government, the school system, or employers. This is in spite of the fact that decreased smell loss can be very debilitating, placing an individual, as well as coworkers, at risk in many occupations (e.g., chemical manufacturing, nuclear plant maintenance, fire fighting, police work, plumbing, aviation, nautical engineering and maintenance, and innumerable military and industrial situations). Furthermore, smell loss can be an early sign of such neurological diseases as Alzheimer's and idiopathic Parkinson's disease.[1] In some cases, early intervention can delay the time of onset or mitigate the degree of symptom development.

The measurement of smell function is a common problem in otolaryngology, neurology, and other medical specialties. Some patients, for example, report decreased smell function when, relative to their peers, their function is within the normal range. Others are unaware of a true dysfunction (e.g., while ~ 90% of patients with Parkinson's disease have a demonstrable deficit, only 28% are aware of the problem prior to testing.[2] Hence, it is important for the clinician to have a reliable and objective assessment of the patient's olfactory dysfunction before therapeutic options are considered or before concluding that no dysfunction is present.

During the last decade, Sensonics, Inc. has pioneered the development and proliferation of easy-to-administer tests of olfactory function. The most popular of these tests -- the 40-item University of Pennsylvania Smell Identification Test or UPSIT (known commercially as the Smell Identification Test™ or SIT)[3] has been administered to an estimated 250,000 persons in Europe and North America alone. While this test has proven practical in the vast majority of applications in which it has been applied, shortened versions have been found useful when less administration time is available. Examples of two such tests are the 12-item Brief Smell Identification Test™ (B-SIT; also known as the Cross-Cultural Smell Identification Test™ or CC-SIT) and the 3-item Pocket Smell Test™ (PST), a very brief screening test for major olfactory dysfunction.

DESCRIPTION OF THE B-SIT

The B-SIT is a brief 12-item self-administered microencapsulated odorant test for measuring olfactory function. It is contained in a single booklet, unlike the 4-booklet UPSIT, and is applicable in any industrial, clinical, or survey setting where a rapid, yet reliable, measure of olfactory function is required. As with the case of the UPSIT, the odorants are embedded in 10-50 μm ureaformaldehyde polymer microcapsules fixed in a proprietary binder and positioned on scent strips at the bottom of the pages of the test booklet. The stimuli are released by scratching the strips with a pencil tip in a standardized manner. Above each odorant strip is a multiple-choice question with four alternative responses. For example, one of the items reads: "This odor smells most like: a) motor oil; b) garlic; c) rose; or d) lemon. The subject is required to mark one of the four alternatives even if no smell sensation is perceived (i.e., the test is forced-choice). The criteria for the selection of the specific stimuli are described later in this manual.

The norms provided for this test allow the administrator to establish the relative degree of loss of function in percentile rank form. Thus, aside from providing an absolute score of value in research settings, a given subject's test score can be compared to that of normal individuals of the same sex and general age to establish whether, in fact, normal function is present.

RELIABILITY OF THE B-SIT

In general, forced-choice odor identification tests are highly reliable, indeed more so than other tests that can be administered in the same time period. In one study, the B-SIT was administered on two test occasions separated by at least a week to the same individuals. The test-retest reliability coefficient was 0.71.[4] This, however, is likely a conservative estimate of its reliability, since the subjects were relatively homogeneous and the reliability of the UPSIT in this study was only 0.91, a value somewhat lower than the ~ 0.95 value seen in other investigations.

According to the Spearman-Brown formula (which relates test length to reliability), a test comprised of 12 UPSIT items (i.e. , a test 30% as long as the UPSIT) would have a reliability of 0.73, compared to the 0.92 test-retest reliability of the whole UPSIT. The aforementioned empirically-determined test-retest reliability coefficient for the B-SIT (r = 0.71) is comparable to this value.[5]

STRENGTHS AND WEAKNESSES OF THE B-SIT

The B-SIT is the test of choice when < 5 minutes is available for testing. It employs the same sound psychometric principles as the UPSIT, and incorporates multicultural items, making it useful in numerous cultures. Moreover, the availability of norms allows for a standardized indication of an individual's ability to smell. This test is particularly useful in surveys, where time is at a premium.

The 12-item B-SIT is admittedly less sensitive in detecting subtle alterations in smell function than the 40-item UPSIT. The decreased sensitivity is due, in part, to its lower reliability. Moreover, the B-SIT has a smaller range in which abnormal scores can fall. Thus, < 8 categories typically exist below the 5th percentile of the B-SIT normative distribution, compared with ~ 30 for the UPSIT.

While the B-SIT is useful screening test, the limited range of available test scores precludes definitive detection of malingerers using statistically improbable responses. Thus, the expected B-SIT score on the basis of random responding (as would occur in total anosmia) is 3; i.e., since there are 4 choices on each item and responding is forced-choice, 25% of the answers, on average, should be correct (0.25 x 12 = 3). However, since the sampling distribution expected from anosmics falls several points around this value, it is difficult to definitively establish statistically whether a low score on the B-SIT is due to olfactory dysfunction or to malingering.

COMMON APPLICATIONS OF THE B-SIT

Like its parent test, the B-SIT has served as the basis for a number of large surveys undertaken by universities and corporations. For example, Graves et al.[6] administered the B-SIT and a neuropsychological test battery to 1,985 older persons along with the Cognitive Screening Instrument (CASI). Of this group, 1,836 were found not to be demented. Two years later, 1,604 of the subjects were retested on both the B-SIT and the CASI; 69% also were genotyped for apolipoprotein E. The authors found that the B-SIT was the best predictor of subsequent cognitive decline. Relative to normosmics, the odds ratio (OR) for cognitive decline in persons with impaired olfaction (microsmics) was 1.25 (95% CI, 0.83 to 1.89); in anosmics, it was 1.92 (95% CI, 1.06 to 3.47). Persons who were anosmic at baseline and who had at least one APOE-epsilon4 allele had 4.9 times the risk of cognitive decline (95% CI, 1.6 to 14.9) compared with normosmics without the epsilon4 allele.

ADMINISTRATION PROCEDURES

The B-SIT was designed to be self-administered by most literate persons. The instructions, printed on the front page of the test, should be read by or to the examinee before beginning the test. Care must be taken to be certain that the instructions are followed exactly, that the information requested on the back of the booklet is accurately provided, and that all items of the test are completed before it is scored. Persons to whom the test is sent through the mail should be instructed, in a cover sheet, as to the importance of providing a response to every item, including ones for which no odor is perceived. Because the normative data are based on all 12 test items, incomplete tests cannot be validly scored.

For subjects being tested under supervision, it is useful for the examiner to demonstrate the release of the first odor by appropriately scratching the stimulus surface and marking the examinee's response in the correct answer column of the booklet. A number of individuals have difficulty in understanding how to release the stimuli and, in some cases, mark or "color in" the microencapsulated test strip so thoroughly that no odor remains. For this reason, it is important the examinee be made aware of the correct procedure for releasing the odors. In general, the microencapsulated strip should be marked with a few strong strokes of the pencil tip across the strip's entire width (I personally have the examinee make a wide letter "z" with a few lines through it) or a series of strokes like those pictured on the cover of the booklet. The subject should be encouraged to sniff the label immediately after it has been scratched to ensure that the odor has not significantly dissipated.

Smell deficient persons are sometimes reluctant to make the forced-choice responses and require reinstruction. In such cases, the test examiner usually needs only to indicate to the examinee that responses must be made for every test item in order to make the test valid, pointing to the written instructions on the first page of the test.

If further reluctance occurs, one can indicate to the examinee that marking an answer ensures that each item is carefully attended to and that, furthermore, correct detection may occur unconsciously in some individuals. Generally, kind authority works in such situations.

The examiner must help administer the test to persons who have impaired eyesight or who, on the basis of age or other factors, cannot read the alternatives or adequately release the odorants. In such cases, the examiner should obtain the information on the back of the first booklet verbally, fill it in for the subject, and place the subject's name on the spaces provided on the other three booklets. The examiner should then use the pencil to release the first odor, hold the microencapsulated strip under the subject's nose, and read aloud the response alternatives while the subject is sniffing the strip. In cases where the subject's eyesight is not impaired, it is permissible to allow the subject to read the alternatives as they are mentioned verbally. Finally, the examiner should mark the subject's response to each item on the columns provided on the last page of each booklet.

In cases where it is not clear whether a person is capable of taking the test or understanding the odor concepts (e.g., in individuals with cognitive deficits secondary to possible dementia or head trauma), one can administer Sensonics' Picture Identification Test™ (PIT; a test analogous to the UPSIT except that only pictures of the concepts are presented) to first determine whether adequate cognitive function is present to take a visually-oriented test). In general, if a subject scores > 35 on the PIT – a test that takes < 5 minutes to administer -- then one can have confidence in the B-SIT scores.

DEVELOPMENT OF THE B-SIT

SELECTION OF TEST ITEMS

The B-SIT was designed to include odors easily recognized by persons from a variety of cultures. Thus, we had foreign nationals help us select the final odorants. Professor Konrad Burdach of the University of Munich indicated that the following UPSIT items may not be familiar to some Germans: cedar, cheddar cheese, cherry, dill pickle, fruit punch, gingerbread, grape, natural gas, root beer, and wintergreen. Dr. Cheng Li from China reported that most of his country-men would be unfamiliar with cedar, cinnamon, clove, dill pickle, gingerbread, mint, pizza, pumpkin pie, root beer, and wintergreen. Professor A. Muratorio of the University of Pisa indicated that the following UPSIT items would be unfamiliar to a number of Italians: cheddar cheese, dill pickle, fruit punch, lilac, lime, pumpkin pie, root beer, and wintergreen. Dr. Igor Kratskin of St. Petersburg reported that many Russians would not recognize the odors of bubble gum, cheddar cheese, clove, coconut, dill pickle, fruit punch, gingerbread, licorice, lime, mint, peanuts, pizza, pumpkin pie, root beer, and wintergreen. Ms. Solange Chadda of Paris opined that some French people may not be familiar with cheddar cheese, dill pickle, gingerbread, peanut, root beer, and wintergreen odors. Professor Alfredo Herrera of Columbia, South America, indicated that the odors of cheddar cheese, dill pickle, gingerbread, licorice, peanut, root beer, and wintergreen are similarly problematic in Columbia.

Ninety-six Swedish painters and military person-nel were administered the 40-item UPSIT by Sandmark et al.,[7] who performed an item analysis on the difficulty of the UPSIT items. As in the United States, most of the UPSIT items were correctly identified by > 90% of the subjects. Fruit punch, the least well identified odorant of the test items, was identified by only 70.76% of the participants. The UPSIT items identified by 85% to 90% of the subjects included cedar (86%), cheddar cheese (87%), grass (89%), menthol (90%), orange (86%), peach (86%), pine (87%), strawberry (88%), and turpentine (89%). Those identified by less than 85% of the sample were cherry (83%), grape (74%), licorice (72%), natural gas (83%), and wintergreen (76%).

In a collaborative study with Dr. Hiroyuki Zusho of the Kanto Rosai Hospital, Kanagawa, Japan, we administered the 40-item UPSIT to 117 male and 191 female native Japanese subjects (mean respective ages: 25.5 and 21.8 yrs).[8] Although 17 (42.5%) of the 40 UPSIT items were correctly identified by over 90% of the subjects, 11 (27.5%) were identified correctly by less than 75%: cedar (74.4%), cheddar cheese (73.4%), cherry (34.4%), clove (55.2%), coconut 65.6%), dill pickle (67.5%), fruit punch (45.8%), ginger-bread (65.9%), licorice (73.7%), lime (72.7%), and wintergreen (74.4%).

Based on the aforementioned information and other considerations, the following odorants were chosen for inclusion in the B-SIT: banana, chocolate, cinnamon, gasoline, lemon, onion, paint thinner, pineapple, rose, soap, smoke, and turpentine. This test set was comprised of six food-related and six nonfood-related odorants. In a few cases, we substituted words for names that were used as response alternatives that may not be culture-free: "dog" for "skunk," "garlic" for "pumpkin pie," "woody" for "pine," "fruit" for "cola," "apple" for "dill pickle," "strawberry" for "root beer," and "chocolate" for "licorice."

COMPARISON OF B-SIT ITEMS TO UPSIT ITEMS FOR B-SIT NORM DEVELOPMENT

For this comparison, 198 healthy persons (83 men, 115 women) representing a wide range of ages were recruited. Of these, 135 were community residents in Lansdale, Pennsylvania, 29 were students and employees of the University of Pennsylvania (obtained largely from advertisements placed on campus bulletin boards), and 34 were healthy residents of retirement homes in or near Philadelphia.

The mean ages (SD) of the male and female participants were 40.68 (25.16) and 44.21 (22.67) yrs, respectively. Most of the retired individuals were living on their own, and none had AD or any other neurodegenerative diseases potentially associated with altered ability to smell. All but 18 of the subjects were nonsmokers. Individuals who noted a history of nasal disorder or any other problem that would preclude participation were excluded from the study group.

We employed the University of Pennsylvania's large UPSIT data base to establish B-SIT norms. To ensure the validity of this process, we first compared, for all 198 subjects, the mean of the 12 B-SIT items to the mean of the 12 analogous UPSIT items using a matched-sample t-test. These means did not differ significantly ($t = 1.40$, $df = 197$, $P > .05$). Since the relatively limited range of test scores available from the B-SIT precluded valid correlation analysis, we determined whether the frequency distribution of the test scores for the B-SIT differed significantly from that of analogous UPSIT test items from the age-, gender-, and smoking-habit-matched controls. A X^2 analysis indicated that the distributions of test scores did not differ significantly from one another ($X^2 = 3.15$, $df = 5$, $P>.50$). Therefore, we concluded that the UPSIT norms could be validly employed in the development of the B-SIT norms which are presented in this administration manual.

DEVELOPMENT OF B-SIT NORMS

Given the aforementioned comparability, B-SIT norms analogous to those developed for the UPSIT were established (see Tables 1 and 2).[3] To achieve this end, we calculated, within successive 5-year age intervals, the number of correctly identified UPSIT items corresponding to the 12 B-SIT items using the Smell and Taste Center's large UPSIT database. These items were selected from 3760 UPSITs administered to 1741 males and 2019 females. Percentile ranks were then determined for each 5-year age category. As can be seen in Tables 1 and 2, women, on average, outperform men on the B-SIT; both sexes evidenced an age-related decline in absolute performance, beginning after the age of 55 years.

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TABLE 1
Male Subjects: Percentile Ranks for Olfactory Function by Age Group in Years

	Age Group																
B-SIT Score	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>84
12	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99
11	95	70	57	47	58	52	55	53	56	67	62	64	77	91	94	97	91
10	81	39	27	16	23	23	23	24	19	37	29	41	51	71	61	85	88
09	63	15	11	06	05	09	05	14	07	15	21	21	34	45	43	71	77
08	47	05	05	04	01	05	02	05	04	04	11	15	28	33	31	54	67
07	33	01				03		01		03	06	12	19	23	28	48	56
06	18					01					03	10	13	19	24	37	51
05	09											03	08	10	19	23	39
04	05												04	03	11	18	37
03	03												02		02	08	25
02	01															05	11
01																02	04
00																	
N:	129	147	196	144	179	154	122	94	72	74	67	62	53	71	55	65	57

GREEN: Normal RED: Abnormal relative to age ORANGE: Deficit relative to younger persons

TABLE 2
Female Subjects: Percentile Ranks for Olfactory Function by Age Group in Years

	Age Group																
B-SIT Score	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>84
12	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99
11	89	53	45	39	49	44	48	48	42	51	57	61	66	83	86	93	93
10	68	23	16	12	16	15	14	18	12	20	27	27	38	59	65	78	82
09	46	07	04	04	06	02	03	06	04	08	12	10	14	34	48	64	69
08	34	04	02	01	02	01		01	01	03	11	08	10	22	36	59	53
07	25	01								01	07	04	03	10	25	40	40
06	19										03	04	03	05	20	29	31
05	13											01		04	16	18	22
04	09													01	10	13	11
03	04														03	05	07
02																04	02
01																	
00																	
N:	134	136	214	229	208	165	147	85	84	75	76	73	71	82	70	80	90

GREEN: Normal RED: Abnormal relative to age ORANGE: Deficit relative to younger persons

Appendix 4. ACQ5

Asthma Control Questionnaire, 5-question Version

Please answer Questions 1-5.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you woken by your asthma during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how limited were you in your activities because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much shortness of breath did you experience because of your asthma?

0 None
1 A very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

5. In general, during the past week, how much of the time did you wheeze?

0 Not at all
1 Hardly any of the time
2 A little of the time
3 A moderate amount of the time
4 A lot of the time
5 Most of the time
6 All the time