ALLAKOS, INC

Clinical Research Protocol

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY TO EVALUATE MULTIPLE DOSES OF AK001 IN PATIENTS WITH MODERATE TO SEVERE NASAL POLYPOSIS

Protocol Number:	AK001-002
Protocol Amendment 2.3:	27OCT2016
Protocol Amendment 1:	27APR2016
Original Protocol:	19FEB2016
Investigational Product:	AK001
EudraCT Number:	2016-000460-42
Study Phase:	2
Sponsor:	Allakos, Inc. 75 Shoreway Road, Suite A San Carlos, CA 94070
Sponsor Medical Monitor:	Name: Alejandro Dorenbaum, MD Telephone: 415-328-9115 E-mail: adorenbaum@allakos.com

Approval:

Alejandro Dorenbaum, MD — 11-11-2016

Sponsor Signature (Name and Title) — *Date*

This confidential information about an investigational product is provided for the exclusive use of Investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the patients enrolled under my supervision and providing Allakos, Inc. with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this investigational site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and to abide by the terms of this protocol.

Protocol Number: AK001-002

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Study to Evaluate Multiple Doses of AK001 in Patients With Moderate to Severe Nasal Polyposis

Protocol Amendment 2.3

Date: 27OCT2016

_____ _____

Investigator Signature *Date*

_____

Print Name and Title

Site # _____

Site Name _____

Address _____

_____

Phone Number _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACT	Asthma Control Test™
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
$AUC_{(inf)}$	Area under the plasma concentration-time curve from zero hours to infinity
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero hours to time (t)
CBC	Complete blood count
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyposis
CRSwNP	Chronic rhinosinusitis with nasal polyposis
CT	Computed tomography
DMC	Data Monitoring Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ET	Early Termination
EU	European Union
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
gMean	Geometric mean
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus

IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL	Interleukin
IEC	Independent Ethics Committee
INS	Intranasal steroid
IRB	Institutional Review Board
IXRS	interactive voice or web response system
IV	Intravenous(ly)
MAb	Monoclonal antibody
MC	Mast cells
MedDRA	Medical Dictionary for Regulatory Activities
PE	Physical examination
PGD2	Prostaglandin D2
PK	Pharmacokinetic(s)
PNIF	Peak nasal inspiratory flow
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SF-36	36-Item Short Form Health Survey
Siglec	Sialic acid-binding, immunoglobulin-like lectin
SNOT-22	Sino-nasal Outcome Test-22
SOC	System organ class
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TPS	Total Polyp Score
ULN	Upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test™
VAS	Visual Analogue Scale
V_z	Volume of distribution
WBC	White blood cell

PROTOCOL SYNOPSIS

TITLE	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Study to Evaluate Multiple Doses of AK001 in Patients With Moderate to Severe Nasal Polyposis
SPONSOR	Allakos, Inc.
NUMBER OF SITES	Approximately 14 investigational sites in the European Union and the United States
RATIONALE	Nasal polyps are benign edematous masses that can cause nasal obstruction, rhinorrhea, facial pressure, postnasal drip, and loss of smell. It is estimated that nasal polyps affect 1% to 4% of the general population with a 2:1 male to female preponderance. The incidence increases with age, with peak incidence between 40 and 60 years of age. Although the etiology of nasal polyposis (recurrent, multiple polyps) is unknown, various comorbidities, such as chronic inflammation of the mucous membranes in the nose and paranasal sinuses, allergic rhinitis, atopy, and asthma have been proposed as factors in the genesis of nasal polyposis. Phenotypically, chronic rhinosinusitis (CRS) can be classified as either without nasal polyposis (CRSsNP) or with nasal polyposis (CRSwNP), which comprises the majority of cases of nasal polyposis. The more common CRSwNP is often characterized by eosinophilic inflammation with high levels of eosinophil cationic protein; interleukins (IL)-4, IL-5, and IL-13; and tissue immunoglobulin E (IgE). Treatment options for nasal polyposis range from topical and/or systemic corticosteroids to functional endoscopic sinus surgery. Patients with CRSwNP and comorbid asthma, in particular, have a poor therapeutic response and high polyp recurrence rate, and their diseases are more difficult to treat. Both diseases have an adverse effect on quality of life and confer a large economic burden. AK001 is a humanized immunoglobulin G4 (IgG4) monoclonal antibody directed against Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (siglecs). No close homolog has been found in other animal or primate species apart from great apes and baboons. Consequently, AK001 has been studied in Siglec-8 humanized and transgenic mouse models and with human blood and tissue cells. Siglec-8 has a restricted tissue distribution and is expressed selectively on the surface of mature eosinophils, mast cells (MCs), and at lower levels on basophils but not in early precursors of these cell populations or other blood cells. Crosslinking of Siglec-8 by AK001 can

	induce apoptosis of eosinophils previously activated by certain cytokines. The antibody does not induce apoptosis in MCs, but inhibits histamine release and de novo synthesis of prostaglandin D2 (PGD2) induced by IgE receptor activation. High levels of eosinophils and of MCs (up to 8% of isolated cells) are evident in nasal polyps. Mast cells and eosinophils isolated from nasal polyps have been shown by flow cytometry to express surface Siglec-8. Single doses of AK001, ranging from 0.01 mg/kg to 10 mg/kg, were evaluated in a Phase 1, double-blind, placebo-controlled, dose-escalation clinical trial (AK001-001) in healthy volunteers and patients with atopic disease. Of the 34 subjects who were enrolled in the study, a total of 26 received AK001 and 8 received placebo. In this study, AK001 was well tolerated. There were no infusion-related reactions or clinically relevant changes in vital signs, electrocardiograms (ECGs), or safety laboratory tests. Following infusion of AK001, values of markers of MC degranulation (serum tryptase and urine histamine/prostaglandin metabolites) remained in the normal ranges for all subjects. Eosinophil granule protein values remained in or close to the normal range in all subjects. Excluding the 2 subjects who received AK001 at a dose of 0.01 mg/kg or 0.1 mg/kg for whom there were no reported adverse events (AEs), 4 of 8 subjects (50%) in the placebo group and 7 of 24 subjects (29.2%) in the AK001 groups had treatment-emergent adverse events (TEAE). One subject (12.5%) in the placebo group and 3 subjects (12.5%) in the AK001 groups had single incidences of upper or viral respiratory infection. Similarly, 1 subject (12.5%) in the placebo group and 3 subjects (12.5%) in the AK001 groups had single incidences of skin and subcutaneous tissue disorders, including alopecia, dermatitis, contact dermatitis, and pruritus and rash at the site of skin testing. Two subjects, 1 in the placebo group and 1 in the AK001 groups, had AEs of urticaria. A single AE of rash that occurred on Day 2 after dosing, which was mild in severity and resolved without intervention, was considered possibly related to study drug. All other AEs were considered not related to study drug. No dose-limiting toxicities were observed, and no subject was discontinued from the study due to an AE. By reducing activated eosinophils and blocking mast-cell histamine and PGD2 release, AK001 may be useful in the treatment of patients with moderate to severe chronic nasal polyposis with predominant eosinophilic and MC inflammation and whose symptoms are resistant to treatment with intranasal steroids (INSs).

STUDY DESIGN	This is a Phase 2, randomized, double-blind, placebo-controlled study of the safety and tolerability of AK001 compared with placebo in patients with moderate to severe chronic nasal polyposis and whose symptoms are resistant to treatment with INSs. At least 50% of patients enrolled will have comorbid asthma. The study will comprise an up to 4-week Screening period and a 4-week Run-in period followed by randomization and dosing with AK001 or placebo for 7 weeks followed by a 17-week observation (Post-treatment) period. There will be 10 scheduled study visits. The total duration of the study will be up to approximately 32 weeks. After the Screening period, approximately 70 eligible patients will be enrolled and enter a Run-in period of 4 weeks to achieve a stable regimen with a common intranasal topical steroid (NASONEX [mometasone furoate monohydrate] 2 sprays in each nostril twice a day) and discontinue any other intranasal topical steroid. Patients will return to the clinic at the end of the Run-in period prior to dosing with study drug for pre-dose evaluations. Patients who continue to meet the eligibility criteria for the study will be randomized, will continue to use NASONEX until the end of the study, and will also receive either 25 mg of AK001 (n=25), 250 mg of AK001 (n=25), or a corresponding placebo (n=20) on Days 0, 21, and 49. The randomization will be stratified based on presence or absence of asthma. Patients will be required to maintain their Baseline treatments for nasal polyposis unchanged throughout participation in this trial. Enrollment will be staggered; no more than 1 patient will be randomized every 4 weeks at each site. If there are any safety concerns, enrollment will be put on hold, and a safety review meeting will occur. A Data Monitoring Committee will be convened periodically to monitor the safety of patients over the course of the study.
PRIMARY OBJECTIVE	To evaluate the effect of 2 different dose levels of AK001 in combination with an INS versus the INS alone on the reduction in size of nasal polyps as evaluated by the change from Baseline to Week 12 after the start of treatment in Total Polyp Score (TPS)

SECONDARY OBJECTIVES	1. To evaluate the effect of 2 different dose levels of AK001 in combination with an INS versus the INS alone on changes from Baseline to Week 12 after the start of treatment in: a) Size of polyps as evaluated by Lund-Mackay score at selected Investigator sites by computed tomography (CT) scan b) Nasal airway patency as evaluated by peak nasal inspiratory flow (PNIF) c) Ability to smell (University of Pennsylvania Smell Identification Test™ [UPSIT]) d) Patient-reported symptoms of sinusitis (Sino-nasal Outcome Test-22 [SNOT-22] and Visual Analogue Scales [VASs]) e) Clinical symptoms improvement scale f) Quality of life (36-Item Short Form Health Survey [SF-36]) 2. To evaluate the time to first response in TPS 3. To evaluate the change in TPS, UPSIT, and patient-reported symptoms of sinusitis over time 4. To evaluate the safety and tolerability of 2 different dose levels of AK001 in combination with an INS during 7 weeks of study drug in patients with moderate to severe nasal polyps and whose symptoms are resistant to INSs
EXPLORATORY OBJECTIVES	In all patients, to: 1. Potentially explore markers of MCs and eosinophils and inflammatory response in blood In patients with comorbid asthma, to explore the effect of 2 different dose levels of AK001 in combination with an INS versus the INS alone on changes from Baseline to Week 12 after the start of treatment in: 1. TPS 2. Pulmonary function (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and forced expiratory flow [FEF]) assessed using spirometry 3. Asthma-related symptoms (Asthma Control Test™ [ACT]) 4. Use of asthma rescue therapy

NUMBER OF PATIENTS	Approximately 70 patients randomized to receive 25 mg of AK001 (n=25), 250 mg of AK001 (n=25), or a corresponding placebo (n=20)
PATIENT SELECTION CRITERIA	**Inclusion Criteria:** Patients are eligible for the study if all of the following criteria are met: 1. Written informed consent 2. Male and female patients aged ≥18 and ≤75 years at the time of Screening 3. SNOT-22 ≥30 4. At Screening, TPS of ≥5 for both nostrils with presence on endoscopy of nasal polyps of grade ≥2 in each nostril according to the polyp grading scale Polyp grading scale for each nostril: 0=no nasal polyps 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate 2=polyps reaching below the lower border of the middle turbinate 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate 4=large polyps causing complete obstruction of the inferior nasal cavity 5. History of at least 2 of the following symptoms for more than 4 weeks prior to Screening: a) Anterior nasal discharge b) Posterior nasal discharge c) Nasal congestion, blockade, or obstruction d) Decreased sense of smell e) Facial pain or pressure 6. Received continuous topical nasal steroids and/or leukotriene receptor antagonists for at least 8 weeks prior to Screening unless failure or no effect of prior nasal steroid or leukotriene receptor antagonist therapy is documented 7. At randomization, received ≥80% of doses of NASONEX scheduled during the Run-in period 8. At randomization, TPS of ≥5 for both nostrils with

	presence on endoscopy of nasal polyps of grade ≥2 in each nostril according to the polyp grading scale (see Inclusion Criterion #4) and despite prior INS treatment during the Run-in period 9. Female patients must be post-menopausal for ≥1 year with documented follicle-stimulating hormone (FSH) >30 IU/L, surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or, if of child-bearing potential, willing to use a highly effective method of contraception from Screening until at least 17 weeks after the last dose of the study drug is administered, which corresponds to approximately 5 half-lives of AK001 10. Male patients with female partners of childbearing potential must agree to use a highly effective method of contraception from Screening until at least 17 weeks after the last dose of the study drug is administered, which corresponds to approximately 5 half-lives of AK001. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation. 11. Negative Screening ova and parasite test 12. No clinically significant Screening 12-lead ECG, vital sign, hematology, chemistry, or urinalysis findings 13. Able to comply with all study procedures including recording scores of symptoms (i.e., anterior nasal discharge; posterior nasal discharge, nasal congestion, blockade, or obstruction; decreased sense of smell; facial pain or pressure) at clinic visits **Exclusion Criteria:** Patients are ineligible for the study if any of the following criteria are met: 1. Use of systemic corticosteroids within 6 weeks prior to Screening (or 5 half-lives, whichever is longer) or scheduled to receive systemic corticosteroids 2. Chronic use of antibiotic therapy within 3 months prior to Screening 3. Receipt of short-term antibiotic therapy within 14 days prior to Screening or use of antibiotics during the Screening period 4. Acute infection that requires antibiotic, antiviral, or antifungal therapy within 30 days prior to Screening

	5. Nasal surgery (including polypectomy) within 6 months prior to Screening 6. Significant mechanical nasal airway obstruction due to septal deviation based on Investigator assessment 7. Use of investigational drugs or participation in another clinical trial within 30 days or 5 half-lives, whichever is longer, prior to Screening 8. Use of any medications that may interfere with the study, such as immunosuppressive drugs during the 2 weeks before Screening, or expected to require such medications through Day 168 9. Receipt of any live attenuated vaccines within 30 days or 5 half-lives, whichever is longer, prior to initiation of treatment in the study or expected to receive such a vaccine during the treatment period 10. Pregnancy or lactation in women 11. In patients with comorbid asthma, either of the following: a) A FEV1 ≤60% at Screening b) An asthma exacerbation requiring systemic (oral and/or parenteral) steroid treatment or hospitalization for >24 hours for treatment of asthma within 30 days prior to Screening 12. History of human immunodeficiency virus infection (HIV) or other severe immunosuppressive disease or positive HIV test at Screening 13. Current diagnosis or prior history of allergic fungal sinusitis, cystic fibrosis, ciliary dyskinesia, Wegener's Granulomatosis, or Churg-Strauss syndrome 14. Current diagnosis or prior history of any other condition likely to present with non-eosinophilic nasal polyps 15. History of hepatitis or active/chronic liver disease of any genesis or positive serology for hepatitis B virus (HBV) surface antigen, hepatitis C virus (HCV) antibody at Screening 16. Current diagnosis or history of cancer 17. A helminthic parasitic infestation, even if treated, within 6 months prior to Screening 18. History of or suspected history of cytokine release syndrome 19. Any disease or condition (medical or surgical) which, in the opinion of the Investigator, might compromise the

	hematologic, cardiovascular, pulmonary, renal, endocrine, autoimmune, gastrointestinal, hepatic, skeletal, or central nervous systems; other conditions that might interfere with the absorption, distribution, metabolism or excretion of AK001 or would place the patient at increased risk (including any condition, such as diabetes, that would make it unsafe for the patient to fast as required by the study) 20. Known hypersensitivity to any constituent of the product 21. Legally institutionalized
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	AK001 25 mg or 250 mg, to be administered intravenously (IV) over approximately 1 hour on Days 0, 21, and 49
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Placebo, to be administered IV over approximately 1 hour on Days 0, 21, and 49
DURATION OF PATIENT PARTICIPATION AND DURATION OF STUDY	Patients will participate in the study for up to approximately 32 weeks as follows: • Screening period: up to 4 weeks • Run-in period: 4 weeks • Treatment period: 7 weeks • Observation (Post-treatment period): 17 weeks

SAFETY EVALUATIONS	The safety and tolerability of 2 different dose levels of AK001 will be assessed by determining the incidence, relationship to study drug, and severity of TEAEs, withdrawals due to AEs, and changes in vital signs, laboratory test (including anti-drug antibody [ADA]) findings, concomitant medication use, and physical examination (PE) findings. Safety results in patients dosed with 2 different dose levels of AK001 will be compared with those in patients dosed with placebo (INS alone). Each patient will remain at the Investigator site for a safety observation period of at least 8 hours following the end of each infusion. At the discretion of the Investigator, a longer monitoring period, if needed, may be implemented before the patient is discharged. Follow-up telephone calls will be made to the patient at 12 and 24 hours following the end of each infusion. Patients will be informed that, from discharge to the 24 hour telephone contact, they must be accompanied by another adult at all times, not travel alone or travel during bad weather, remain close to the location of the site, and have access to a telephone and transportation.
DRUG LEVEL EVALUATIONS	Blood samples will be obtained at pre-defined intervals for assessment of serum concentrations of AK001 using a validated enzyme-linked immunosorbent assay (ELISA) method.
EFFICACY EVALUATIONS	The following specific efficacy evaluations will be conducted in all patients: • TPS of nasal endoscopy (blinded centralized evaluation) • Size of polyps as evaluated by Lund-Mackay score at selected Investigator sites by CT scan • Nasal airway patency as evaluated by PNIF • Ability to smell (UPSIT) • SNOT-22 (patient-reported symptoms) • VASs (patient-reported symptoms) • Clinical symptoms improvement scale • SF-36 (quality of life) • Blood eosinophil and basophil absolute counts • Potentially explore markers of MCs and eosinophils and inflammatory response in blood The following specific additional efficacy evaluations will be conducted in asthmatic patients: • TPS of nasal endoscopy (blinded centralized evaluation) • Pulmonary function (FEV1, FVC, and FEF) assessed using spirometry

	• ACT • Use of asthma rescue therapy
STATISTICS	**Sample Size** This study will evaluate the effect of 2 different dose levels of AK001 in combination with an INS versus the INS plus placebo on the reduction in size of nasal polyps. Assuming equal efficacy effect of the 2 active treatment arms, a sample size of approximately 70 patients (25 mg of AK001 [n=25], 250 mg of AK001 [n=25], and a corresponding placebo (n=20]) will ensure at least 80% power to detect a difference in mean nasal polyp scores between the placebo group (Mean= -0.3; standard deviation [SD] ≤1.128) and each of the AK001 groups (Mean= -1.9; SD ≤2.064) with an alpha of 0.05. **Safety** All safety analyses will be performed in the Safety Population, defined as all patients who were randomized and received at least 1 dose of the study drug. Patients will be analyzed according to the study drug they received. Safety measures including AEs, clinical safety laboratory tests (including ADA), vital signs, PEs, and concomitant medication usage) will be summarized descriptively. For quantitative variables, descriptive statistics including number of observations, mean, median, SD, and range will be provided for the values themselves as well as for the changes from Baseline by treatment group at each study visit. Qualitative variables will be summarized using counts and percentages in each treatment group at each study visit. **Drug Level Analysis** Pharmacokinetic analysis of AK001 will be carried out for patients with the serum concentration data obtained at pre-defined time points. **Efficacy** The main population for efficacy will be the Modified Intention-to-Treat Population, defined as all patients randomized who receive at least 1 dose of study drug and have a valid Baseline measurement and at least 1 post-baseline efficacy assessment. Patients will be analyzed for efficacy according to the group to which they were randomized. In addition, the primary efficacy analysis will also be performed for the Per-Protocol Population, defined as patients who have a Week 12 visit and valid efficacy measurements. The effect of 2 different dose levels of AK001 in combination with an INS versus the INS alone on the reduction in size of

	nasal polyps as evaluated by the change from Baseline to Week 12 after the start of treatment in TPS will be displayed for each treatment group by study visit, using summary statistics including the number of observations, the mean, median, SD, and range. Each active treatment group will be compared separately with the placebo group for change from Baseline in TPS by utilizing a mixed effect repeated measures analysis of variance (ANOVA) model with specific contrast statement for Week 12 and for each comparison separately. Adjustment in alpha for multiple comparison will be controlled according to the Hochberg method, in which, if the efficacy comparison of the high active arm versus placebo is statistically significant at the 0.05 level, no penalty will be assessed to the comparison of low active arm versus placebo. Otherwise, the low active arm versus placebo will be compared at the 0.025 level. Additional efficacy measures will be analyzed in support of the primary efficacy endpoint results. In addition to change from Baseline in TPS, absolute values and percentage changes from Baseline will be analyzed separately using the same repeated measures model described above. A responder analysis will also be considered. Examination of treatment effect over time for TPS, UPSIT, and patient-reported symptoms of sinusitis (SNOT-22) will be examined using appropriate similar repeated measures ANOVA. The stratification factor, presence or absence of asthma, may be included in the model. Size of polyps as evaluated by Lund-Mackay score at selected Investigator sites by CT scan (the CT scans are optional and will only be done at Investigator sites at which appropriate and timely regulatory approval or authorization can be granted); PNIF; UPSIT; and patient-reported SNOT-22, VAS, clinical symptoms improvement scale, and SF-36 scores will be compared between each of the 2 active treatment groups and the placebo group using a repeated measure ANOVA with contrast statements for comparison at Week 12 as well as at other time points in the study.

1 BACKGROUND

Nasal polyps are benign edematous masses that can cause nasal obstruction, rhinorrhea, facial pressure, postnasal drip, and loss of smell. It is estimated that nasal polyps affect 1% to 4% of the general population with a 2:1 male to female preponderance. The incidence increases with age, with peak incidence between 40 and 60 years of age.[1,2] Although the etiology of nasal polyposis (recurrent, multiple polyps)[2] is unknown, various comorbidities, such as chronic inflammation of the mucous membranes in the nose and paranasal sinuses, allergic rhinitis, atopy, and asthma, have been proposed as factors in the genesis of nasal polyposis.[3,4]

Phenotypically, chronic rhinosinusitis (CRS) can be classified as either without nasal polyposis (CRSsNP) or with nasal polyposis (CRSwNP), which comprises the majority of cases of nasal polyposis. The more common CRSwNP is characterized by eosinophilic inflammation with high levels of eosinophil cationic protein; interleukin (IL)-4, IL-5, and IL-13; and tissue immunoglobulin E (IgE).[2,5]

Treatment options for nasal polyposis range from topical and/or systemic corticosteroids to functional endoscopic sinus surgery.[5] Patients with CRSwNP and comorbid asthma, in particular, have a poor therapeutic response and high recurrence rate, and their diseases are more difficult to treat. Both diseases have an adverse effect on quality of life and confer a large economic burden.[3]

AK001 is a humanized immunoglobulin G4 (IgG4) monoclonal antibody (MAb) directed against Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (siglecs). No close homolog has been found in other animal or primate species apart from great apes and baboons. Consequently, AK001 has been studied in Siglec-8 humanized and transgenic mouse models and with human blood and tissue cells. Siglec-8 has a restricted tissue distribution and is expressed selectively on the surface of mature eosinophils, mast cells (MCs), and at lower levels on basophils but not in early precursors of these cell populations or other blood cells. Crosslinking of Siglec-8 by AK001 can induce apoptosis of eosinophils previously activated by certain cytokines. The antibody does not induce apoptosis in MCs, but inhibits histamine release and de novo synthesis of prostaglandin D2 (PGD2) induced by IgE-receptor activation.

High levels of eosinophils and of MCs (up to 8% of isolated cells) are evident in nasal polyps. Mast cells and eosinophils isolated from nasal polyps have been shown by flow cytometry to express surface Siglec-8.[6]

By reducing activated eosinophils and blocking mast-cell histamine and PGD2 release, AK001 may be useful in the treatment of patients with moderate to severe chronic nasal polyposis with predominant eosinophilic and MC inflammation and whose symptoms are resistant to treatment with intranasal steroids (INSs).

1.1 Overview of Nonclinical Studies

Siglec-8 is expressed only in humans and other high-level primates. However, AK001 has been evaluated in 2 in vivo murine models: a humanized mouse containing abundant human MCs and eosinophils and a Siglec-8 transgenic mouse model in which, similar to

humans, functional human Siglec-8 is expressed selectively on MCs, eosinophils, and basophils and not in other cells.

In the humanized mouse model engrafted with human hematopoietic stem cells in which human eosinophils and enhanced numbers of human MCs are present, anti-Siglec-8 antibodies reduce IL-5–induced eosinophilia and prevent an IgE-mediated ear swelling response (Type I hypersensitivity reaction known as passive cutaneous anaphylaxis). AK001 also prevents Type 1 hypersensitivity reactions known as passive cutaneous anaphylaxis mediated by human MCs when administered either before or after sensitization of the mice with specific IgE.

In the transgenic mouse model, AK001 binding to Siglec-8 leads to inhibition of IgE-mediated MC histamine release as is seen in vitro in cultured human MCs. AK001 also inhibits IgE-mediated release of MC protease-1 from mucosal MCs in Siglec-8 transgenic mice without significantly affecting the number of MCs in these mice, consistent with the inhibition of MC degranulation and lack of apoptosis shown by AK001 on human MCs in vitro. The in vivo demonstration of activity of AK001 in Siglec-8 transgenic mice is consistent with the in vitro effects on human MCs and eosinophils, which indicates that AK001 is pharmacologically active in this model and supports the use of this mouse strain as a relevant species for safety testing.

No adverse effects on body weight or clinical signs of AK001 treatment have been observed in preliminary studies in Siglec-8 transgenic mice receiving up to 4 doses of AK001 at a 5-mg/kg dose at 3-day intervals, weekly doses of 100 mg/kg for 12 weeks, or a single 5-mg/kg dose in a passive systemic anaphylaxis model, a dose that is pharmacologically active in this model.

For toxicity testing, Siglec-8 transgenic mice received a single intravenous (IV) bolus of AK001 at 2 dose levels, 50 and 100 mg/kg. The high dose, 100 mg/kg, was selected to represent a dose 10-fold higher than the highest proposed clinical dose, 10 mg/kg. At both dose levels, there were no adverse AK001-related effects on survival, body weights, clinical observations, clinical pathology, or anatomic pathology. The no-observed-adverse-effect level following a single IV administration of AK001 to transgenic mice was 100 mg/kg.

1.2 Overview of Clinical Studies

AK001 was evaluated in a Phase I, double-blind, placebo-controlled, dose escalation clinical trial (AK001-001) in healthy volunteers and patients with atopic disease. In this study, subjects received single doses of AK001 ranging from 0.01 mg/kg to 10 mg/kg.

Of the 34 subjects who were enrolled in the study, a total of 26 received AK001 and 8 received placebo. The mean age (standard deviation [SD]) at enrollment was 39.6 ±11.89 years (range, 22 to 62); 62% of subjects were males and 38% of subjects were females. The majority of subjects were White (53%), 21% of subjects were Asian, 18% of subjects were Black or African American, and the rest of the subjects were Hawaiian, Pacific Islander or had races designated as “Other.” There were no major imbalances in age, sex, race, or ethnicity among the treatment groups.

AK001 was well tolerated in this study. There were no infusion-related reactions. Following infusion of AK001, values of markers of MC degranulation (serum tryptase and

urine histamine/prostaglandin metabolites) remained in the normal ranges for all subjects. Eosinophil granule protein values remained in or close to the normal range in all subjects. Excluding the 2 subjects who received AK001 at a dose of 0.01 mg/kg or of 0.1 mg/kg for whom there were no reported adverse events (AEs), 4 of 8 subjects (50%) in the placebo group and 7 of 24 subjects (29.2%) in the AK001 groups had treatment-emergent adverse events (TEAE). One subject (12.5%) in the placebo group and 3 subjects (12.5%) in the AK001 groups had single incidences of upper or viral respiratory infection. Similarly, 1 subject (12.5%) in the placebo group and 3 subjects (12.5%) in the AK001 groups had single incidences of skin and subcutaneous tissue disorders, including alopecia, dermatitis, contact dermatitis, and pruritus and rash at the site of skin testing. Two subjects, 1 in the placebo group and 1 in the AK001 groups, had AEs of urticaria. A single AE of rash that occurred on Day 2 after dosing, which was mild in severity and resolved without intervention, was considered possibly related to study drug. All other AEs were considered not related to study drug. There were no clinically relevant changes in vital signs, electrocardiograms (ECGs), or safety laboratory tests, including serum chemistries, hematology, and urinalysis. No dose-limiting toxicities were observed, and no subject was discontinued from the study due to an AE.

2 RATIONALE FOR STUDY AND DOSE SELECTION

The present study is a Phase 2, randomized, double-blind, placebo-controlled study of the safety and tolerability of 2 different dose levels of AK001 compared with placebo in patients with moderate to severe chronic nasal polyposis and whose symptoms are resistant to treatment with INSs.

In Study AK001-001, dose-related pharmacokinetic (PK) parameters, including maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from zero hours to time (t) ($AUC_{[0\text{-}t]}$), and area under the plasma concentration-time curve from zero hours to infinity ($AUC_{[inf]}$), increased in a dose-proportional manner. The geometric mean (gMean) terminal elimination half-life ($t_{1/2}$) was in the range of 20 to 27 days, which is typical for a MAb. The gMean clearance ranged from 4.85 to 6.86 mL/hour and did not appear to be a function of body weight or body mass index (BMI). The gMean volume of distribution (V_z) was 0.060 L/kg, also typical for a MAb.

Siglec-8 internalization was durable and persisted as long as AK001 was present in serum. Siglec-8 internalization was not observed at Day 28 in the lowest dose cohort, 0.01 mg/kg, consistent with the undetectable levels of serum AK001 at Day 28. In all other dose cohorts, Siglec-8 internalization was maintained through Day 28.

The recommended Phase 2 doses of 25 mg and 250 mg administered IV every 3 to 4 weeks were calculated on the basis of nonclinical PK and pharmacodynamic data and on the PK and safety data collected in the Phase 1 study. These doses are expected to maintain 60% to 80% engagement and internalization of the Siglec-8 receptor; 60% to 80% internalization of the Siglec-8 receptor is associated with substantial inhibition of MCs and killing of activated eosinophils in in vitro experiments.

For additional information, please see the Investigator's Brochure (IB).

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to evaluate the effect of 2 different dose levels of AK001 in combination with an INS versus the INS alone on the reduction in size of nasal polyps as evaluated by the change from Baseline to Week 12 after the start of treatment in Total Polyp Score (TPS) (Appendix 2 Section 19.2).

3.2 Secondary Objectives

The secondary objectives are:

1. To evaluate the effect of 2 different dose levels of AK001 in combination with an INS versus the INS alone on changes from Baseline to Week 12 after the start of treatment in:

   a) Size of polyps as evaluated by Lund-Mackay score (Appendix 3 Section 19.3) at selected Investigator sites by computed tomography (CT) scan

   b) Nasal airway patency as evaluated by peak nasal inspiratory flow (PNIF)

   c) Ability to smell by the University of Pennsylvania Smell Identification Test™ (UPSIT) (Appendix 4 Section 19.4)

   d) Patient-reported symptoms of sinusitis (Sino-nasal Outcome Test-22 [SNOT-22] [Appendix 5 Section 19.5] and Visual Analogue Scales [VASs] [Appendix 6 Section 19.6])

   e) Clinical symptoms improvement scale[3] (Appendix 6 Section 19.6)

   f) Quality of life (36-Item Short Form Health Survey [SF-36] Appendix 7 Section 19.7)
2. To evaluate the time to first response in TPS (Appendix 2 Section 19.2)
3. To evaluate the change in TPS (Appendix 2 Section 19.2), UPSIT (Appendix 4 Section 19.4), and patient-reported symptoms of sinusitis (Appendix 4 Section 19.6) over time
4. To evaluate the safety and tolerability of 2 different dose levels of AK001 in combination with an INS during 7 weeks of study drug in patients with moderate to severe nasal polyps and whose symptoms are resistant to INSs

3.3 Exploratory Objectives

The exploratory objectives are to:

1. Potentially explore markers of MCs and eosinophils and inflammatory response in blood

In addition, in patients with comorbid asthma, the exploratory objectives are to explore the effect of 2 different dose levels of AK001 in combination with an INS versus the INS alone on changes from Baseline to Week 12 after the start of treatment in:

1. TPS (Appendix 2 Section 19.2)
2. Pulmonary function (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and forced expiratory flow [FEF]) assessed using spirometry
3. Asthma-related symptoms (Asthma Control Test™ [ACT] Appendix 8 Section 19.8)
4. Use of asthma rescue therapy

4 STUDY DESIGN

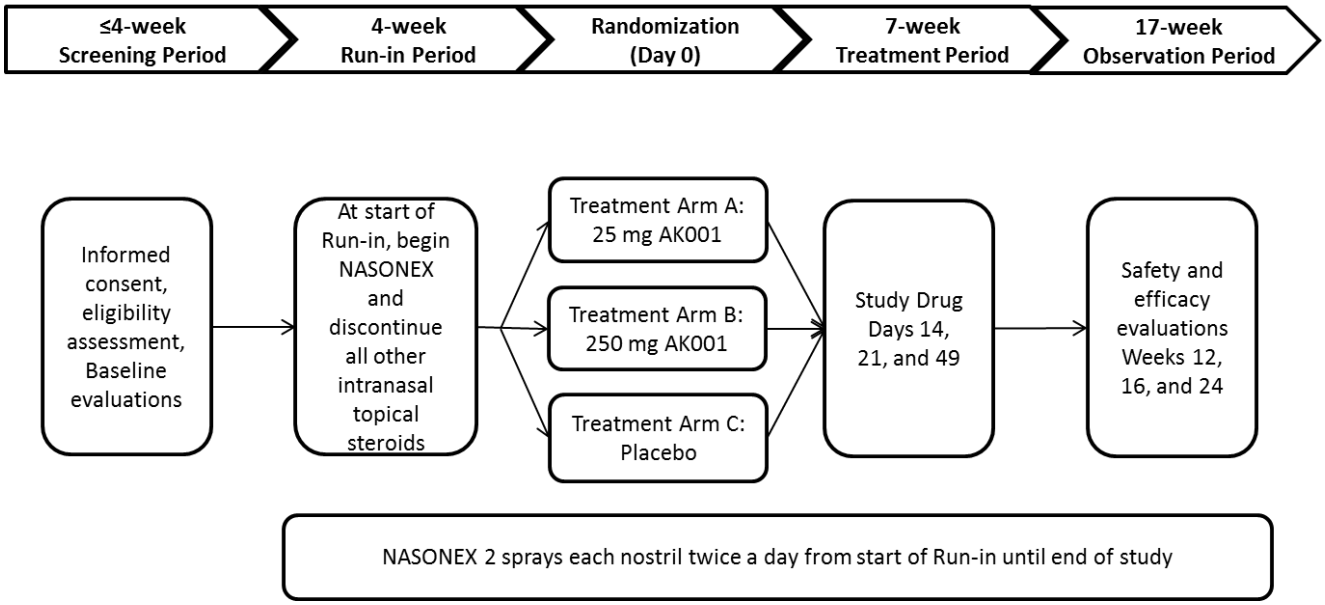
4.1 Study Overview

This is a Phase 2, randomized, double-blind, placebo-controlled study of the safety and tolerability of 2 different dose levels of AK001 compared with placebo in combination with an INS in patients with moderate to severe chronic nasal polyposis and whose symptoms are resistant to treatment with INSs. At least 50% of patients enrolled will have comorbid asthma.

As presented in Figure 1, the study will comprise an up to 4-week Screening period and a 4-week Run-in period followed by randomization and dosing with AK001 or placebo for 7 weeks followed by a 17-week observation (Post-treatment) period. There will be 10 scheduled study visits. The total duration of the study will be up to approximately 32 weeks.

After the Screening period, which will last up to 4 weeks, approximately 70 eligible patients will be enrolled and enter a Run-in period of 4 weeks to achieve a stable regimen with a common intranasal topical steroid (NASONEX; [mometasone furoate monohydrate] 2 sprays in each nostril twice a day) and discontinue any other intranasal topical steroid. Patients will return to the clinic at the end of the Run-in period prior to dosing with study drug for pre-dose evaluations. Patients who continue to meet the eligibility criteria for the study will be randomized, will continue to use NASONEX until the end of the study, and will also receive 25 mg of AK001 (n=25), 250 mg of AK001 (n=25), or a corresponding placebo (n=20) on Days 0, 21, and 49. Patients will be required to maintain their Baseline treatments for nasal polyposis unchanged throughout participation in this trial.

Figure 1 Study Schema



A Data Monitoring Committee (DMC) will be convened periodically to monitor the safety of patients over the course of the study. Members of the DMC can request the identities of patients' study drugs if needed. Additional information about the DMC can be found in the DMC charter.

Enrollment will be staggered; no more than 1 patient will be randomized every 4 weeks at each site.

If there are any safety concerns, enrollment will be put on hold, and a safety review meeting will occur.

The schedule of the required evaluations is provided in Table 1.

4.2 Schedule of Events

Table 1 Schedule of Events

Procedure	**Screening Period**	**Run-in Period[1]**		**Treatment Period**										**Post-treatment Period**		
Visits	**Screening**	**Run-in[2]**	**Day -3**	**Day 0**		**Day 1**	**Day 14**	**Day 21**		**Day 22**	**Day 49**		**Day 50**	**Day 84**	**Day 112**	**Day 168/ ET**
Days	**-56 to -29[3]**	**-28[4]**	**-3±2**	**0 (Pre-dose**	**0**	**1**	**14±2**	**21±2 (Pre-dose)**	**21±2**	**22±2**	**49±2 (Pre-dose)**	**49±2**	**50±2**	**84±4**	**112± 4**	**168± 7 (or ET)**
Weeks	**-8 to -5**	**-4[5]**	**-1**	**0**	**0**	**0**	**2**	**3**	**3**	**3**	**7**	**7**	**7**	**12**	**16**	**24**
Informed consent	X															
Eligibility assessment	X		X													
Randomization				X[6]												
Intranasal steroid adjustment[7]		X														
Study drug[8]					**X**				**X**			**X**				
Medical history[9]	X															
Complete PE[10]	X															
Symptom-directed PE[11]				X	X		X	X	X		X	X		X	X	X
Follow-up telephone call[12]					X	X			X	X		X	X			

Procedure	**Screening Period**	**Run-in Period[1]**		**Treatment Period**										**Post-treatment Period**		
Visits	**Screening**	**Run-in[2]**	**Day -3**	**Day 0**		**Day 1**	**Day 14**	**Day 21**		**Day 22**	**Day 49**		**Day 50**	**Day 84**	**Day 112**	**Day 168/ ET**
Days	**-56 to -29[3]**	**-28[4]**	**-3±2**	**0 (Pre-dose**	**0**	**1**	**14±2**	**21±2 (Pre-dose)**	**21±2**	**22±2**	**49±2 (Pre-dose)**	**49±2**	**50±2**	**84±4**	**112± 4**	**168± 7 (or ET)**
Weeks	**-8 to -5**	**-4[5]**	**-1**	**0**	**0**	**0**	**2**	**3**	**3**	**3**	**7**	**7**	**7**	**12**	**16**	**24**
Body weight and height[13]	X			X											X	X
Vital signs[14]	X		X	X[15]	X[15]		X	X[15]	X[15]		X[15]	X[15]		X	X	X
12-lead ECG	X															
Serum pregnancy test and FSH (if indicated)[16]	X		X					X			X					X
Fecal sample for ova and parasites	X															
HIV, HBV surface antigen, HCV antibody	X															
Hematology[17]	X		X				X	X			X			X	X	X
Chemistry[17]	X		X				X	X			X			X	X	X
Urinalysis	X		X				X				X			X	X	X
Nasal endoscopy[18]	X		X					X			X			X	X	
CT scan			X[19]											X[19]		

Procedure	**Screening Period**	**Run-in Period[1]**		**Treatment Period**										**Post-treatment Period**		
Visits	**Screening**	**Run-in[2]**	**Day -3**	**Day 0**		**Day 1**	**Day 14**	**Day 21**		**Day 22**	**Day 49**		**Day 50**	**Day 84**	**Day 112**	**Day 168/ ET**
Days	**-56 to -29[3]**	**-28[4]**	**-3±2**	**0 (Pre-dose**	**0**	**1**	**14±2**	**21±2 (Pre-dose)**	**21±2**	**22±2**	**49±2 (Pre-dose)**	**49±2**	**50±2**	**84±4**	**112± 4**	**168± 7 (or ET)**
Weeks	**-8 to -5**	**-4[5]**	**-1**	**0**	**0**	**0**	**2**	**3**	**3**	**3**	**7**	**7**	**7**	**12**	**16**	**24**
PNIF				X				X						X	X	
UPSIT				X			X	X			X			X	X	
SNOT-22	X			X			X	X			X			X	X[20]	
VASs and clinical symptoms improvement scale[21]	X	X	X	X			X	X			X			X	X[20]	
SF-36				X				X			X			X	X	
Spirometry[22]	X							X			X					
ACT[23]	X			X				X			X			X	X[20]	
Blood for PK				X[24]			X	X[24]			X[24]			X	X	X
ADA[25]				X											X	X
Blood for potential exploratory biomarker analysis[26]			X					X			X			X		
Total serum IgE			X													
ImmunoCAP test			X													

Procedure	**Screening Period**	**Run-in Period[1]**		**Treatment Period**										**Post-treatment Period**		
Visits	**Screening**	**Run-in[2]**	**Day -3**	**Day 0**		**Day 1**	**Day 14**	**Day 21**		**Day 22**	**Day 49**		**Day 50**	**Day 84**	**Day 112**	**Day 168/ ET**
Days	**-56 to -29[3]**	**-28[4]**	**-3±2**	**0 (Pre-dose**	**0**	**1**	**14±2**	**21±2 (Pre-dose)**	**21±2**	**22±2**	**49±2 (Pre-dose)**	**49±2**	**50±2**	**84±4**	**112± 4**	**168± 7 (or ET)**
Weeks	**-8 to -5**	**-4[5]**	**-1**	**0**	**0**	**0**	**2**	**3**	**3**	**3**	**7**	**7**	**7**	**12**	**16**	**24**
Prior[27]/concomitant medications	X	X	X	X	X	X	X	X	X		X	X		X	X	X
AEs					X	X	X	X	X	X	X	X	X	X	X	X
SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ACT = Asthma Control Test™; ADA = anti-drug antibody; AE = adverse event; BMI = body mass index; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ET = Early Termination; FEF = forced expiratory flow; FEV1 = forced expiratory volume in 1 second; FSH = follicle-stimulating hormone; FVC = forced vital capacity; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgE = immunoglobulin E; IV = intravenous; IXRS = interactive voice or web response system; PE = physical examination; PNIF = peak nasal inspiratory flow; PK = pharmacokinetic(s); SAE = serious adverse event; SF-36 = 36-Item Short Form Health Survey; SNOT-22 = Sino-nasal Outcome Test-22; TPS = Total Polyp Score; UPSIT = University of Pennsylvania Smell Identification Test™; VAS = Visual Analogue Scale.

1. The Run-in period is from Day -28 (or Day -29 or Day -30) through Day -1.
2. The Run-in clinic visit at Day -28 (or Day -29 or Day -30) may be replaced by telephone contact at the Investigator's discretion for selected patients. If so, the patient will have been provided with NASONEX and copies of the VASs and clinical symptoms improvement scale at Screening and will be contacted by phone on Day -28 (or Day -29 or Day -30) and instructed to begin NASONEX, complete the scales, and bring the completed scales to the next (Day -3) clinic visit.
3. The Screening period is from Day -56 through Day -29 (or, if Run-in starts on Day -29 or Day -30, on Day -30, or Day -31, respectively).
4. The Run-in clinic visit or telephone contact will occur at Day -28 (or Day -29 or Day -30). The Day -28 visit may occur as soon as the day after Screening. Inclusion and exclusion criteria may continue to be assessed while the patient is in the Run-in period.
5. The Run-in period will start during Week -5 if the Run-in clinic visit or telephone contact occurs at Day -29 or Day -30.
6. Randomization will occur via IXRS after confirmation that the patient meets all inclusion and no exclusion criteria.
7. All patients will use NASONEX (2 nasal inhalations in each nostril twice a day) and discontinue any other intranasal topical steroid from the start of the Run-in period through the end of the study.

8. Study Drug (AK001 or placebo) will be administered as a single IV infusion through a peripheral vein per additional specific instructions provided in the pharmacy manual. Each patient will remain at the Investigator site for a safety observation period of at least 8 hours following the end of each infusion. At the discretion of the Investigator, a longer monitoring period, if needed, before the patient is discharged may be implemented. Patients will be informed that, from discharge to the 24-hour telephone contact, they must be accompanied by another adult at all times, not travel alone or travel during bad weather, remain close to the location of the site, and have access to a telephone and transportation. If there are any safety concerns, enrollment will be put on hold.
9. The medical history will include all relevant medical history for the 5 years before Screening (e.g., history of current disease, other pertinent respiratory history, and information regarding aspirin sensitivity [obtained in response to a specific question] and underlying diseases).
10. A complete PE will be performed by either the Investigator or a qualified Sub-investigator and include the following body system or organ assessments: skin; head, eyes, ears, nose and throat; thyroid; lungs; cardiovascular; abdomen; extremities; lymph nodes; and a brief neurological examination.
11. A symptom-directed PE, including assessments of possible infusion site reactions, will be performed by either the Investigator or a qualified Sub-investigator pre-dose (and post-dose as indicated) on Days 0, 21, and 49 and on Days 14, 84, 112, and 168 or ET.
12. Follow-up telephone calls will be made to the patient at 12 and 24 hours following the end of each infusion.
13. At Screening, height (in cm) and weight (in kg) will be recorded and BMI will be calculated. Pre-dose on Day 0 and on Day 112 and Day 168 or ET, weight (in kg) only will be recorded.
14. Vital signs, including supine systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate, will be measured after the patient has been in the supine position for ≥5 minutes.
15. On Days 0, 21 and 49, vital signs will be measured pre-dose, every 15 minutes after the start of infusion, and immediately following the end of infusion.
16. For all female patients, blood will be obtained for a serum pregnancy test at Screening, and blood or urine is to be obtained for pregnancy tests on Day -3, pre-dose on Days 21 and 49, and on Day 168 or ET. Blood for FSH is to be obtained only at Screening to confirm postmenopausal status (FSH level >30 IU/L).
17. Patients will refrain from alcohol and strenuous exercise (e.g., heavy lifting, weight training, aerobics) for at least 48 hours and fast overnight (8 hours) from food and beverages other than water prior to each blood collection for clinical safety laboratory tests as detailed in Section 9.3.3.
18. Nasal endoscopies (blinded centralized evaluation) will be performed at Screening, on Day -3, pre-dose on Days 21 and 49, and on Days 84, and 112 or ET for efficacy analyses.
19. CT scans will be performed at selected Investigator sites on Day -3 and on Day 84 or ET. CT scans are optional and will only be done at Investigator sites at which appropriate and timely regulatory approval or authorization can be granted.
20. These evaluations will be performed only at ET if not obtained on Day 112.
21. Patients will complete VASs and the clinical symptoms improvement scale at Screening; at start of Run-in; on Day -3; pre-dose on Days 0, 21, and 49; and on Days 14, 84, and 112 or ET. The VASs and clinical symptoms improvement scale will be completed at clinic visits; however, if the Run-in clinic visit is replaced by telephone contact, the patient will complete the scales at home and bring them to the next (Day -3) clinic visit.
22. Spirometry will be performed at Screening and pre-dose on Days 21 and 49 to assess FEV1, FVC, and FEF.
23. The ACT will be performed only in patients with comorbid asthma.
24. Blood samples for PK on Days 0, 21, and 49 will be obtained pre-dose.
25. Blood samples for ADA will be collected pre-dose on Day 0 and, should a related AE suspected of being associated with immunogenicity occur, post-dose, as well as on Day 112 and Day 168 or ET.
26. Blood samples (5 mL serum, 5 mL plasma, and 5 mL RNAlater solution) will be obtained on Day -3, pre-dose on Days 21 and 49, and on Day 84 and stored.
27. All prior medications, including both prescribed and over-the-counter medications, started within the 30 days before Screening will be recorded.

5 CRITERIA FOR EVALUATION

5.1 Safety Endpoints

The primary safety endpoints of this study are:

- TEAEs
- Withdrawals from study due to AEs
- Vital sign findings
- Laboratory test (including anti-drug antibody [ADA]) findings
- Concomitant medication use
- Physical examination (PE) findings

5.2 Pharmacokinetic Endpoints

Blood samples will be obtained pre-dose on Days 0, 21, and 49 and on Days 14, 84, 112, and 168 for PK analyses.

Serum concentrations of AK001 will be measured using a validated enzyme-linked immunosorbent assay (ELISA) method.

5.3 Efficacy Endpoints

The following specific efficacy endpoints will be evaluated:

- TPS (Appendix 2 Section 19.2) by blinded centralized evaluation of endoscopy
- Size of polyps as evaluated by Lund-Mackay score (Appendix 3 Section 19.3) at selected Investigator sites by CT scan
- Nasal airway patency as evaluated by PNIF
- UPSIT (Appendix 4 Section 19.4)
- SNOT-22 (patient-reported symptoms) (Appendix 5 Section 19.5)
- VASs (patient-reported symptoms) (Appendix 6 Section 19.6)
- Clinical symptoms improvement scale[3] (Appendix 6 Section 19.6)
- SF-36 (quality of life) (Appendix 7 Section 19.7)
- Blood eosinophil and basophil absolute counts

The following specific additional efficacy endpoints will be evaluated in patients with comorbid asthma:

- TPS (Appendix 2 Section 19.2) by blinded centralized evaluation of endoscopy
- Pulmonary function (FEV1, FVC, and FEF) assessed using spirometry

- ACT (Appendix 8 Section 19.8)
- Use of asthma rescue therapy

5.4 Exploratory Biomarkers

Blood samples (5 mL serum, 5 mL plasma, 5 mL RNAlater solution) will be obtained on Day -3, pre-dose on Days 21and 49, and on Day 84. The samples will be stored per instructions in a separate manual for potential exploratory analysis of markers of MCs and eosinophils and of inflammatory response in blood. In the event that a patient does not provide consent for future analyses or storage of these samples, they will be destroyed according to the country-specific informed consent form (ICF).

6 PATIENT SELECTION

6.1 Study Population

Male and female patients, aged ≥18 and ≤75 years, with moderate to severe chronic nasal polyposis and whose symptoms are resistant to treatment with INSs who fulfill the inclusion criteria and none of the exclusion criteria specified below.

6.2 Inclusion Criteria

Patients are eligible for the study if all of the following criteria are met:

1. Written informed consent
2. Male and female patients aged ≥18 and ≤75 years at the time of Screening
3. SNOT-22 (Appendix 5 Section 19.5) ≥30
4. At Screening, TPS of ≥5 for both nostrils with presence on endoscopy of nasal polyps of grade ≥2 in each nostril according to the polyp grading scale (Appendix 2 Section 19.2)

   Polyp grading scale for each nostril:

   0=no nasal polyps

   1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate

   2=polyps reaching below the lower border of the middle turbinate

   3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate

   4=large polyps causing complete obstruction of the inferior nasal cavity
5. History of at least 2 of the following symptoms for 4 weeks prior to Screening:
   a) Anterior nasal discharge
   b) Posterior nasal discharge
   c) Nasal congestion, blockade, or obstruction

d) Decreased sense of smell

e) Facial pain or pressure

6. Received continuous topical nasal steroids and/or leukotriene receptor antagonists for at least 8 weeks prior to Screening unless failure or no effect of prior nasal steroid or leukotriene receptor antagonist therapy is documented
7. At randomization, received ≥80% of doses of NASONEX scheduled during the Run-in period
8. At randomization, TPS of ≥5 for both nostrils with presence on endoscopy of nasal polyps of grade ≥2 in each nostril according to the polyp grading scale (see Inclusion Criterion #4 and Appendix 2 Section 19.2) and despite prior INS treatment during the Run-in period
9. Female patients must be post-menopausal for ≥1 year with documented follicle-stimulating hormone (FSH) >30 IU/L, surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or, if of child-bearing potential, willing to use a highly effective method of contraception (Appendix 1 Section 19.1) from Screening until at least 17 weeks after the last dose of the study drug is administered, which corresponds to approximately 5 half-lives of AK001
10. Male patients with female partners of childbearing potential must agree to use a highly effective method of contraception (Appendix 1 Section 19.1) from Screening until at least 17 weeks after the last dose of the study drug is administered, which corresponds to approximately 5 half-lives of AK001. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
11. Negative Screening ova and parasite test
12. No clinically significant Screening 12-lead ECG, vital sign, hematology, chemistry, or urinalysis findings
13. Able to comply with all study procedures including recording scores of symptoms (i.e., anterior nasal discharge; posterior nasal discharge, nasal congestion, blockade, or obstruction; decreased sense of smell; facial pain or pressure) at clinic visits

6.3 Exclusion Criteria

Patients are ineligible for the study if any of the following criteria are met:

1. Use of systemic corticosteroids within 6 weeks prior to Screening (or 5 half-lives, whichever is longer) or scheduled to receive systemic corticosteroids
2. Chronic use of antibiotic therapy within 3 months prior to Screening
3. Receipt of short-term antibiotic therapy within 14 days prior to Screening or use of antibiotics during the Screening period

4. Acute infection that requires antibiotic, antiviral, or antifungal therapy within 30 days prior to Screening
5. Nasal surgery (including polypectomy) within 6 months prior to Screening
6. Significant mechanical nasal airway obstruction due to septal deviation based on Investigator assessment
7. Use of investigational drugs or participation in another clinical trial within 30 days or 5 half-lives, whichever is longer, prior to Screening
8. Use of any medications that may interfere with the study, such as immunosuppressive drugs during the 2 weeks before Screening, or expected to require such medications through Day 168
9. Receipt of any live attenuated vaccines within 30 days or 5 half-lives, whichever is longer, prior to initiation of treatment in the study or expected to receive such a vaccine during the treatment period
10. Pregnancy or lactation in women
11. In patients with comorbid asthma, either of the following:
    a) A FEV1 ≤60% at Screening
    b) An asthma exacerbation requiring systemic (oral and/or parenteral) steroid treatment or hospitalization for >24 hours for treatment of asthma within 30 days prior to Screening
12. History of human immunodeficiency virus (HIV) infection or other severe immunosuppressive disease, or positive HIV test at Screening
13. Current diagnosis or prior history of allergic fungal sinusitis, cystic fibrosis, ciliary dyskinesia, Wegener's Granulomatosis, or Churg-Strauss syndrome
14. Current diagnosis or prior history of any other condition likely to present with non-eosinophilic nasal polyps
15. History of hepatitis or active/chronic liver disease of any genesis or positive serology for hepatitis B virus (HBV) surface antigen or hepatitis C virus (HCV) antibody at Screening
16. Current diagnosis or history of cancer
17. A helminthic parasitic infestation, even if treated, within 6 months prior to Screening
18. History of or suspected history of cytokine release syndrome
19. Any disease or condition (medical or surgical) which, in the opinion of the Investigator, might compromise the hematologic, cardiovascular, pulmonary, renal, endocrine, autoimmune, gastrointestinal, hepatic, skeletal, or central nervous system; other conditions that might interfere with the absorption, distribution, metabolism or excretion of AK001 or would place the patient at increased risk (including any condition, such as diabetes, that would make it unsafe for the patient to fast as required by the study)

20. Known hypersensitivity to any constituent of the product
21. Legally institutionalized

7 PRIOR AND CONCURRENT MEDICATIONS

Prior and concomitant medications include both prescribed and over-the-counter medications. The Investigator is to record the use of all prior medications started within the 30 days before Screening and of all concomitant medications during the study in the Electronic Case Report Form (eCRF). Continuous topical nasal steroids and/or leukotriene receptor antagonists are to have been received for at least 8 weeks prior to Screening (Inclusion Criterion #6).

No medications as specified in Exclusion Criteria #1, #2, #3, #4, #7, #8, #9, and #11b are to have been received. On Day 0 before randomization, investigational site personnel should ensure that patients meet none of the exclusion criteria pertaining to medications. Patients should be advised against taking any new medication, both prescribed and over the counter, without consulting the Investigator, unless the new medication is required for emergency use.

7.1 Prohibited Medications

All medications taken during the conduct of this study must be documented on the eCRF. The use of immunosuppressive drugs is prohibited during the 2 weeks before Screening and systemic corticosteroids is prohibited during the 6 weeks before Screening (or 5 half-lives, whichever is longer) and during the study, except as necessary to treat AEs under the direction of the Investigator.

7.2 Allowed Medications

Medications (other than those that are prohibited [Section 7.1]), such as asthma medications, are allowed during the study and, unless dose changes are required due to unforeseen medical necessities, doses are to remain stable. All medication use will be documented in the eCRF.

If a patient experiences an infusion-related reaction that is considered mild to moderate (e.g., itching or a localized rash), an antihistamine, acetaminophen, and, if needed, a glucocorticoid (e.g., IV methylprednisolone 125 mg) may be administered. If a patient experiences signs or symptoms of anaphylaxis, the patient will be treated with standard-of-care medications, such as diphenhydramine, acetaminophen, methylprednisolone, epinephrine, and other supportive measures along with cessation of the infusion.

8 STUDY TREATMENTS

8.1 Method of Assigning Patients to Treatment Groups

Each patient who provides informed consent will be assigned a Screening number that uniquely identifies him or her.

Approximately 70 patients who complete the Screening and Run-in periods of the study will be randomized in a double-blind fashion to receive 1 of the following treatments:

- Arm A: AK001 25 mg (n=25)
- Arm B: AK001 250 mg (n=25)
- Arm C: Matching placebo (n=20)

The randomization will be stratified by the presence of comorbid asthma. Enrollment will be staggered; no more than 1 patient will be randomized every 4 weeks at each site.

Randomization will occur on Day 0 via interactive voice or web response system (IXRS) after confirmation that the patient meets all inclusion and no exclusion criteria. An unblinded non-study statistician will produce the randomization schedule with a fixed reproducible random seed for use in the IXRS.

8.2 Intranasal Steroid Adjustment

After the patient has completed the Screening procedures, the patient will enter a 4-week Run-in period to achieve a stable regimen with a common intranasal topical steroid (NASONEX [mometasone furoate monohydrate]) and discontinue any other intranasal topical steroids. The Day -28 visit may occur as soon as the day after Screening. Patients will be instructed to self-administer 2 NASONEX nasal inhalations in each nostril twice a day from the start of the Run-in period through the end of the study. The patient will record the date and time of each dose taken in a dosing diary. Inclusion and exclusion criteria may continue to be assessed while the patient is in the Run-in period.

Patients must have received ≥80% of doses of NASONEX scheduled for the Run-in period to be randomized.

8.3 Blinding

The identity of test and control treatments will not be known to Investigators, research staff, patients, or the study monitor. Members of the DMC can request the identity of treatments if needed. The following study procedures will be in place to ensure double-blind administration of study treatments:

- Access to the randomization codes will be strictly controlled via IXRS
- Throughout the study, the blind should remain unbroken except and only for an emergency when knowledge of the patient's study medication is necessary for further patient management or if required for regulatory reporting. When possible, the Investigator should discuss the emergency with the Medical Monitor prior to unblinding.
- The prepared test and control IV infusion solutions will be identical in appearance

Other than under the conditions described above, the study blind will be broken on completion of the study after the study database has been locked.

8.4 Formulation of Test and Control Products

8.4.1 Formulation of Test Product

AK001 is a humanized IgG4 MAb directed against Siglec-8. AK001 Drug Product is supplied as a sterile liquid in a single-use 10R glass vial with a fill volume of not less than 10 mL. The product is stored at 2 to 8°C. The AK001 formulation is 15 ±1.5 mg/mL AK001 in 125 mM arginine, 80 mM sodium chloride, 20 mM succinate and 0.025% polysorbate 80 (w/v), pH 6.0, in sterile water for injection.

AK001 is administered by IV infusion. Dose preparation and administration details are provided in the study pharmacy manual.

8.4.2 Formulation of Control Product

The placebo is supplied as a sterile liquid in a single-use 10R glass vial with a fill volume of not less than 10 mL. The placebo contains 125 mM arginine, 80 mM sodium chloride, 20 mM succinate and 0.025% polysorbate 80 (w/v), pH 6.0, in sterile water for injection. The vial is indistinguishable from the AK001 active product. The placebo is stored at 2 to 8°C.

8.4.3 Packaging and Labeling

AK001 Drug Product and placebo are supplied as a sterile liquid in a single-use 10R glass vials with a fill volume of at least 10 mL. Each vial will be labeled with information required by the Food and Drug Administration (FDA) and according to pertinent European Union (EU) and national regulations, as appropriate for the country in which the study drug is being used.

Each carton (kit) of study drug will be labeled with the required FDA investigational use statement, a lot number, name of the Sponsor, and directions for storage.

8.5 Supply of Study Drug at the Site

The Sponsor (or designee) will ship study drug to the investigational sites. The initial shipment will occur after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed).

8.5.1 Dosage/Dosage Regimen

AK001 25 mg and 250 mg and placebo will each be administered as a single IV infusion of over approximately 1 hour through a peripheral vein.

8.5.2 Preparation

Using the IXRS, the unblinded study pharmacist will prepare the AK001 or placebo for IV administration to each patient on Days 0, 21, and 49. Preparation of individual solutions for IV administration will be performed at the investigational site by the designated unblinded study pharmacist using the randomization code provided. Each vial is assigned a kit

number that can be associated with a treatment assignment in the system by a list accessible to an unblinded monitor, independent of the study. The diluted IV solution container will be identified with the patient identifier, but will not indicate the treatment assignment. Appropriate aseptic technique will be used, and the drug will be prepared according to the pharmacy manual for AK001.

8.5.3 Administration Instructions

Specific instructions for study drug administration are detailed in the pharmacy manual. In general, AK001 and placebo will be infused over approximately 1 hour through a peripheral vein. The IV will be kept open before and after the infusion with sufficient quantities of 0.9% saline to assure it remains patent.

Each patient will remain at the Investigator site for a safety observation period of at least 8 hours following the end of each infusion. At the discretion of the Investigator, a longer monitoring period, if needed, before the patient is discharged, may be implemented. Follow-up telephone calls will be made to the patient at 12 and 24 hours following the end of each infusion. Patients will be informed that, from discharge to the 24-hour telephone contact, they must be accompanied by another adult at all times, not travel alone or travel during bad weather, remain close to the location of the site, and have access to a telephone and transportation. If there are any safety concerns, enrollment will be put on hold, and a safety review meeting will occur.

The IV infusion may be interrupted for 5 to 30 minutes and the rate may be reduced and gradually increased in 15-minute intervals if a patient experiences infusion-related reactions. Acetaminophen and, if needed, a glucocorticoid (e.g., 125 mg methylprednisolone IV) may be administered to the patient if the patient experiences reactions that is considered mild to moderate (e.g., itching or a localized rash). If a patient experiences signs or symptoms of anaphylaxis, the patient will be treated with standard-of-care medications, such as diphenhydramine, acetaminophen, methylprednisolone, epinephrine, and other supportive measures along with cessation of the infusion. Administration will be discontinued if, in the opinion of the Investigator, the infusion cannot be restarted after 30 minutes for safety reasons.

8.6 Supply of Study Drug at the Site

AK001 (15 mg/mL) and placebo will be provided by the Sponsor in 10R single-use vials. Study drug may be prepared on the morning of Day 0. Any patient who is randomized but not treated will be replaced by another patient and new study drug will be prepared for the alternate patient.

8.6.1 Storage

AK001 and placebo will be stored by the investigational site at 2ºC to 8ºC under lock at each site's pharmacy room, pending drug preparation. Access will be restricted to designated study pharmacy staff. All clinical supplies will be temperature controlled and monitored. If the temperature of study drug storage in the clinic/pharmacy exceeds or falls

below this range, this will be reported to the Sponsor or designee and considered a deviation, and study drug should be quarantined until further notice from Sponsor.

8.7 Study Drug Accountability

The unblinded study pharmacist will keep accurate and current accounting of the preparation and dose of study drug for each patient, with sources and quantities of study drug received, quantities of study drug dispensed for and used by each individual patient specified, and quantities of study drug returned, if applicable. A drug dispensing and accountability log will be maintained by the unblinded study pharmacist.

8.8 Measures of Treatment Compliance

The study drug will be administered under supervision of the Investigator or designee. The calendar date and 24-hour clock times each infusion is initiated and concluded and, as necessary, interrupted and resumed will be documented in the eCRF.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events depicting the required procedures to be performed for the duration of the study is provided in Table 1.

Prior to conducting any study-related activities, the ICF and any other required country-specific documents must be signed and dated by the patient.

9.1 Dietary and Lifestyle Restrictions

Patients will refrain from alcohol and strenuous exercise (e.g., heavy lifting, weight training, aerobics) for at least 48 hours prior to each blood collection for clinical safety laboratory tests.

Patients will be required to fast overnight (8 hours) from food and beverages other than water before blood is drawn for clinical safety laboratory tests. The duration of the fast should be no longer than the typical overnight sleeping period for the patient.

9.2 Clinical Assessments

9.2.1 Prior and Concomitant Medications

All prior medication and therapies received between 30 days before Screening and start of study drug will be documented at Screening and at Days -3, and pre-dose on Day 0.

All concomitant medication and concurrent therapies will be documented post-dose on Day 0 and on Days 14, 21, 49, 84, 112, and 168 or at Early Termination (ET). Dose, route, unit, frequency of administration, indication for administration, and dates of each medication will be recorded.

9.2.2 Demographics

Demographic information (date of birth, gender, and race) will be recorded at Screening.

9.2.3 Medical History

A medical history will be obtained at Screening and include all relevant medical history information (e.g., history of current disease, other pertinent respiratory system history, information regarding aspirin sensitivity [obtained in response to specific question(s) about aspirin sensitivity], and underlying diseases) for the 5 years before Screening.

9.2.4 Physical Examination

A complete PE will be performed by either the Principal Investigator or a qualified Sub-investigator at Screening. A complete PE will include the following body system or organ assessments: skin; head, eyes, ears, nose, and throat (HEENT); thyroid; lungs; cardiovascular system; abdomen; extremities; lymph nodes; and a brief neurological examination. Height (in cm) and weight (in kg) will be measured at Screening, and BMI will be calculated. Weight only will be measured on Day 0, Day 112, and Day 168 or ET. A symptom-directed PE, including assessments of possible infusion site reactions, will be performed by either the Investigator or a qualified Sub-investigator pre-dose (and post-dose as indicated) on Days 0, 21, and 49 and on Days 14, 84, 112, and 168 or ET. New abnormal PE findings must be documented and will be followed by the Investigator or qualified Sub-investigator at the next scheduled visit.

9.2.5 Vital Signs

Body temperature, supine systolic and diastolic blood pressure, pulse, and respiratory rate will be measured at Screening and on Days -3, 0, 14, 21, 49, 84, 112, and 168 or ET. On Days 0, 21, and 49, vital signs will be measured pre-dose, every 15 minutes after the start of infusion, and immediately following the end of infusion. All vital signs will be measured after the patient has been in the supine position for ≥5 minutes.

9.2.6 Electrocardiogram

A 12-lead ECG will be performed at Screening.

9.2.7 Fecal Collection

Fecal samples will be collected at Screening for ova and parasite tests.

9.2.8 Adverse Events

Information regarding AEs will be obtained from the time of the first study drug administration until completion of the last study-related procedure (Day 168 or ET). Information regarding serious adverse events (SAEs) will be obtained from the time the patient signs an ICF until completion of the last study-related procedure (Day 168 or ET).

Duration (start and stop dates and times), severity, outcome, treatment, and relation to study drug will be recorded on the eCRF.

9.3 Clinical Safety Laboratory Measurements

Blood and urine samples will be obtained for clinical safety laboratory tests (hematology, chemistries, and urinalyses) and for ADA as specified in Table 1 and Sections 9.3.2, 9.3.3, and 9.3.5. Blood for clinical safety laboratory tests will be collected following an overnight fast (8 hours) from food and beverages other than water. The duration of the fast should be no longer than the typical overnight sleeping period for the patient.

Certified laboratories will be used to process and provide results for the clinical safety laboratory tests. The Baseline laboratory test result will be defined as the last measurement prior to the first infusion of study drug.

For any laboratory test value outside the reference range that the Investigator considers clinically significant, the Investigator will:

- Repeat the test to verify the out-of-range value
- Follow the out-of-range value to a satisfactory clinical resolution

The Investigator will record as an AE any laboratory test value that (1) is confirmed and the Investigator considers clinically significant, (2) that requires a patient to be discontinued from the study, or (3) that requires a patient to receive treatment.

9.3.1 Serology

Blood will be obtained at Screening for HIV, HBV surface antigen, and HCV antibody testing.

9.3.2 Hematology

Blood will be obtained at Screening; on Day -3; pre-dose on Days 21 and 49, and on Days 14, 84, 112, and 168 or ET for a complete blood count (CBC) with differential: hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count, WBC differential, and platelet count.

9.3.3 Blood Chemistry Profile

Blood will be obtained at Screening; on Day -3; pre-dose on Days 21 and 49; and on Days 14, 84, 112, and 168 or ET for determination of serum sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, creatinine kinase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyl transferase, albumin, and lactate dehydrogenase.

9.3.4 Pregnancy and Follicle-Stimulating Hormone Tests

For all female patients, blood will be obtained for a serum pregnancy test at Screening, and blood or urine is to be obtained for pregnancy tests on Day -3, pre-dose on Days 21 and 49, and on Day 168 or ET. Blood for FSH is to be obtained only at Screening to confirm postmenopausal status (FSH level >30 IU/L).

9.3.5 Urinalysis

Urine will be obtained at Screening; pre-dose on Days -3 and 49; and on Days 14, 84, 112, and 168 or ET for determination of color, specific gravity, pH, protein, glucose, ketones, and blood.

9.4 Anti-drug Antibodies

Blood will be collected for determination of ADA pre-dose on Day 0 and, should a related AE suspected of being associated with immunogenicity occur, post-dose, and on Days 112 and 168 or ET.

9.5 Pharmacokinetic Measurements

Blood samples for serum concentrations of AK001 will be obtained pre-dose on Days 0, 21, and 49 and on Days 14, 84, 112, and 168 or ET for PK analyses. AK001 concentrations will be determined by a central laboratory using an ELISA method. Specific information on PK collection, processing, storage, and shipment will be provided in a separate manual.

9.6 Efficacy Measurements

Specific information on the collection, processing storage, and shipment of samples will be provided in a separate manual.

9.6.1 Serum Samples for Total Immunoglobulin E

Blood will be collected for the testing of total IgE on Day -3.

9.6.2 Serum Samples for ImmunoCAP

Blood will be collected for the determination of allergen specific IgE on Day -3. Allergens to be used in testing are house dust mites (*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*), birch, timothy grass (*Phleum pretense*), mugwort (*Artemisia vulgarism*), cat, orchard, and ragweed.

9.6.3 Total Polyp Score

Polyps will be evaluated in each nostril by means of nasal endoscopy and graded based on polyp size, resulting in scores of 0 to 4 (Appendix 2 Section 19.2). The TPS is the sum of the left and right nostril scores. The TPS values for efficacy analyses will be determined from blinded central evaluations of nasal endoscopies performed at Screening, on Day -3, pre-dose on Days 21 and 49, and on Days 84, and 112 or ET. Videos of the endoscopies will be evaluated by independent blinded reviewer. The primary endpoint of this study is the reduction in TPS values from Baseline to Week 12 after the start of treatment.

9.6.4 Nasal Endoscopy

Nasal endoscopies (blinded centralized evaluation) will be performed at Screening, on Day -3, pre-dose on Days 21 and 49, and on Days 84 and 112 or ET for efficacy analyses. Videos of the endoscopy will be evaluated by independent blinded reviewer.

9.6.5 Computed Tomography Scan

At selected Investigator sites, CT scans will be performed at Days -3 and 84 or ET to assess size of nasal polyps based on Lund-Mackay score (Appendix 3 Section 19.3). The CT scans are optional and will only be done at Investigator sites at which appropriate and timely regulatory approval or authorization can be granted.

9.6.6 Peak Nasal Inspiratory Flow

Peak nasal inspiratory flow will be performed pre-dose on Days 0 and 21 and on Day 84 and 112 or ET to assess the extent of nasal airway patency.

9.6.7 University of Pennsylvania Smell Identification Test™

The UPSIT (Appendix 4 Section 19.4) will be self-administered by patients pre-dose on Days 0, 21, and 49 and on Days 14, 84, and 112 or ET to assess ability to smell.

9.6.8 Sino-nasal Outcome Test-22

The SNOT-22 (Appendix 5 Section 19.5) will be completed by patients at Screening; pre-dose on Days 0, 21, and 49, and on Days 14, 84, and 112 or ET to assess rhinosinusitis symptoms.

9.6.9 Visual Analogue Scale and Clinical Symptoms Improvement Scale

Visual analogue scales and the clinical symptoms improvement scale[3] (Appendix 6 Section 19.6) will be completed by patients at Screening; at start of Run-in; on Day -3, pre-dose on Days 0, 21, and 49; and on Days 14, 84, and 112 or ET to assess rhinosinusitis symptom severity. The VASs and clinical symptoms improvement scale[3] will be completed at clinic visits; however, if the Run-in clinic visit is replaced by telephone contact, the patient will complete the scales at home and bring them to the next (Day -3) clinic visit.

9.6.10 36-Item Short Form Health Survey

The SF-36 (Appendix 7 Section 19.7) will be completed by patients pre-dose on Days 0, 21, and 49 and on Days 84 and 112 or ET to assess quality of life.

9.6.11 Spirometry

Spirometry will be performed at Screening and pre-dose on Days 21 and 49 to assess FEV1, FVC, and FEF.

9.6.12 Asthma Control Test™

In patients with comorbid asthma, the ACT (Appendix 8 Section 19.8) will be completed by patients at Screening; pre-dose on Days 0, 21, and 49; and on Days 84, and 112 or ET to assess the frequency of shortness of breath and general asthma symptoms, use of asthma rescue medications, the effect of asthma on daily functioning, and overall asthma control.

9.6.13 Exploratory Biomarkers

Blood samples (5 mL serum, 5 mL plasma, and 5 mL RNAlater solution) will be obtained on Day -3, pre-dose on Days 21 and 49, and on Day 84 and stored for potential analyses of markers of MCs and eosinophils and of inflammatory response in blood. In the event that a patient does not provide consent for future analyses or storage of these samples, they will be destroyed according to the country-specific ICF.

Specific details of sampling and sample storage and processing procedures will be documented in a separate manual to be filed in the trial master file. The results of the analyses will be reported in an appendix to the clinical study report.

10 EVALUATIONS BY VISIT

Evaluations and procedures by visit are depicted in Table 1.

11 ADVERSE EVENT REPORTING AND DOCUMENTATION

11.1 Adverse Events

In accordance with 21 Code of Federal Regulations (CFR) 312.32(b), an AE is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current IB or of greater severity or frequency than expected based on the information in the IB.

AE Recording:

At each evaluation, the Investigator will determine whether any AEs have occurred. The assessment of an AE will be done pursuant to definitions set forth by International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) Guidelines and other applicable regulatory requirements. The patient will be questioned in a general manner and no specific symptoms will be suggested (e.g., ask the patient if he/she has had have had any "changes in health" since the last visit or assessment).

The Investigator or designee will be notified if any patient experiences an AE. Any initial information discovered by the Investigator or designee (i.e., complaint[s] and known start/end dates and times) will be documented on the patient's AE form. The Investigator or

designee will assess the initial AE finding(s) to determine if the medical occurrence is in fact an AE by officially documenting the condition/diagnosis on the AE form.

In the event that the Investigator is not available, the assigned staff will page the Sub-investigator on-call and have the AE documented by telephone contact. The medication dispensed will be documented on an Investigator order form, and the phone call will be documented on the same form (if applicable). The patient will be seen by the Investigator as soon as possible.

Action taken will be categorized as "none," "study drug discontinued," "dose modified," "required concomitant medication," "required procedure," or "other."

Event outcome at resolution or time of last follow-up will be recorded as "recovered," "recovering," "not recovered," "recovered with sequelae," "fatal," or "unknown."

AE Severity:

Adverse events are to be recorded on the AE page of the eCRF. Severity will be graded according to the definitions, based on the Common Terminology Criteria for Adverse Events, Version 4.0,[7] listed in Table 2. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

When the intensity of an AE changes more than once a day, the maximum severity for the event should be listed. If the intensity changes over a number of days, these changes should be recorded separately (i.e., having distinct onset dates).

Table 2 Adverse Event Severity Grading

Grade	Severity	Description
1	Mild	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The patient may be aware of the sign or symptom but tolerates it reasonably well.
2	Moderate	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
3	Severe	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
4	Life-threatening	The patient is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.
5	Death	Any adverse event for which the outcome is death.

Adverse Event Relationship to Study Drug:

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 3.

Table 3 Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Related	There is clear evidence that the event is related to the use of study drug (e.g., confirmation by positive re-challenge test).
Possible	The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and study drug administration.
Unlikely/Remote	An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to study drug administration and/or exposure suggests that a causal relationship is unlikely. (For reporting purposes, "Unlikely/Remote" will be grouped together with "Not Related.")
Not Related	The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and, therefore, the Investigator believes no relationship exists between the event and study drug.

11.2 Serious Adverse Events

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening AE; the patient is at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the patient or require intervention to prevent one of the outcomes listed.

Note:

Medical and scientific judgment should be exercised in deciding whether SAE reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent 1 of the outcomes listed in the definition above (including suspected transmission of an infectious agent by a medicinal product should be reported as an SAE). Any AE is considered an SAE if it is associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact.

11.3 Procedures

11.3.1 All Adverse Events

In the event that a patient completes a study with an ongoing AE, investigational site personnel will continue to follow-up with the patient until AE resolution is reached and documented. If, after 30 days from the study completion date, the AE is still continuing but not assessed as serious, the outcome will be recorded as "not recovered," and no further follow-up will be necessary.

All AEs identified will be recorded in the eCRF from the time of study drug administration until completion of the last study-related procedure (Day 168 or ET). All SAEs will be reported from the time the patient signs an ICF until completion of the last study-related procedure (Day 168 or ET).

All AEs, regardless of seriousness, severity, or presumed relationship to investigational product, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., dysuria and urinary nitrites should be reported as a urinary tract infection). Investigators must record their opinions concerning the relationship of the AE to the investigational product in the eCRF.

Patients (or their designees, if appropriate) may be provided with a "study card" indicating the name of the investigational product, the study number, the Investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

11.3.2 Serious Adverse Event Reporting

In the event of any SAE reported or observed during the study (whether or not attributable to the study drug), investigational site personnel will report it immediately (within 24 hours of becoming aware of the SAE) by telephone call, fax, or email to Allakos, Inc.

Serious Adverse Event Report Forms will be provided to the investigational site to assist in collecting, organizing, and reporting SAEs, and follow-up information will be completed within 24 hours.

The Investigator will notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to its guidelines. All SAE forms will be completed within 24 hours. All efforts will be made to obtain accurate and complete medical records for the SAE.

The patient's condition will be followed by the Investigator or designated Sub-investigator. If additional visits are required, the patient will be asked to return to the clinic for further follow-up. As additional information becomes available, such as hospital discharge notes and patient medical records, the Investigator will be notified and provided with all relevant information.

All SAEs that have not resolved by the end of the study or that have not resolved upon discontinuation of the patient's participation in the study must be followed until any of the following occurs:

- The event resolves

- The event stabilizes
- The event returns to Baseline, if a Baseline value is available
- The event can be attributed to agents other than the investigational product or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refuses to provide additional information, patient is lost to follow-up after demonstration of due diligence with follow-up efforts)

11.3.3 Pregnancy

Female patients must inform the study Investigator immediately if they become pregnant during the study.

The Investigator must report any pregnancy to Allakos, Inc. within 24 hours of becoming aware of it using the provided pregnancy reporting forms. The patient must be immediately discontinued from further treatment with study drug. An uncomplicated pregnancy will not be considered an AE or SAE, but all pregnancies will be followed through term.

Pregnancies are reported if they occur in female patients or in the sexual partners of male patients from the time the patient is first exposed to the investigational product until Day 168 or ET.

Any congenital abnormalities noted at birth in the offspring of a patient who received study drug will be reported as an SAE. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the source documentation and reported to the Medical Monitor and Sponsor.

11.4 Anaphylaxis

Signs or symptoms of anaphylaxis will be carefully monitored and treated according to standard of care. Emergency crash cart equipment will be available at all times during the conduct of the study.

11.5 Medical Monitoring

The regional Medical Monitor will be the primary point of contact to report medical concerns or questions regarding study eligibility or patient safety.

EU Regional Medical Monitor:

Name:	Edgar J. Fenzl, MD
Mobile:	+49-172-673 8556
Email:	edgar.fenzl@fgk-cro.com

Sponsor and US Regional Medical Monitor:

Name: Alejandro Dorenbaum, MD
Mobile: 1-415-328-9115
Email: adorenbaum@allakos.com

12 DISCONTINUATION AND REPLACEMENT OF PATIENTS

12.1 Early Discontinuation of Study Drug

A patient may be discontinued from study treatment at any time if the patient, the Investigator, or the Sponsor feels that it is not in the patient's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Patient's withdrawal of consent
- Patient is not compliant with study procedures
- AE that, in the opinion of the Investigator, results in it being in the best interest of the patient to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Loss to follow-up
- Sponsor's request for ET of study
- Positive pregnancy test (females)

If a patient is withdrawn from treatment due to an AE, the patient will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All patients who discontinue study treatment should come in for an ET visit as soon as possible.

All patients are free to withdraw from participation at any time for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the Investigator to provide a reason for patient withdrawals. The reason for the patient's withdrawal from the study will be specified in the patient's source documents. Refer to Table 1 for ET procedures.

12.2 Withdrawal of Patients from the Study

Participation of a patient will be discontinued in the event that:

- An AE or SAE that, in the judgment of the Investigator, requires treatment withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to treatment
- Protocol violations, including non-compliance, loss to follow-up

- Occurrence of an exclusion criterion that is clinically relevant and affects the patient's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Serum transaminases (ALT and/or AST) >3 × upper limit of normal (ULN) AND total bilirubin >2 × ULN (confirmed by subsequent repeat) without an alternative explanation
- Elevation of ALT or AST >3 × ULN (confirmed by repeat) with the appearance or worsening of symptoms felt by the Investigator to be potentially related to hepatic inflammation, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
- Use of a non-permitted concomitant drug, as defined in Section 7.1
- Withdrawal of the patient's consent
- Participation in any other trial during the duration of this trial
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Discretion of the Investigator

All patients are free to withdraw from participation at any time for any reason specified or unspecified, and without prejudice.

Reasonable attempts will be made by the Investigator to provide a reason for patient withdrawals. The reason for the patient's withdrawal from the study will be specified in the patient's source documents. As noted above, patients who discontinue study treatment early (i.e., they withdraw prior to Day 168) should have an ET visit. Refer to Table 1 for ET procedures. Patients who withdraw after Day 84 but prior to Day 168 should be encouraged to come in for a final visit.

12.3 Replacement of Patients

Patients who do not meet all eligibility criteria at Screening or who qualify at Screening but do not enter the Run-in period within 6 weeks may be rescreened once and assigned a new Screening number.

Patients who withdraw prematurely from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the patient, Investigator, or Allakos, Inc., fails to adhere to protocol requirements affecting the inclusion or exclusion criteria, patient safety, or primary endpoint. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

- Failure to comply with GCP guidelines will also result in a protocol violation

Allakos, Inc., will determine if a protocol violation will result in withdrawal of a patient.

When a protocol violation occurs, it will be discussed with the Investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the investigational site's regulatory binder and in the Sponsor's files.

14 DATA SAFETY MONITORING

14.1 General Safety Monitoring

The Sponsor's Medical Monitor will review data relating to safety and to the conduct of the study as it becomes available.

14.2 Data Monitoring Committee

A DMC will be convened periodically to monitor the safety of patients over the course of the study. Members of the DMC can request the identities of patients' study drugs if needed. Other information about the DMC can be found in the DMC charter.

14.3 Study Stopping Rules

The trial must be discontinued prematurely in the event of any of the following:

- A life-threatening adverse event that is possibly or probably related to treatment
- A fatal adverse event that is possibly or probably related to treatment
- New information leading to unfavorable risk-benefit judgment of the study drug, e.g., occurrence of significant previously unknown adverse reactions, unexpectedly high intensity or incidence of known adverse reactions, or other unfavorable safety findings
- >25% of patients at any time have been withdrawn due to drug-related AEs, including those related to abnormal laboratory results, or other safety findings
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Poor enrollment of patients making completion of the trial within an acceptable time frame unlikely
- Discontinuation of development of the Sponsor's study drug

Regulatory Authorities and IRBs/IECs will be informed about the discontinuation of the trial in accordance with applicable regulations. The trial may be terminated or suspended upon request of Regulatory Authorities.

15 STATISTICAL METHODS AND CONSIDERATIONS

This section outlines the nature and rationale for the statistical methods to be used for the analysis of the data from the study. Baseline will be defined as the last measurement before the patient is randomized. All data will be included in data listings. A separate Statistical Analysis Plan (SAP), which must be documented as completed prior to unblinding the study, will describe data handling and statistical techniques in full detail, except missing PK data handling and PK analysis methods will be described in the PK report. The SAP will contain any modifications to the analysis plan described below in this section.

15.1 Analysis Populations

15.1.1 Safety Population

All safety analyses will be performed in the Safety Population, defined as all patients who were randomized and received at least 1 dose of the study drug. Patients will be analyzed according to the study drug they received.

15.1.2 Pharmacokinetics Population

The PK analysis of AK001 will be performed in the PK Population, defined as patients with serum concentration data obtained at pre-defined time points.

15.1.3 Efficacy Populations

The main population for efficacy will be the Modified Intention-to-Treat Population, defined as all patients randomized who receive at least 1 dose of study drug and have a valid Baseline measurement and at least 1 post-baseline efficacy assessment. Patients will be analyzed for efficacy according to the group to which they were randomized.

In addition, the primary efficacy analyses will also be performed for the Per-Protocol Population, defined as patients who have a Week 12 visit and valid efficacy measurements.

15.2 Demographic and Baseline Characteristics

Demographic and Baseline variables that will be summarized by treatment and dose group include:

- Demographics
- Medical history
- Complete PE
- Safety variables including vital signs and laboratory tests (including chemistries, hematology, and urinalysis) obtained at Screening, and ADA obtained on Day 0 pre-dose

15.3 Analysis of Primary Endpoint

The effect of 2 different dose levels of AK001 in combination with an INS versus the INS alone on the reduction in size of nasal polyps as evaluated by the change from Baseline to

Week 12 after the start of treatment in TPS (Appendix 2 Section 19.2) will be displayed for each treatment group by study visit using summary statistics, including the number of observations, the mean, median, standard deviation (SD), and range. Each active treatment group will be compared separately with the placebo group for change from Baseline in TPS by using a mixed effect repeated measures analysis of variance (ANOVA) model with specific contrast statement for Week 12 and for each comparison separately. Adjustment in alpha for multiple comparisons will be controlled according to the Hochberg method, in which, if the efficacy comparison of the high active arm versus placebo is statistically significant at the 0.05 level, no penalty will be assessed to the comparison of the low active arm versus the placebo arm. Otherwise, the low active arm versus the placebo arm will be compared at the 0.025 level.

Missing values for the primary endpoint will be imputed by 2 methods: last observation carried forward and worst observation carried forward. Imputations will be done on the total score level and not on the individual item level. Due to the sample size, no multiple imputation technique is intended.

15.4 Analysis of Secondary Endpoints

Additional efficacy measures will be analyzed in support of the primary efficacy endpoint results.

In addition to change from Baseline in TPS (Appendix 2 Section 19.2), absolute values and percentage changes from Baseline will be analyzed separately using the same repeated measures model described above. A responder analysis will also be considered. The response definition and its appropriate analysis methodology will be presented in the SAP. The numbers (percentages) of patients who are responders and time to first response for each active treatment group will be compared separately with the placebo group, if feasible.

Examination of the treatment effect over time for TPS (Appendix 2 Section 19.2), UPSIT (Appendix 4 Section 19.4), and patient-reported symptoms of sinusitis (SNOT-22) (Appendix 5 Section 19.5) will be examined using an appropriate similar repeated measures ANOVA. The stratification factor, presence or absence of asthma, may be included in the model. The details of the analytical methods will be presented in the SAP.

Size of polyps as evaluated by Lund-Mackay score (Appendix 3 Section 19.3) at selected Investigator sites by CT scan (CT scans are optional and will only be done at Investigator sites at which appropriate and timely regulatory approval or authorization can be granted); PNIF; UPSIT (Appendix 4 Section 19.4); and patient-reported SNOT-22 (Appendix 5 Section 19.5), VAS (Appendix 6 Section 19.6), clinical symptoms improvement scale[3] (Appendix 6 Section 19.6), and SF-36 (Appendix 7 Section 19.7) scores for each active treatment group will be compared separately with the placebo group using a repeated measure ANOVA with contrast statements for comparison at Week 12 as well as other time points in the study.

15.5 Analysis of Exploratory Endpoints

The exploratory analyses are not powered for statistical significance.

Potentially, markers of MCs and eosinophils and inflammatory response in blood for each active treatment group will be compared separately with the placebo group, with suitable analyses that will be described in the SAP.

Enrollment in this study is designed for presence or absence of asthma as a stratification factor; thus, asthma will be equally distributed among the 3 groups. This stratification factor may be used in the analyses of the primary and secondary analyses described above. Additional exploratory analyses are planned to explore any possible trend in favor of AK001 in the subgroup of asthmatic patients.

In patients with comorbid asthma, use of asthma rescue therapy will be summarized by number and percentage. Changes from Baseline; percentage changes from Baseline; absolute TPS (Appendix 2 Section 19.2); pulmonary function (assessed using spirometry) as evaluated by FEV1, FVC, FEF; and ACT (Appendix 8 Section 19.8) for each active treatment group will be compared separately with the placebo group using the same repeated measures model described above, to detect any potential trend at Week 12 and at other visits.

15.6 Safety Analysis

Safety and tolerability will be assessed throughout the study by monitoring and evaluating TEAEs, including any complications resulting from the IV infusion, and changes in vital signs and in clinical safety laboratory test (including ADA) and PE findings. All safety and tolerability endpoints will be summarized by treatment. Baseline for all safety endpoints will be defined as the last recorded observation before the administration of the IV infusion of study drug. Safety measures, including AEs, clinical safety laboratory tests (including ADA), vital signs, PEs, and concomitant medication usage, will be summarized descriptively. For quantitative variables, descriptive statistics, including number of observations, means, medians, SDs, and ranges, will be provided for the values themselves as well as for the changes from Baseline by treatment group at each study visit. Qualitative variables will be summarized using counts and percentages in each treatment group at each study visit.

Adverse Events:

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA system organ class (SOC) and preferred term. The summaries of AEs will be based on TEAEs. A TEAE is defined as an AE reported in the clinical database with a date of onset (or worsening) on or after the start date of study drug through the end of the study.

The following information will be presented for AEs:

- TEAEs by SOC and preferred term
- TEAEs by maximum severity, SOC, and preferred term
- Drug-related TEAEs by SOC and preferred term
- TEAEs leading to withdrawal by SOC and preferred term
- Serious TEAEs by SOC and preferred term

All AEs will be collected starting from the first study drug administration through Day 168 or ET. Severity will be assessed by the Investigator using the protocol-defined grading scales (Section 11.1). All AEs will also be judged by the Investigator as to whether they are clinically significant and related to study drug.

Vital Signs:

Body temperature, supine systolic and diastolic blood pressure, pulse, and respiratory rate will be measured at Screening and on Days -3, 0, 14, 21, 49, 84, 112, and 168 or ET. On Days 0, 21, and 49, vital signs will be measured pre-dose, every 15 minutes after the start of infusion, and immediately following the end of infusion. All vital signs will be measured after the patient has been in the supine position for ≥5 minutes.

Descriptive statistics will be used to summarize vital signs at Baseline, each visit and time point, and the change from Baseline for each visit and time point.

Laboratory Assessments:

Samples will be obtained for the clinical safety laboratory tests (hematology, chemistry, urinalysis) and for ADA specified in Table 1 and Sections 9.3.2, 9.3.3, 9.3.5, and 9.4.

Descriptive statistics will be used to summarize laboratory results at Baseline, each visit, and the change from Baseline for each visit. In addition, shift tables will summarize the laboratory results relative to normal reference ranges at Baseline and each post-baseline time point.

Physical Examinations:

A complete PE will be performed at Screening, and symptom-directed PEs will be performed pre-dose (and post-dose as indicated) on Days 0, 21, and 49 and on Days 14, 21, 84, 112, and 168 or ET. Shift tables will summarize the examination results as normal or abnormal at Baseline and at the end of study.

Prior and Concomitant Medications:

All medications (prior and current) will be coded using the latest version of the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System. Concomitant medications will be summarized by ATC Class 1, ATC Class 3, and preferred term.

15.7 Sample Size and Randomization

The study will be conducted at approximately 14 investigational sites in the European Union and the United States, and approximately 70 patients will be enrolled.

This study will evaluate the effect of 2 different dose levels of AK001 in combination with an INS versus the INS plus placebo on the reduction in size of nasal polyps. Assuming equal efficacy effect of the 2 active treatment arms, a planned sample size of approximately 70 patients (25 mg of AK001 [n=25], 250 mg of AK001 [n=25], and a corresponding placebo (n=20]) will ensure at least 80% power to detect a difference in mean nasal polyp scores between the placebo group (Mean= -0.3; SD ≤1.128) and each of the AK001 groups (Mean= -1.9; SD ≤2.064) with an alpha of 0.05. PASS 11, Version 11.0.10, was used for this power analysis.

15.8 Interim Monitoring

No interim analyses are planned for evaluating efficacy. However interim safety monitoring will be performed according to the DMC charter.

16 DATA COLLECTION, RETENTION, AND MONITORING

16.1 Data Collection Instruments

All staff at each investigational site will adhere to Good Documentation Practices. Data will be entered into eCRFs using source document data. Source documents may include, but are not limited to, laboratory data, recorded data from automated instruments, medical progress notes, and email correspondence.

16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices that meet FDA and local applicable authority guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the electronic data capture system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archiving of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

In accordance with 21 CFR 312.62(c) and ICH/GCP 4.9.5 and all other applicable regulatory requirements, following completion or termination of the study, the investigational sites will retain a copy of all study records in a limited-access storage room for a minimum of 2 years after notification that the investigations have been discontinued and the FDA has been notified or for 2 years after all marketing applications have been

approved. The Trial Master File will be created during the implementation phase of a study, maintained on an ongoing basis throughout the duration of the project, and collated at the end of the study. The files will contain folders that may include, but are not limited to, the following sub-categories:

- Financial agreements
- Regulatory documents
- IRB/IEC documents
- Drug accountability
- Correspondence
- Medical reports
- Patient data
- Monitoring visit reports
- Sample eCRFs and eCRF guidelines

16.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the United States CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate Regulatory Authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Patient Confidentiality

Only the patient's number and demographics will be recorded in the eCRF. If the patient's name appears on any other source document collected (e.g., hospital discharge summary), it must be removed from the document before the document is transcribed to the eCRF. All study findings will be stored in electronic databases. The patients will give explicit written permission for representatives of the Sponsor, Regulatory Authorities, and the IRB/IEC to inspect their medical records to verify the information collected about them. Patients will be informed that all personal information made available for inspection will kept confidential to the extent permitted by all applicable state, local, and federal data protection/privacy laws and/or regulations and will not be made publically available. If the results of the trial are published, the patient's identity will remain confidential.

Patients will be advised not to share their study information with other patients.

17 ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

The study will be conducted in a manner consistent with all applicable Regulatory Authority and IRB/IEC regulations (e.g., ICH Guideline for Good Clinical Practice [GCP, CPMP/ICH/135/95], the Declaration of Helsinki [in its currently acknowledged version], Institutional Review Boards [21 CFR 56], and Obligations of Clinical Investigators

[21 CFR 312]) as well as in keeping with applicable local law(s) and regulation(s). This may include audits by the Sponsor and the Sponsor representatives, respectively, and/or inspections by Regulatory Authority representatives at any time. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996 [HIPAA], European Union Data Protection Directive 95/46/EC). In addition, the Investigator must agree to the inspection/audit of study-related records by the Regulatory Authority/Sponsor and Sponsor representatives and must allow direct access to source documents to the Regulatory Authority/Sponsor and Sponsor representatives.

17.1 Protocol Amendments

Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. Written approval of a protocol amendment is not required prior to implementation of changes to the protocol that eliminate immediate hazard to the patient; however, approval must be obtained as soon as possible thereafter. Any agreed amendments must also be signed by the Investigator.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and ICF will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse events, regardless of causality, will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as the protocol; protocol amendments; the IB; ICFs; information concerning patient recruitment, payment, and compensation procedures; and other pertinent information) will be submitted to the IRB/IEC. The IRB's/IEC's written unconditional approval of the study protocol and the ICF will be in the possession of the Investigator before the study is initiated. The IRB's/IEC's unconditional approval statement will be transmitted by the Investigator to Allakos, Inc., prior to the shipment of study supplies to the investigational site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such changes will be submitted to the IRB/IEC, and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review, serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB/IEC, new information that may affect adversely the safety of the patients of the conduct of the study, annual updates and/or requests for re-approval, and completion of the study.

17.3 Informed Consent Form

Prior to undergoing any study-related procedures, all patients must consent to participate in the study.

In accordance with ICH GCP Guidelines 4.3.3, the Investigator must inform the patient's primary physician about the patient's participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.

The process of obtaining the informed consent will be in compliance with all federal regulations, ICH requirements, and local laws.

The Investigator or a designee will review the study and the ICF with each patient. The review will include the nature, scope, procedures, and possible consequences of the patient's participation in the study. The ICF and review must be understandable to the patient. The Investigator or designee and the patient must both sign and date the ICF after review and before the patient can undergo any study-related procedures. The patient will receive a copy of the signed and dated ICF, and the original will be retained in the investigational site's study files. The Investigator or designee must emphasize to the patient that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the patient is otherwise entitled.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between Allakos and each investigational site. The publication or presentation of any study results shall comply with all applicable privacy laws, for example, the HIPAA.

17.5 Clinical Trial Registration

This clinical trial will be registered in the US on the "clinicaltrials.gov" clinical trial registry website, as required by 121 STAT. 823, and on EudraCT in Europe, as necessary.

18 REFERENCES

1. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol 1999;28(4):717-22.

2. Mygind N, Dahl R, Bachert C. Nasal polyposis, eosinophil dominated inflammation, and allergy. Thorax 2000;55 Suppl 2:S79-83.

3. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012(23):3 p preceding table of contents, 1-298.

4. Pearlman AN, Chandra RK, Conley DB, Kern RC. Epidemiology of nasal polyps. In: Nasal Polyposis, eds. T.M. Onerci and B.J. Ferguson. Springer-Verlag: Berlin Heidelberg 2010. In.

5. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. J Allergy Clin Immunol 2001;107(4):607-14.

6. Kiwamoto T, Kawasaki N, Paulson JC, Bochner BS. Siglec-8 as a drugable target to treat eosinophil and mast cell-associated conditions. Pharmacol Ther 2012;135(3):327-36.

7. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events Version 4.0. 28May2009. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed 01Feb2016.

19 APPENDICES

19.1 Appendix 1: Contraception Guidelines

Contraception guidelines vary by location; local guidelines will be followed.

Female patients must be post-menopausal for at least 1 year with documented follicle-stimulating hormone (FSH) >30 IU/L, surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or, if of child-bearing potential, willing to use a highly effective method of contraception from Screening until at least 17 weeks after the last dose of the study drug is administered, which corresponds to approximately 5 half-lives of AK001.

Male patients with female partners of childbearing potential must agree to use a highly effective method of contraception from Screening until at least 17 weeks after the last dose of the study drug was administered, which corresponds to approximately 5 half-lives of AK001. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

Highly effective methods of contraception include the following practices:

a) Complete abstinence (acceptable only if it is established before the patient participates in the trial that this is the preferred and usual lifestyle of the patient)

b) Prescription hormonal contraceptives (oral, injected, or implanted) for 2 or more menstrual cycles prior to Screening

c) Intrauterine device

d) Surgical sterilization for male patients with female partners

   i. Tubal ligation/hysterectomy/bilateral oophorectomy or

   ii. Vasectomy

The double barrier method of contraception (e.g., condom with cap, diaphragm, or sponge with spermicide) alone is not considered a highly effective method but may be used in conjunction with 1 of the above methods.

19.2 Appendix 2: Polyp Scoring System

Polyp Scoring System Used to Evaluate Polyp Size in Each Nostril by Nasal Endoscopy

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 below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity

Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol 2013;131(1):110-6 e1.

19.3 Appendix 3: Lund-Mackay Scoring System

The Lund-Mackay scoring system as presented in the table below will be used to measure the polyp size in each nostril by computed tomography (CT) at selected Investigative sites. The CT scans are optional and will only be done at Investigator sites at which appropriate and timely regulatory approval or authorization can be granted.

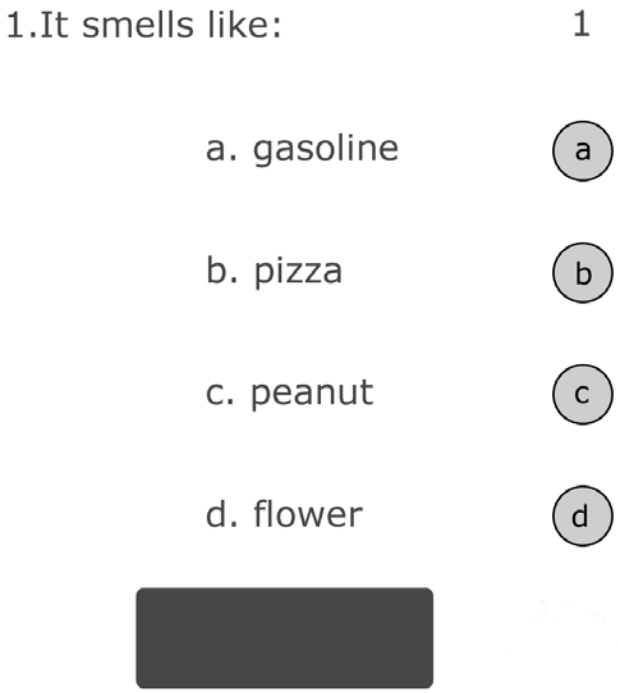
Lund-Mackay Scoring System

	Possible Scores[1]
Maxillary	0-2
Anterior ethmoid	0-2
Posterior ethmoid	0-2
Sphenoid	0-2
Frontal	0-2
Osteomeatal complex	0 or 2
Total	

1. Scale: 0 = absence; 1 = partial opacification; 2 = complete opacification.

19.4 Appendix 4: University of Pennsylvania Smell Identification Test™

The University of Pennsylvania Smell Identification Test consists of 4 booklets, each containing 10 odorants with 1 odorant per page. The stimuli are embedded in plastic microcapsules on brown strips at the bottom of each page. Above each odorant strip is a multiple-choice question with 4 alternative words to describe the odor as in the model of a test page below. The patient is asked to release the odorant by rubbing the brown-strip with the tip of a pencil and to indicate which of 4 words best describes the odor. Thus, each subject receives a score out of 40 possible correct answers (Scadding G, Hellings P, Alobid I, Bachert C, Fokkens W, van Wijk RG, et al. Diagnostic tools in Rhinology EAACI position paper. Clin Transl Allergy 2011;1[1]:2).



Fornazieri MA, Pinna Fde R, Bezerra TF, Antunes MB, Voegels RL. Applicability of the University of Pennsylvania Smell Identification Test (SIT) in Brazilians: pilot study. Braz J Otorhinolaryngol 2010;76(6):695-9.

19.5 Appendix 5: Sino-nasal Outcome Test-22

I.D.:_____ SINO-NASAL OUTCOME TEST (SNOT-22) DATE:_____

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Very Mild Problem	Mild or slight Problem	Moderate Problem	Severe Problem	Problem as bad as it can be		5 Most Important Items
1. Need to blow nose	0	1	2	3	4	5		O
2. Nasal Blockage	0	1	2	3	4	5		O
3. Sneezing	0	1	2	3	4	5		O
4. Runny nose	0	1	2	3	4	5		O
5. Cough	0	1	2	3	4	5		O
6. Post-nasal discharge	0	1	2	3	4	5		O
7. Thick nasal discharge	0	1	2	3	4	5		O
8. Ear fullness	0	1	2	3	4	5		O
9. Dizziness	0	1	2	3	4	5		O
10. Ear pain	0	1	2	3	4	5		O
11. Facial pain/pressure	0	1	2	3	4	5		O
12. Decreased Sense of Smell/Taste	0	1	2	3	4	5		O
13. Difficulty falling asleep	0	1	2	3	4	5		O
14. Wake up at night	0	1	2	3	4	5		O
15. Lack of a good night's sleep	0	1	2	3	4	5		O
16. Wake up tired	0	1	2	3	4	5		O
17. Fatigue	0	1	2	3	4	5		O
18. Reduced productivity	0	1	2	3	4	5		O
19. Reduced concentration	0	1	2	3	4	5		O
20. Frustrated/restless/irritable	0	1	2	3	4	5		O
21. Sad	0	1	2	3	4	5		O
22. Embarrassed	0	1	2	3	4	5		O

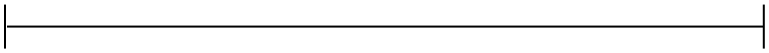
2. Please mark the most important items affecting your health (maximum of 5 items)_____ ↑

19.6 Appendix 6: Visual Analogue Scales for Symptoms of Rhinosinusitis and Clinical Symptoms Improvement Scale

The VASs rank symptoms from 0 (not troublesome) to 10 (most troublesome) on 10 cm-long scales as below.

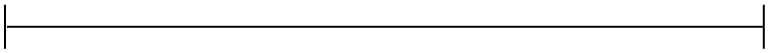
How troublesome are each of your following symptoms of rhinosinusitus?

a) Anterior nasal discharge



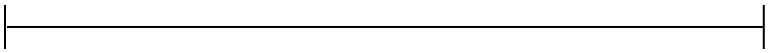
Not troublesome Most troublesome

b) Posterior nasal discharge



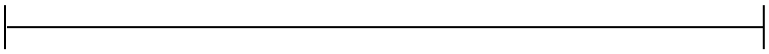
Not troublesome Most troublesome

c) Nasal congestion, blockade, or obstruction



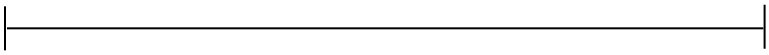
Not troublesome Most troublesome

d) Decreased sense of smell



Not troublesome Most troublesome

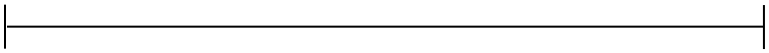
e) Facial pain or pressure



Not troublesome Most troublesome

The clinical symptoms improvement scale* ranks symptom troublesomeness from 0 (not troublesome) to 10 (worst thinkable troublesome) on a 10 cm-long scale as below.

How troublesome are your symptoms of rhinosinusitis?



Not troublesome Worst thinkable troublesome

The symptomatology or symptom troublesomeness can be divided into "mild," "moderate," and "severe" categories based on total score:

- Mild=0 through 3
- Moderate= >3 through 7
- Severe= >7 through 10

*Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012(23):3 p preceding table of contents, 1-298.

19.7 Appendix 7: 36-Item Short Form Health Survey

SF-36v2 Health Survey Single-Item Presentation Text Standard, United States (English)

Note: Item SF36v2_BP1 (Item #21) has 6 answers, not 5 answers; see entry for item at end of sheet for more detail.

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
	Your Health and Well-Being						
		This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please select the one box that best describes your answer.					
SF36v2_GH1	None	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor
SF36v2_HT	None	Compared to one year ago, how would you rate your health in general now?	Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
SF36v2_PF01	The following question is about activities you might do during a typical day.	Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF02	The following question is about activities you might do during a typical day.	Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF03	The following question is about activities you might do during a typical day.	Does your health now limit you in lifting or carrying groceries? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF04	The following question is about activities you might do during a typical day.	Does your health now limit you in climbing several flights of stairs? If so, how much?	Yes, limited a	Yes, limited a	No, not limited at		

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
			lot	little	all		
SF36v2_PF05	The following question is about activities you might do during a typical day.	Does your health now limit you in climbing one flight of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF06	The following question is about activities you might do during a typical day.	Does your health now limit you in bending, kneeling, or stooping? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF07	The following question is about activities you might do during a typical day.	Does your health now limit you in walking more than a mile? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF08	The following question is about activities you might do during a typical day.	Does your health now limit you in walking several hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF09	The following question is about activities you might do during a typical day.	Does your health now limit you in walking one hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF10	The following question is about activities you might do during a typical day.	Does your health now limit you in bathing or dressing yourself? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_RP1	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?	Cut down on the amount of time you spent on work or other activities as a result of your physical health	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RP2	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?	Accomplished less than you would like as a result of your physical health	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RP3	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?	Were limited in the kind of work or other activities as a result of your physical health	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RP4	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?	Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)	All of the time	Most of the time	Some of the time	A little of the time	None of the time

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
SF36v2_RE1	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?	Cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RE2	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?	Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RE3	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?	Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_SF1	None	During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Not at all	Slightly	Moderately	Quite a bit	Extremely
SF36v2_BP1	None	How much bodily pain have you had during the past 4 weeks?	See end of document for answers #1-#6				
SF36v2_BP2	None	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A little bit	Moderately	Quite a bit	Extremely
SF36v2_VT1	This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past 4 weeks did you feel full of life?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH1	This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past 4 weeks have you been very nervous?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH2	This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past 4 weeks have you felt so down in the dumps that nothing could cheer you up?	All of the time	Most of the time	Some of the time	A little of the time	None of the time

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
SF36v2_MH3	This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past 4 weeks have you felt calm and peaceful?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_VT2	This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past 4 weeks did you have a lot of energy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH4	This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past 4 weeks have you felt downhearted and depressed?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_VT3	This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past 4 weeks did you feel worn out?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH5	This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past 4 weeks have you been happy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_VT4	This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past 4 weeks did you feel tired?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_SF2	None	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_GH2	How TRUE or FALSE is the following statement for you?	I seem to get sick a little easier than other people.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
SF36v2_GH3	How TRUE or FALSE is the following statement for you?	I am as healthy as anybody I know.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
SF36v2_GH4	How TRUE or FALSE is the following statement for you?	I expect my health to get worse.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
SF36v2_GH5	How TRUE or FALSE is the following statement for you?	My health is excellent.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false

(SF-36v2® Health Survey Standard, United States (English)).

Data for item SF36v2_BP1 (item #21 in the survey template)

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
SF36v2_BP1	None	How much bodily pain have you had during the past 4 weeks?	None	Very mild	Mild	Moderate	Severe	Very severe

(SF-36v2® Health Survey Single-Item Presentation Text Standard, United States (English)).

19.8 Appendix 8: Asthma Control Test™

Asthma Control Test™ Single-Item Presentation Text, United States (English)

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
	Asthma Control Test™						
	This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. For each of the following questions, please select the one box that best describes your answer.						
ACT1	None	In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
ACT2	None	During the past 4 weeks, how often have you had shortness of breath?	More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
ACT3	None	During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?	4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
ACT4	None	During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, or Maxair®)?	3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
ACT5	None	How would you rate your asthma control during the past 4 weeks?	Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled

Single-Item Presentation Text, United States (English).